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Mathematical Modeling and Analysis of Leukemia: Effect of External Engineered T Cells Infusion

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Abstract

In this paper, a nonlinear model is proposed and analyzed to study the spread of Leukemia by considering the effect of genetically engineered patients T cells to attack cancer cells. The model is governed by four dependent variables namely; naive or susceptible blood cells, infected or dysfunctional blood cells, cancer cells and immune cells. The model is analyzed by using the stability theory of differential equations and numerical simulation. We have observed that the system is stable in the local and global sense if antigenicity rate or rate of stimulation of immune cells is greater than a threshold value dependent on the density of immune cells. Further, external infusion of T cells (immune cells) reduces the concentration of cancer cells and infected cells in the blood. It is observed that the infected cells decrease with the increase in antigenicity rate or stimulation rate of immune response due to abnormal cancer cells present in the blood. This indicates that immune cells kill cancer cells on being stimulated and as antigenicity rate increases rate of destruction of cancer cells also increase leading to decrease in the concentration of cancer cells in the body. This decrease in cancer cells further causes decrease in the concentration of infected or dysfunctional cells in the body.

Keywords: Blood cells; Cancer cells; Blood transfusion; Immune response

MSC 2010: 93A30, 92D30

1. Introduction

Leukemia means "white blood" but it is not as commonly called, blood cancer. It is a cancer of the tissues in which blood is formed. Bone marrow is the soft, spongy center of the bone that produces red blood cells, white blood cells and platelets. Red blood cells carry oxygen to cells throughout the body and, if there are too few red blood cells, symptoms such as anemia, shortness of breath appear. White blood cells fight infection, and platelets, which control blood clotting, prevent hemorrhaging. The spleen and the lymph nodes produce a type of white blood cell called lymphocyte. Lymphocytes produce antibodies, act against infection, and contribute to the body's own immune system. All blood-forming tissues daily release millions of each type of cell into one of the body's two circulatory systems—the blood vessel system and the lymph system. When leukemia strikes, millions of abnormal, immature white blood cells called leukocytes are released into these circulatory systems. Because these cells are immature, they cannot carry out their basic function of fighting infection. In advanced leukemia, the uncontrolled multiplication of abnormal cells results in crowding out the production of normal white cells to fight infections, of platelets to control hemorrhaging and of red blood cells to prevent anemia (Indian Cancer Society). In 2000, approximately 256,000 children and adults around the world developed a form of leukemia, and 209,000 died from it. This represents about 3% of the almost seven million deaths due to cancer that year, and about 0.35% of all deaths from any cause. Of the sixteen separate sites the body compared, leukemia was the 12th most common class of neoplastic disease, and the 11th most common cause of cancer-related death, Mathers et al. (2001).

The most common treatment for cancer is chemotherapy. But chemotherapy, though helpful, also causes unwanted side effects. Therefore, an alternative solution has developed which is termed as Adoptive Immunotherapy. Adoptive Immunotherapy is a form of immunotherapy used in the treatment of cancer in which an individual's own white blood cells are coupled with a naturally produced growth factor to enhance their cancer-fighting capacity. Then, these are injected into tumor site to increase immune response locally.

In a potential breakthrough in cancer research, scientists at the University of Pennsylvania have genetically engineered patients' T cells — a type of white blood cell — to attack cancer cells in advanced cases of a common type of leukemia. Two of the three patients who received doses of the designer T cells in a clinical trial remained cancer-free for more than a year, Eryn (2011).

To build the cancer-attacking cells, the researchers modified a virus to carry instructions for making a molecule that binds with leukemia cells and directs T cells to kill them. Then they drew blood from three patients who suffered from chronic lymphocytic leukemia and infected their T cells with the virus. When they infused the blood back into the patients, the engineered T cells successfully eradicated cancer cells, multiplied to more than 1,000 times in number and survived for months. They even produced dormant "memory" T cells that might spring back to life if the cancer was to return. On average, the team calculated, each engineered T cell eradicated at least 1,000 cancer cells. The findings, published simultaneously on August 2011, in the *New England Journal of Medicine and Science Translational Medicine*, were the first demonstration of the use

of gene transfer therapy to create "serial killer" T cells aimed at cancerous tumors, Eryn (2011). We focus on this therapy in our model.

There is an extensive body of work on the study of spread of an infectious agent from cell to cell within one patient. Nowak and May (2000) have proposed a detailed surveys of the main ideas developed through such models. Several diseases with immune system response have been modeled in literature, for example, tuberculosis by Wigginton and Kirschner (2001) and hepatitis B disease by Nowak et al. (1996). H.I. Freedman (2000) presents a detailed mathematical study of cancer immunotherapy. They presented a model of cancer treatment by immunotherapy, treating normal cells and cancer cells as competitors for common resources. The anti-cancer cells were thought of as predators on the cancer cells. Kolev (2003) also presented a mathematical model, showing competition between tumors and immune system, considering the role of antibodies. Early modeling of leukemia includes models given by Cronkite and Vincent (1969), Rubinow and Lebowitz (1975), and Rubinow (1969).

In this paper, a nonlinear mathematical model is proposed and analyzed to study the spread of leukemia with the effect of external engineered T cells infusion into the cancer patients. Our model consists of a system of four nonlinear ordinary differential equations for naive or susceptible blood cells, infective or dysfunctional blood cells, cancer cells and immune cells. We consider a source term for naive blood cells entering into the circulatory blood from other compartments like bone marrow, lymph nodes and thymus as well as from transfusion. The encounter of naive blood cells with the cancer cells are considered according to the law of mass action. On being infected by cancer cells, naive blood cells become dysfunctional and enter into the class of infectives. Further, we consider blood transfusion also in the model since blood transfusions are likely to be done in blood cancer patients by their family members. Immune cells are assumed to be activated and proliferated in the presence of costimulators and immunotherapy.

2. Mathematical Model

To model the problem, let us consider the spread of leukemia in the blood circulating system. Let x be the population of naive/susceptible blood cells, y be the population of infected or dysfunctional blood cells. c_s is the population of leukemic or cancer cells (abnormal cells) and z is the population of white blood cells or immune cells. Following the basic intracellular process of bilinear mass action for cancer growth, the epidemic model is proposed as follows:

$$\begin{aligned}\frac{dx}{dt} &= A - a_0x - \beta xc_s, \\ \frac{dy}{dt} &= \beta xc_s - \beta_0 y, \\ \frac{dc_s}{dt} &= k - k_0c_s - k_1c_s z, \\ \frac{dz}{dt} &= B + bc_s - b_0z - b_1zc_s.\end{aligned}\tag{2.1}$$

First term on the first equation of right hand side of model (2.1) is the recruitment rate of naive or susceptible blood cells entering into the circulatory blood from compartments like bone marrow, lymph nodes and thymus, A_n as well as from transfusion, A_t . It is considered to be a constant A , thus $A = A_t + A_n$. The second term is the natural death rate constant of naive blood cells which is considered to be proportional to its concentration, a_0 being a constant. β is the decay rate constant of naive blood cells because of being killed/ infected by the cancer cells and becoming dysfunctional. It is assumed to be a bilinear mass action term, which says that the total number of encounters between members of two populations is proportional to the product of the sizes of two populations.

In the second equation of the model (2.1), the bilinear term describes the change of susceptible blood cells to infected or dysfunctional blood cells and the second term is the natural death rate, β_0 of these cells.

In third equation of the model (2.1), first term k is a constant recruitment rate of cancer cells into the blood system and k_0 is the natural death rate constant of cancer cells. The third term with coefficient k_1 represents the loss of cancer cells due to encounter with the immune cells.

Similarly, the fourth equation of the model (2.1) represents the rate of change of immune cells with time. B is the rate of external intravenous re-infusion of T cells into the cancer patients. b is the proliferation rate of T cells (immune cells) due to cancer antigen presenting cells in the blood if cancer relapse. b_0 is the natural death rate of immune cells and fourth term with coefficient b_1 is loss rate of immune cells due to encounter with cancer cells. This term represents the competition among cancer and immune cells for its survival.

The following lemma gives the region of attraction of the solution of the model (2.1) which we state without proof:

Lemma 1.

Solutions of the system (2.1) are bounded within a region Ω ,

where

$$\Omega = \left\{ \begin{array}{l} (x, y, c_s, z) : 0 < x(t) \leq A/a_0, \quad 0 < x(t) + y(t) \leq A/\eta, \\ \quad \quad \quad 0 < c_s \leq k/k_0 \quad \text{and} \quad 0 < z(t) \leq (B + bk/k_0)/b_0 \end{array} \right\}$$

and $\eta = \min(a_0, \beta_0)$.

3. Equilibrium Analysis

The model (2.1) has only one equilibrium point, namely, $E^*(x^*, y^*, c_s^*, z^*)$ whose components x^*, y^*, c_s^* and z^* are the positive solutions of the following algebraic equations:

$$A - a_0x - \beta xc_s = 0, \tag{3.1}$$

$$\beta xc_s - \beta_0 y = 0, \tag{3.2}$$

$$k - k_0 c_s - k_1 c_s z = 0, \tag{3.3}$$

$$B + bc_s - b_0 z - b_1 z c_s = 0. \tag{3.4}$$

From (3.3) we have,

$$c_s = \frac{k/k_0}{1 + k_1 z/k_0}. \tag{3.5}$$

Using (3.5) in (3.4) we have the following quadratic equation in z :

$$k_1 b_0 z^2 + (k_0 b_0 + k b_1 - B k_1) z - (k b + B k_0) = 0. \tag{3.6}$$

It can be easily observed that (3.6) has a unique positive root by Descartes' rule of sign, z^* (say).

Using value of z^* in (3.5) we get

$$c_s^* = \frac{k/k_0}{1 + k_1 z^*/k_0}, \tag{3.7}$$

$$x^* = \frac{A(1 + k_1 z^*/k_0)}{a_0 + \beta k/k_0 + a_0 k_1 z^*/k_0},$$

and

$$y^* = \frac{\beta}{\beta_0} \left(\frac{A}{a_0 + \beta k/k_0 + a_0 k_1 z^*/k_0} \right) \frac{k}{k_0}.$$

Now we perform local and global stability analysis of the equilibrium point E^* .

4. Local Stability Analysis

We present here local stability analysis of the equilibrium point E^* by linearization in the following theorem:

Theorem 4.1.

The interior equilibrium point E^* is locally asymptotically stable.

Proof:

See Appendix A.

5. Global Stability Analysis

In the following theorem, we will show the global stability of the equilibrium point. In order to prove this theorem we will use lemma 1 that establishes a region of attraction for model (2.1).

Theorem 5.1.

If the inequality $2k_1b_1z_{\max}^2 < k_0b$ holds then the interior equilibrium point E^* is globally asymptotically stable.

Proof:

See Appendix B.

The above theorem gives a sufficient condition for the interior equilibrium E^* to be globally asymptotically stable. It states that dormant memory or antigenicity of immune cells should be greater than a threshold value the magnitude of which depends on the equilibrium level of immune cells, death rate of cancer cells due to immune cells, death rate of immune cells due to its competition with cancer cells and natural death rate of cancer cells. Under condition

$$2k_1b_1z_{\max}^2 < k_0b,$$

the immunotherapy will be able to cure cancer.

From (3.7) we observe that when $k \rightarrow \infty$, that is, the case when number of immature white blood cells becomes very large then susceptible blood cells concentration, $x^* \rightarrow 0$. This may be due to complete infection of blood cells in blood circulatory system due to cancer cells. However, infected cell concentration in the blood also reaches a high equilibrium value given by

$$y^* = \frac{A}{\beta_0} \text{ as } k \rightarrow \infty.$$

6. Particular Cases

Case I:

In the model (2.1) if we neglect the immune response of the body i.e. $z = 0$, then the model is simplified as follows:

$$\begin{aligned} \frac{dx}{dt} &= A - a_0x - \beta xc_s, \\ \frac{dy}{dt} &= \beta xc_s - \beta_0 y, \\ \frac{dc_s}{dt} &= k - k_0 c_s. \end{aligned} \tag{6.1}$$

This situation in the body takes place in severe cases when the immune system is very weak. In such cases, cancer cells and infected cells continue to grow without any inhibition leading to worsening of clinical condition of the patient. The model (6.1) has following equilibrium:

$$\bar{x} = \frac{A}{a_0 + \beta k/k_0}, \tag{6.2}$$

$$\bar{y} = \frac{\beta}{\beta_0} \left(\frac{A}{a_0 + \beta k/k_0} \right) \frac{k}{k_0}, \tag{6.3}$$

$$\bar{c}_s = \frac{k}{k_0}, \tag{6.4}$$

$$\bar{z} = 0. \tag{6.5}$$

In this case, cancer cells grow without any constraint and approach its maximum possible limit in the blood.

Case II:

If we consider immunotherapy and assume that there is no dormant memory or immune response activation from professional antigen presenting cells, then we have the following mathematical model:

$$\begin{aligned} \frac{dx}{dt} &= A - a_0x - \beta xc_s, \\ \frac{dy}{dt} &= \beta xc_s - \beta_0 y, \end{aligned}$$

$$\begin{aligned}\frac{dc_s}{dt} &= k - k_0c_s - k_1c_sz, \\ \frac{dz}{dt} &= B - b_0z - b_1zc_s.\end{aligned}\tag{6.6}$$

This model also has only one equilibrium point $\hat{E}(\hat{x}, \hat{y}, \hat{c}_s, \hat{z})$.

When $\frac{dc_s}{dt} = 0$, we have

$$c_s = \frac{k/k_0}{1 + k_1z/k_0}.\tag{6.7}$$

Using (6.7), white blood cell population \hat{z} (say) is determined by the unique root of the equation,

$$k_1b_0z^2 + (k_0b_0 + kb_1 - Bk_1)z - Bk_0 = 0.\tag{6.8}$$

It can be easily observed that (6.8) has a unique positive root by Descartes' rule of sign.

Equilibrium values of population of other cells in the blood system are given by

$$\hat{x} = \frac{A(1 + k_1\hat{z}/k_0)}{a_0 + \beta k/k_0 + a_0k_1\hat{z}/k_0},\tag{6.9}$$

$$\hat{y} = \frac{\beta}{\beta_0} \left(\frac{A}{a_0 + \beta k/k_0 + a_0k_1\hat{z}/k_0} \right) \frac{k}{k_0},\tag{6.10}$$

and

$$\hat{c}_s = \frac{k/k_0}{1 + k_1\hat{z}/k_0}.\tag{6.11}$$

We observe that equilibrium value of cancer cells in this case is less than that in case I due to immune response activation by immunotherapy. Thus, in this case, growth of cancer cell or immature white blood cells is checked by the immune response activation due to infusion of engineered T cells (immune cells) in the blood. It implies that immunotherapy by engineered T cells is helpful in controlling the number of cancer cells in the blood even when no antigenicity due to cancer cells is present.

Case III:

Now, if we consider immune response due to natural stimulation only and no immunotherapy is done then model (2.1) becomes:

$$\begin{aligned} \frac{dx}{dt} &= A - a_0x - \beta xc_s, \\ \frac{dy}{dt} &= \beta xc_s - \beta_0y, \\ \frac{dc_s}{dt} &= k - k_0c_s - k_1c_sz, \\ \frac{dz}{dt} &= bc_s - b_0z - b_1zc_s. \end{aligned} \tag{6.12}$$

The model (6.12) also has only one equilibrium point that is obtained by equating to zero right hand side of the system (6.12). We have

$$c_s = \frac{k/k_0}{1 + k_1 z/k_0}. \tag{6.13}$$

using (6.13), white blood cell population \tilde{z} (say) is determined by the unique root of the equation,

$$k_1b_0z^2 + (k_0b_0 + kb_1)z - bk = 0. \tag{6.14}$$

It can be easily observed that (6.14) has a unique positive root by Descartes' rule of sign.

Equilibrium values of population of other cells in the blood system are given by

$$\tilde{x} = \frac{A(1 + k_1 \tilde{z}/k_0)}{a_0 + \beta k/k_0 + a_0k_1 \tilde{z}/k_0}, \tag{6.15}$$

$$\tilde{y} = \frac{\beta}{\beta_0} \left(\frac{A}{a_0 + \beta k/k_0 + a_0k_1 \tilde{z}/k_0} \right) \frac{k}{k_0}, \tag{6.16}$$

$$\tilde{c}_s = \frac{k/k_0}{1 + k_1 \tilde{z}/k_0}. \tag{6.17}$$

From (6.17), we observe that concentration of cancer cells case III is lesser than that in case I because of the presence of immune response in the blood by natural stimulation.

Equilibrium value of cancer cells in case II and III depend on the number of immune cells in either case. However, in practice equilibrium value of immune cells due activation by immunotherapy by external infusion of engineered T cells is more than that in case without immunotherapy thus, number of cancer cells in the blood can be controlled better by immunotherapy rather than by natural stimulation of immune cells.

In each case, we observe that susceptible or naive blood cells tend to extinction and each susceptible blood cell becomes infected if concentration of cancer cells or abnormal immature white blood cells increases to a large value (that is $k \rightarrow \infty$). However, in the presence of immune response equilibrium level of cancer cells can be controlled to a lower level.

7. Numerical Simulation

Here we justify our analytical findings numerically by choosing the following parameter values in the model (2.1):

$$\begin{aligned} A = 1.5, a_0 = 0.01, \beta = 0.00001, \beta_0 = 0.003, k = 10, k_0 = 5, \\ k_1 = 0.005, B = 2, b = 0.01, b_0 = 0.05, b_1 = 0.001. \end{aligned} \quad (7.1)$$

We observe that model (2.1) has a unique positive equilibrium for the above set of parameters. The numerical value of equilibrium point is:

$$x^* = 149.7118, \quad y^* = 0.9607, \quad c_s^* = 1.9251, \quad z^* = 38.8877$$

In addition, global stability condition of the system is also satisfied. To see the effect of various parameters on the dynamics of the system, we plot the graphs with the help of MATLAB software.

Figures 1 and 2 are drawn to show variation of cancer cells and infected cells with time for different growth rate of cancer cells in the body, k . It is observed that the number of cancer cells and infected cells increases with the increase in k . This is obvious, as due to increase in the recruitment rate of immature white blood cells in the blood, number of immature white blood cells in the blood will increase. Due to increase in number of immature white blood cells, rate of infection of susceptible blood cells due to overcrowding will also increase. This will increase the concentration of infected cells in the blood. Further, increase in cancer cells in the blood due to increase in its growth rate from bone marrow is obvious.

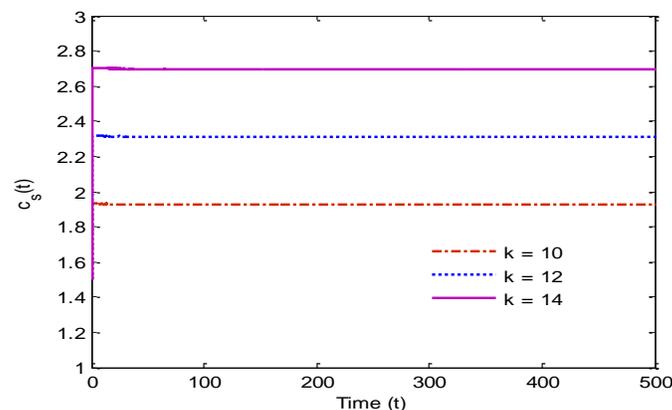


Figure 1. Variation of cancer cells with time for different growth rate of cancer cells in the body k

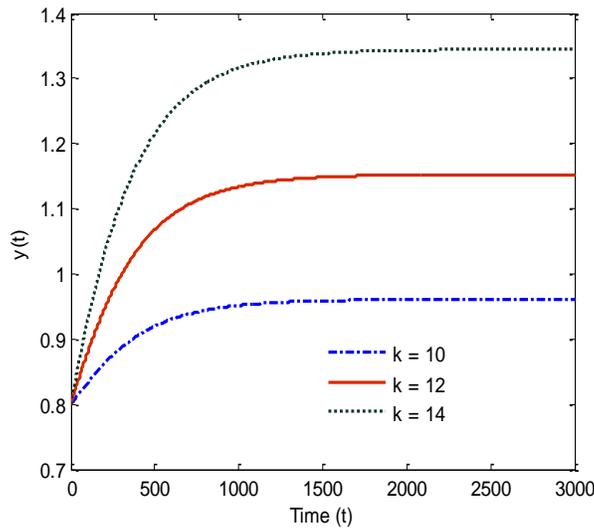


Figure 2. Variation of infected cells with time for different growth rate of cancer cells in the body k

Figure 3 shows the effect of decay rate coefficient of susceptible or naive blood cells due to interaction with the cancer cells on the infected cells with time, β . We note here that the number of infected cells increase with the increase in β . It implies that interaction of cancer cells with uninfected cells give rise to infected cells and as interaction rate increases, number of infected cells increase significantly.

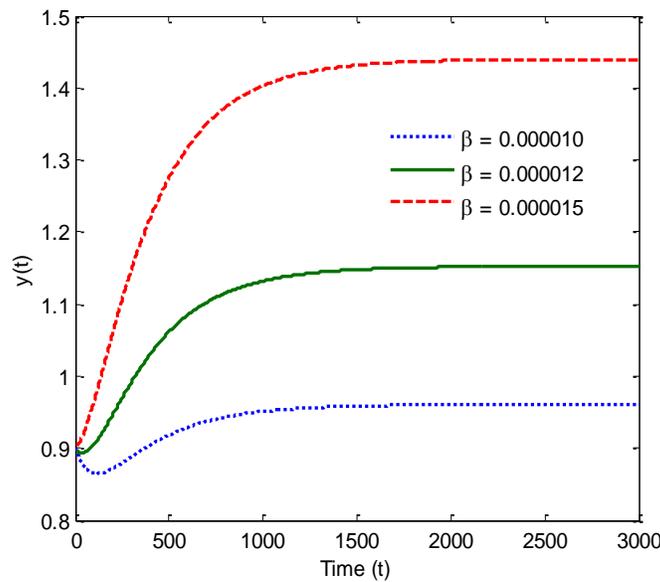


Figure 3. Variation of infected cells with time for different decay rate coefficient of susceptible or naive blood cells due to interaction with the cancer cells β

From the figure, we observe that first infected cell population rises and finally obtain a steady state. It implies that initially cancer cells or abnormal white blood cells divide out of control and crowd out the normal cells in the bloodstream. Resulting in an abrupt increase in number of infected blood cells that could not function properly. However, later with the time, infected cell lysis due to apoptosis takes place and infected cells reach a constant equilibrium level.

Figure 4 displays variation of cancer cell concentration with time for different rate of external re-infusion of T cells (immune cells) into the cancer patients, B . It is observed that when immunotherapy is not done, concentration of cancer cells in the blood is high. However, when immunotherapy is done it decrease. Further, if B is increased according to the need of the patient, concentration of cancer cells decreases. It may be due to an increase in cancer fighting capability of immune cells due to immunotherapy because of which cancer cells are destroyed and their concentration in the blood decreases.

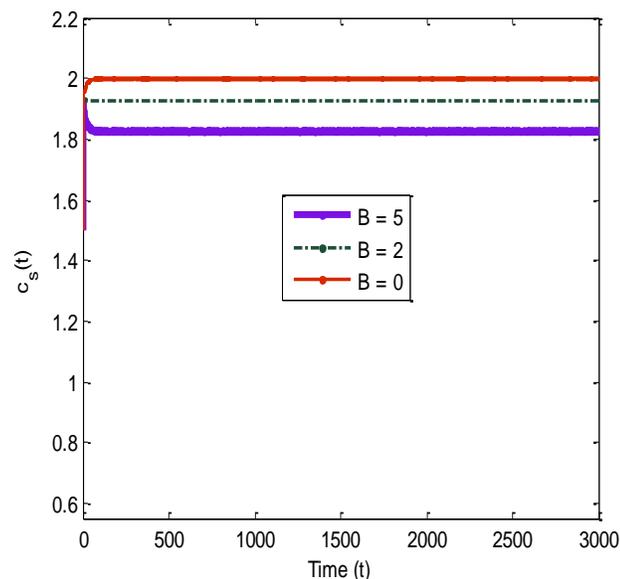


Figure 4. Variation of cancer cell concentration with time for different rate of external re-infusion of T cells (immune cells) into the cancer patients B

Figure 5 displays the effect of variation of B on infected or dysfunctional cells. It is observed that infected cells also decrease with the increase in B and equilibrium level of infected cells without therapy is more than the case when therapy is not done in the patients. In addition, since number of cancer cells in the blood decrease due to therapy, infected cells also decrease due to lesser overcrowding of susceptible cells by cancer cells.

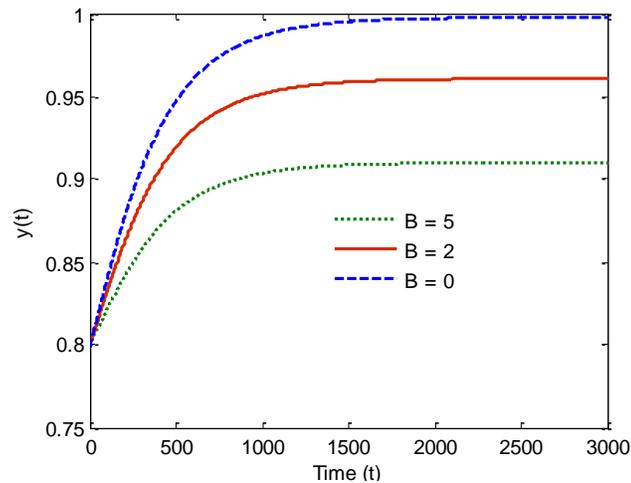


Figure 5. Variation of B on infected or dysfunctional cells with time

Figure 6 displays the variation of cancer cells with time for different antigenicity rate or stimulation rate of immune response due to abnormal cancer cells present in the blood, b . It is observed that the infected cells decrease with the increase in b . This is an indication of the fact that immune cells kill cancer cells on being stimulated and as antigenicity rate increases rate of destruction of cancer cells also increase leading to decrease in the concentration of cancer cells in the body. This is achieved in practice by Immunotherapy.

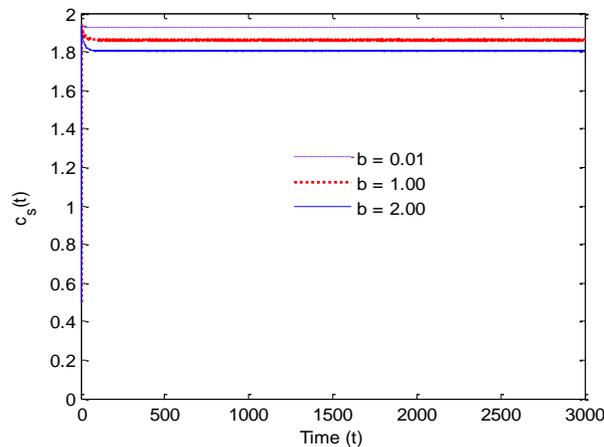


Figure 6. Variation of cancer cells with time for different antigenicity rate or stimulation rate of immune response due to abnormal cancer cells present in the blood b

Figure 7 is drawn to show variation of infected cells with time for different antigenicity rate or stimulation rate of immune response due to abnormal cancer cells present in the blood, b . It is found that infected cells also decrease with the increase in b . This indicates elimination of infected cells from the system by the immune response of the body. With the increase in stimulation rate, number of cancer cells are reduced due to which lesser number of susceptible cells are killed by them and hence concentration of infected cells in the blood also decreases. Thus, immune response reduces the concentration of cancer cells and infected cells in the body.

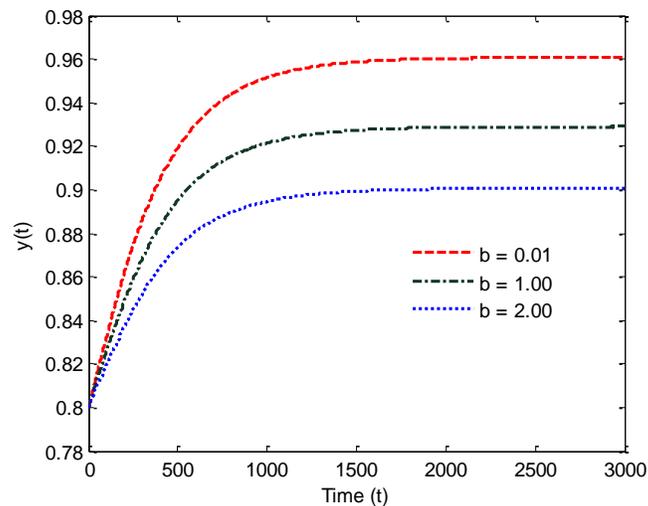


Figure 7. Variation of infected cells with time for different antigenicity rate or stimulation rate of immune response due to abnormal cancer cells present in the blood b

8. Conclusion

In this paper, a nonlinear model is proposed and analyzed to study the spread of Leukemia by considering the effect of genetically engineered patients T cells to attack cancer cells. The model is governed by four dependent variables namely; naive or susceptible blood cells, infected or dysfunctional blood cells, cancer cells and immune cells. The model is analyzed by using the stability theory of differential equations and numerical simulation.

Analytically, we have determined that the system is stable in the local and global sense if antigenicity rate of stimulation of white blood cells is greater than a threshold value dependent on the density of immune cells. Further, it is observed that number of cancer cells in the blood can be controlled by external infusion of genetically engineered patients T cells.

Numerical simulation of the model demonstrates some important results given below: It is observed that the number of cancer cells and infected cells increases with the increase in growth rate of cancer cells. It is observed that the number of infected cells increase with the increase in β . It implies that interaction of cancer cells with uninfected cells give rise to more infected cells and as interaction rate increases, number of infected cells increase significantly.

In addition, we studied the effect of external intravenous infusion of T cells (immune cells) on the spread of leukemia numerically and found that the number of cancer cells in the blood decrease due to it. Further, infected cells also decrease due to lesser overcrowding of susceptible cells by cancer cells.

It is observed that the infected cells decrease with the increase in antigenicity rate or stimulation rate of immune response due to abnormal cancer cells present in the blood. This indicates that immune cells kill cancer cells on being stimulated and as antigenicity rate increases rate of destruction of cancer cells also increase leading to decrease in the concentration of cancer cells in the body. Decrease in cancer cells further causes decrease in the concentration of infected or dysfunctional cells in the body.

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APPENDICES

Appendix A

Proof of Theorem 4.1:

Using the transformation

$$x = x^* + X, \quad y = y^* + Y, \quad c_s = c_s^* + C_s, \quad z = z^* + Z$$

we transform the model (2.1) into an equivalent system given below having the origin as equilibrium.

$$\begin{aligned} \frac{dX}{dt} &= -a_0X - \beta x^* C_s - \beta X c_s^*, \\ \frac{dY}{dt} &= \beta x^* C_s + \beta X c_s^* - \beta_0 Y, \\ \frac{dC_s}{dt} &= -k_0 C_s - k_1 c_s^* Z - k_1 C_s z^*, \\ \frac{dZ}{dt} &= b C_s - b_0 Z - b_1 z^* C_s - b_1 Z c_s^*. \end{aligned} \quad (\text{A.1})$$

We consider following positive definite function:

$$W = \frac{1}{2} X^2 + c_1 \frac{1}{2} Y^2 + c_2 \frac{1}{2} C_s^2 + c_3 \frac{1}{2} Z^2,$$

where, c_1, c_2, c_3 are positive constants to be chosen later suitably.

Differentiating W with respect to t along the solution of model (2.1), we get

$$\begin{aligned} \dot{W} &= -X^2 \{a_0 + \beta c_s^*\} - Y^2 \{c_1 \beta_0\} - C_s^2 \{c_2 (k_0 + k_1 z^*)\} - Z^2 \{c_3 (b_0 + b_1 c_s^*)\} \\ &\quad + C_s X \{-\beta x^*\} + C_s Z \{-c_2 k_1 c_s^* + c_3 (b - b_1 z^*)\} \\ &\quad + C_s Y \{c_1 \beta x^*\} + XY \{c_1 \beta c_s^*\}. \end{aligned} \quad (\text{A.2})$$

$$\begin{aligned} \dot{W} &\leq -\frac{1}{2} a_{11} X^2 + a_{12} X C_s - \frac{1}{2} a_{22} C_s^2 \\ &\quad - \frac{1}{2} a_{11} X^2 + a_{13} XY - \frac{1}{2} a_{33} Y^2 \\ &\quad - \frac{1}{2} a_{22} C_s^2 + a_{23} C_s Y - \frac{1}{2} a_{33} Y^2 \\ &\quad - \frac{1}{2} a_{22} C_s^2 + a_{24} C_s Z - \frac{1}{2} a_{44} Z^2, \end{aligned} \quad (\text{A.3})$$

Where

$$\begin{aligned}
 a_{11} &= \beta c_s^*, & a_{22} &= \frac{2}{3} c_2 k_1 z^*, & a_{33} &= c_1 \beta_0, & a_{44} &= 2c_3 b_1 c_s^*, \\
 a_{12} &= -\beta x^*, & a_{13} &= c_1 \beta c_s^*, & a_{23} &= c_1 \beta x^*, & a_{24} &= -c_2 h_1 c_s^* + c_3 (b - b_1 z^*).
 \end{aligned}
 \tag{A.4}$$

Sufficient condition for \dot{W} to be negative definite are that following inequalities hold:

$$a_{12}^2 < a_{11} a_{22} \tag{A.5}$$

$$a_{13}^2 < a_{11} a_{33} \tag{A.6}$$

$$a_{23}^2 < a_{22} a_{33} \tag{A.7}$$

$$a_{24}^2 < a_{22} a_{44} \tag{A.8}$$

If we choose

$$c_1 = \frac{\beta_0}{2\beta c_s^*}, \quad c_2 = \frac{2\beta x^{*2}}{k_1 c_s^* z^*}, \quad \text{and} \quad c_3 = \frac{c_2 k_1 c_s^*}{b - b_1 z^*}, \quad b > b_1 z^*,$$

then it can be checked that (A.6), (A.5) and (A.8) are automatically satisfied. Using c_1 and c_2 in (A.7) we can see easily that it also holds.

Appendix B

Proof of Theorem 5.1:

We consider following positive definite function around the endemic equilibrium point E^*

$$W_1 = \frac{1}{2}(x - x^*)^2 + d_1 \frac{1}{2}(y - y^*)^2 + d_2 \frac{1}{2}(c_s - c_s^*)^2 + d_3 \frac{1}{2}(z - z^*)^2 \tag{B.1}$$

where d_1, d_2, d_3 are positive constants to be chosen suitably.

Differentiating W_1 with respect to t along the solution of model (2.1), we get

$$\begin{aligned}
 \dot{W}_1 &= -(x - x^*)^2 \left\{ a_0 + \beta c_s^* \right\} - (y - y^*)^2 \left\{ d_1 \beta_0 \right\} - (c_s - c_s^*)^2 \left\{ d_2 (k_0 + k_1 z^*) \right\} \\
 &\quad - (z - z^*)^2 \left\{ d_3 (b_0 + b_1 c_s^*) \right\} + (x - x^*) (c_s - c_s^*) \left\{ -\beta x \right\} \\
 &\quad + (y - y^*) (c_s - c_s^*) \left\{ d_1 \beta x \right\} + (x - x^*) (y - y^*) \left\{ d_1 \beta c_s^* \right\}
 \end{aligned}$$

$$\begin{aligned}
& + (c_s - c_s^*)(z - z^*) \{-d_2 k_1 c_s^* + d_3 b\} \\
& + (c_s - c_s^*)(z - z^*) \{-d_3 b_1 z\}.
\end{aligned} \tag{B.2}$$

$$\begin{aligned}
\dot{W}_1 \leq & -\frac{1}{2} b_{11} (x - x^*)^2 + b_{12} (x - x^*) (c_s - c_s^*) - \frac{1}{2} b_{22} (c_s - c_s^*)^2 \\
& - \frac{1}{2} b_{11} (x - x^*)^2 + b_{13} (x - x^*) (y - y^*) - \frac{1}{2} b_{33} (y - y^*)^2 \\
& - \frac{1}{2} b_{22} (c_s - c_s^*)^2 + b_{23} (c_s - c_s^*) (y - y^*) - \frac{1}{2} b_{33} (y - y^*)^2 \\
& - \frac{1}{2} b_{22} (c_s - c_s^*)^2 + b_{24} (c_s - c_s^*) (z - z^*) - \frac{1}{2} b_{44} (z - z^*)^2 \\
& - \frac{1}{2} b_{22} (c_s - c_s^*)^2 + b_{25} (c_s - c_s^*) (z - z^*) - \frac{1}{2} b_{44} (z - z^*)^2,
\end{aligned} \tag{B.3}$$

where,

$$\begin{aligned}
b_{11} &= \beta c_s^*, \quad b_{22} = \frac{1}{2} d_2 k_0, \quad b_{33} = d_1 \beta_0, \quad b_{44} = d_3 b_1 c_s^*, \quad b_{12} = -\beta x, \\
b_{13} &= d_1 \beta c_s^*, \quad b_{23} = d_1 \beta x, \quad b_{24} = -d_2 k_1 c_s^* + d_3 b, \quad b_{25} = -d_3 b_1 z.
\end{aligned} \tag{B.4}$$

Sufficient condition for \dot{W} to be negative definite are that following inequalities hold:

$$b_{12}^2 < b_{11} b_{22} \tag{B.5}$$

$$b_{13}^2 < b_{11} b_{33} \tag{B.6}$$

$$b_{23}^2 < b_{22} b_{33} \tag{B.7}$$

$$b_{24}^2 < b_{22} b_{44} \tag{B.8}$$

$$b_{25}^2 < b_{22} b_{44} \tag{B.9}$$

If we choose

$$d_1 = \frac{\beta_0}{2\beta c_s^*}, \quad d_2 = \frac{3\beta A^2}{k_0 c_s^* a_0^2} \quad \text{and} \quad d_3 = \frac{d_2 k_1 c_s^*}{b},$$

then it can be checked that (B.6), (B.5) and (B.8) hold respectively. Further, using values of d_1 and d_2 we find that (B.7) also holds provided that $2k_1 b_1 z_{\max}^2 < k_0 b$.