Advances in Engineering Research, volume 209
International Joint Conference on Science and Engineering 2021 (IJCSE 2021)

The Effect of Immunotherapy Treatment on Leukaemia Growth Dynamic Model

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ABSTRACT

Cancer is one of the leading causes of death globally, claiming ten million lives in 2020. Leukaemia, also known as blood cancer, is a condition in which the growth of white blood cells occurs uncontrollably. This study aims to simulate the mathematical model for the dynamics of leukaemia growth. The simulation shows that when immunotherapy is not present ($B = 0$), the number of infected and cancer cells is massive. As immunotherapy is applied and present ($B > 0$), the concentration of immune cells surges in the blood therefore the number of infected cells and cancer cells declines because the external re-infusion rate of immune cells increases in the blood, and the number of infected cells decreases due to the interaction between cancer cells and immune cells.

Keywords: *Immunotherapy treatment, Dynamics of leukaemia growth, Mathematical model.*

1. INTRODUCTION

Cancer is one of the leading causes of death globally, claiming ten million lives in 2020. On different sex, cancer could be found in certain part of the body, for instance in men, Lung, prostate, colorectal, stomach cancers are the most common, while in women, colorectal, lung, cervical and thyroid cancers are the most common [1]. Leukaemia is a type of cancer caused by the uncontrolled development of leukocytes in the body. In 2019, the percentage of deaths from leukaemia in Indonesia was 5.5% or around 14,862 people, and the mortality rate increased every year [2].

Leukaemia is a mysterious disease because blood transfused from a leukaemia patient to a healthy person will not cause the person to become infected. This case is due to the robust immune system of a healthy person. Leukaemia has two phases: acute and chronic phases [3]. Acute leukaemia usually affects children, where immature lymphoid cells proliferate in the blood, while in chronic leukaemia, lymphoid cells grow slowly and usually in adults over fifty-five years. In addition, the three types of blood cells, which are white blood cells--specifically the T cells, red blood cells, and platelets, progressively die due to specific abnormalities in the blood in which cells proliferate, and these anomalous cells control healthy blood cells in the bone marrow [4,5]. Mathematical model on non-communicable diseases has fascinated researchers over the years. A different model of mathematical models on cancer immunotherapy has been studied by Mamat et al. [3], Nani & Freedman [6], and Nowak & May [7]. Previous studies in a mathematical model on leukaemia have been studied by Afenya & Bentil. [8], Clapp & Levy [9], Agarwal & Bhadauria [10], Stiehl et. al [11]. and Khartun & Biswas [12].

This research was inspired by the research conducted by Khartun & Biswas entitled Modelling the Effect of Adoptive T-cell Therapy for the Treatment of Leukaemia [12]. Khartun and Biswas describe the interaction between susceptible cells, infected cells, cancer cells, and immune cells to immunotherapy with the mathematical model used to develop a modified model from Agarwal and Bhadauria [10]. Their work is based on the characteristics of the spread of leukaemia in the blood and used to respond to the human immune system to leukaemia with immunotherapy. We are interested in reconstructing the dynamic model and conducting experiments on the parameter values used.

2. METHODS

This research is an experimental study using software to discuss the dynamic system of the effect of

Immunotherapy on the treatment of Leukaemia which refers to the article Modelling the Effect of Adoptive T-cell Therapy for the Treatment of Leukaemia using a SIR model reconstruction approach, stability analysis, numerical simulation, sensitivity analysis. Parameters on response to quantitative numerical solutions and chemotherapy control.

The research will be done in three phases; the first is the preparatory phase which is literature study, formulating assumptions and problem boundaries. The second phase is the modelling and simulation phase which started by determining the equilibrium point and carrying out a stability analysis, determining the basic reproduction number, conducting a sensitivity analysis, followed by a simulation of the leukaemia model with the influence of chemotherapy. The data for simulation is estimated and taken from Moore & Li [13] and some expected values.

3. MODEL RECONSTRUCTION

In this section, the results and discussion of the reconstruction of the dynamic model of leukaemia with immunotherapy and chemotherapy treatment and the simulation results are presented. These are the assumptions used in reconstructing the dynamic model: In this section, the results and discussion of the reconstruction of the dynamic model of leukaemia with immunotherapy and chemotherapy treatment and the simulation results are presented. These are the assumptions used in reconstructing the dynamic model:

3.1. Cell populations at the body

There are four cells' types inside the human body: susceptible cells, infected cells, cancer cells, and immune cells.

- Susceptible cells are the cells that can be infected, denoted by S.
- Infected cells are the cells that are infected and can spread the leukaemia; the population is denoted by I.
- Cancer/leukemic cells are the infected white blood cells and the population is denoted by C.
- Immune cells are the infected cells or the recovered cancerous cells, its population denoted by W.

3.2. Susceptible cells growth

The population of susceptible blood cells comes from A that is cells that enters the blood vessel from bone marrow, lymph nodes, and thymus. The natural death rate of susceptible cells is given bya_0. Susceptible cells S are differentiated into C cells with a growth rate of β, where β is the infection rate of susceptible cells due to cancer cells C. The growth rate of susceptible cells is mathematically expressed by $A - a_0 S - \beta SC$ with the number of susceptible cells not exceeding $Aa_0{}^{-1}$. The term $a_0 S$ is the number of natural death susceptible cells and βSC is the number of susceptible cells differentiate into cancer cells.

3.3. Infected cells growth

The growth of infected cells comes from the number of susceptible cells infected due to cancer cell βSC. Every time a susceptible cell divides, it will increase the population of infected cells. The natural death rate of infected cells is denoted by β_0 and the rate of loss of infected cells due to cancer cells is denoted by β_1. The growth rate of infected cells is mathematically written $\beta SC - \beta_0 I - \beta_1 CI$ with the number of susceptible cells and infected cells more than 0 and the number is less than $A\eta^{-1}$ or maximum $A\eta^{-1}$, where $\eta = (a_0, \beta_0)$. The term $\beta_0 I$ is the number of infected cells that die naturally, while $\beta_1 CI$ is the number of infected cells that die because of the cancer cells.

3.4. Cancer cell growth

The growth of cancer cells comes from white blood cells infected by cancer, the rate of recruitment of cancer cells is expressed by k, while the natural death rate of cancer cells is expressed by k_0, and the rate of loss of cancer cells due to interactions with immune cells is expressed by k_1. The growth rate of cancer cells is mathematically written $k - k_0 C - k_1 CW$ with the maximum number of cancer cell populations at time (t) is $kk_0{}^{-1}$. The term $k_0 C$ is the number of cancer cells that die naturally, while $k_1 CW$ is the number of cancer cells that die because of interacting with immune cells.

3.5. Immune cell growth

The growth of immune cells depends on the number of reinfused white blood cells where white blood cells function to help the body fight infection. The term B represents the rate of external infusion T cells or white blood cells into the body of a leukaemia patient. When cancer cells grow, immune cells will multiply at a constant rate or the rate of proliferation of immune cells is expressed by b, while the rate of decay of immune cells due to the presence of leukaemia cells or cancer cells in the blood is expressed by b_1 and natural death of immune cells is expressed by b_0. The growth rate of immune cells is mathematically written as $B + bC - b_0 W - b_1 WC$ with the cells population at maximum time t is $\left(B + bkk_0{}^{-1}\right)k_0{}^{-1}$. The term bC is the number of immune cells that develop due to the appearance of cancer cells in the body, the term $b_0 W$ is the number of immune cells that die naturally, while $b_1 WC$ represents the number of immune cells that have decayed due to the presence of leukaemia cells or cancer cells.

3.6. Leukaemia dynamic models

Interactions with immune cells cause cancer cell death. So that when immunotherapy is applied, the number of immune cells (white blood cells) in the body increases and the number of cancer cells decreases.

At any given time t, the total cells population at the body is denoted by $N = S + I + C + W$ as the diagram below

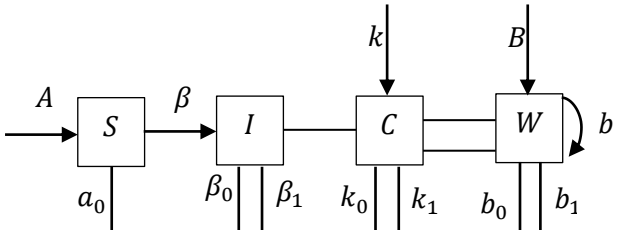

Figure 1. Transmission diagram of leukaemia

Based on the above assumptions, the dynamic system of leukaemia growth with immunotherapy is stated as follows:

$$\frac{dS}{dt} = A - a_0 S - \beta SC \quad (1)$$

$$\frac{dI}{dt} = \beta SC - \beta_0 I - \beta_1 CI \quad (2)$$

$$\frac{dC}{dt} = k - k_0 C - k_1 CW \quad (3)$$

$$\frac{dW}{dt} = B + bC - b_0 W - b_1 WC \quad (4)$$

Lemma 1. Solution of the system of equations (1) to (4) are bounded within a region Ω, where

$$\Omega = \{(S,I,C,W): 0 < S(t) \leq Aa_0^{-1}, 0 < S(t) + I(t) \leq A\eta^{-1}, 0 < C(t) \leq kk_0^{-1} \text{ and } 0 < W(t) \left(B + bkk_0^{-1}\right)b_0^{-1}\}$$

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

3.7. Parameter specification

The parameter used in this paper are in Table 1 below. These parameters and values are taken from the work of Khatun & Biswas [12], Agarwal & Bhaduria [10], Moore & Li [13], and some expected values.

Table 1. Parameter specification used in the model

Description	Parameter	Values	Units
Source for susceptible blood cells	A	1.6	Cells $\mu l^{-1} day^{-1}$
Susceptible blood cells' death rate	a_0	10^{-2}	day^{-1}
Susceptible blood cells' infection rate	β	10^{-5}	$\mu l\ Cells^{-1} day^{-1}$
Infected cells' death rate	β_0	3×10^{-3}	day^{-1}
Infected cells' decay rate	β_1	5×10^{-3}	$\mu l\ Cells^{-1} day^{-1}$
Cancer cells' recruitment rate	k	10	day^{-1}
Cancer cells' natural death rate	k_0	5	day^{-1}
Cancer cells' loss rate	k_1	5×10^{-3}	$\mu l\ Cells^{-1} day^{-1}$
Immune cells' external reinfusion	B	15	day^{-1}
Immune cells' proliferation rate	b	10^{-2}	day^{-1}
Immune cells' death rate	b_0	5×10^{-2}	day^{-1}
Immune cells' loss rate	b_1	10^{-3}	$\mu l\ Cells^{-1} day^{-1}$

4. Model Analysis

In this section, we investigate the existence of the solution, the equilibria, basic reproduction number and check the stability of the model at disease-free and endemic equilibrium points.

4.1 Existence of the solution

We will have the solution for the model if all the equations are positives. If $S(t) > 0, I(t) \geq 0, C(t) \geq 0$ and $W(t) \geq 0$ then the solutions for those equations are positives. The proof of this existence can be found in [12].

4.2 Disease-free equilibrium

The disease-free point is a condition where there is no spread of cancer cells in the blood, which means that there are no infected cells in the body. The disease-free point is denoted by $\zeta^0 = (S^0, I^0, C^0, W^0)$.

The disease-free equilibrium points of the dynamic model of the dynamic system (1) to (4) is obtained by making the right-hand side of the system of equations zero. Because there is no spread of cancer cells $I = C = W = 0$), then the disease-free equilibrium point is $\zeta^0 = (177{,}5; 0; 0; 0)$.

4.3 Endemic equilibrium

Endemic equilibrium occurs when there is growth of cancer cells in the body is called an endemic condition. The endemic equilibrium point is obtained by making zeros on the right-hand side of the dynamic system (1) to (4) and denoted by $\zeta^* = (S^*, I^*, C^*, W^*)$ that is:

$$S^* = \frac{A\left(1 + \frac{k_1 W^*}{k_0}\right)}{a_0 + \frac{a_0 k_1 W^*}{k_0} - \frac{\beta k}{k_0}}$$

$$I^* = \left(\frac{\beta}{\left(\beta_0 + \frac{\frac{\beta_1 k}{k_0}}{1 + \frac{k_1 W^*}{k_0}}\right)}\right)\left(\frac{A\left(\frac{k}{k_0}\right)}{a_0 + a_0\left(\frac{k_1 W}{k_0}\right) - \beta\left(\frac{k}{k_0}\right)}\right)$$

$$C^* = \frac{k/k_0}{1 + \frac{k_1 W^*}{k_0}}$$

$$W^* = \frac{-(k_0 b_0 + k b_1 - B k_1) + \sqrt{(k_0 b_0 + k b_1 - B k_1)^2}}{2 b_0 k_1}$$

$$\frac{\sqrt{+4 b_0 k_1 (kb + B k_0)}}{2 b_0 k_1}$$

By substituting the parameter from Table 1, the endemic equilibrium is $R^* = (176.1, 1.3, 1.5, 291.2)$.

4.4 Basic Reproduction Number

The basic reproduction ratio of leukaemia model spread is $\gamma_0 = \frac{A\beta}{a_0(\beta_0 + \beta_1)}$. Since $\gamma_0 > 1$, It means the cancer will spread.

4.5 Stability Analysis

We would like to investigate the stability analysis on two points: disease-free equilibrium and endemic equilibrium.

4.5.1. Disease-free equilibrium

Theorem 1. The disease-free equilibrium of equations (1) to (4) is asymptotically stable if the eigenvalue of the Jacobian matrix is negative.

Proof. Consider

$$\begin{cases} f_1 = \frac{dS}{dt} \\ f_2 = \frac{dI}{dt} \\ f_3 = \frac{dC}{dt} \\ f_4 = \frac{dW}{dt} \end{cases}$$

where

$$f_1 = A - a_0 S - \beta S C \quad (5)$$

$$f_2 = \beta S C - \beta_0 I - \beta_1 C I \quad (6)$$

$$f_3 = k - k_0 C - k_1 C W \quad (7)$$

$$f_4 = B + bC - b_0 W - b_1 W C \quad (8)$$

The Jacobian matrix of those equations is

$$\mathrm{J} = \begin{bmatrix} \frac{\partial f_1}{\partial S} & \frac{\partial f_1}{\partial I} & \frac{\partial f_1}{\partial C} & \frac{\partial f_1}{\partial W} \\ \frac{\partial f_2}{\partial S} & \frac{\partial f_2}{\partial I} & \frac{\partial f_2}{\partial C} & \frac{\partial f_2}{\partial W} \\ \frac{\partial f_3}{\partial S} & \frac{\partial f_3}{\partial I} & \frac{\partial f_3}{\partial C} & \frac{\partial f_3}{\partial W} \\ \frac{\partial f_4}{\partial S} & \frac{\partial f_4}{\partial I} & \frac{\partial f_4}{\partial C} & \frac{\partial f_4}{\partial W} \end{bmatrix}$$

$$= \begin{bmatrix} -a_0 - \beta C & 0 & -\beta S & 0 \\ \beta C & -\beta_0 - \beta_1 C & \beta S - \beta_1 I & 0 \\ 0 & 0 & -k_0 - k_1 W & -k_1 C \\ 0 & 0 & b - b_1 W & -b_0 - b_1 C \end{bmatrix}$$

By substituting the disease-free equilibrium $\zeta^0 = (A a_0^{-1}, 0, 0, 0)$, we can obtain:

$$J = \begin{bmatrix} -a_0 & 0 & -\frac{\beta A}{a_0} & 0 \\ 0 & -\beta_0 & \frac{\beta A}{a_0} & 0 \\ 0 & 0 & -k_0 & 0 \\ 0 & 0 & b & -b_0 \end{bmatrix}$$

The eigenvalues of Jacobian matrix J are $\lambda_1 = -a_0$, $\lambda_2 = -\beta_0$, $\lambda_3 = -k_0$, $dan\ \lambda_4 = -b_0$. By substituting the parameters from Table 1 into the eigenvalues, we understand that the eigenvalues are all real numbers. Since λ_1, λ_2, λ_3, and λ_4 are negative, therefore the disease-free equilibrium is asymptotically stable.

4.5.2 Endemic equilibrium

Analogous with the disease-free equilibrium, we investigate the stability for the endemic equilibrium.

Lemma 2. The endemic equilibrium of equations (1) to (4) is asymptotically stable if the eigenvalue of the Jacobian matrix is negative.

Proof. We obtain the Jacobian matrix

$$\zeta^* = \begin{bmatrix} -a_0 - \beta C^* & 0 & -\beta S^* & 0 \\ \beta C^* & -\beta_0 - \beta_1 C^* & \beta S^* - \beta_1 I & 0 \\ 0 & 0 & -k_0 - k_1 W^* & -k_1 C^* \\ 0 & 0 & b - b_0 W^* & -b_0 - b_1 C^* \end{bmatrix}$$

Where

$$S^* = \frac{A\left(1+\frac{k_1 W*}{k_0}\right)}{a_0 + \frac{a_0 k_1 W*}{k_0} + \frac{\beta k}{k_0}},$$

$$I^* = \frac{\beta}{\beta_0 + \frac{\frac{\beta_1 k}{k_0}}{1+\frac{k_1 W*}{k_0}}}\left(\frac{A}{a_0 + \frac{a_0 k_1 W*}{k_0} + \frac{\beta k}{k_0}}\right)\frac{k}{k_0},$$

$$C^* = \frac{\frac{k}{k_0}}{1+\frac{k_1 W*}{k_0}},$$

$$W^* = \frac{-(k_0 b_0 + k b_1 - B k_1)}{2 b_0 k_1} + \frac{\sqrt{(k_0 b_0 + k b_1 - B k_1)^2 + 4 b_0 k_1 (k b + B k_0)}}{2 b_0 k_1}.$$

By substituting the parameters from Table 1, the eigenvalues of Jacobian matrix J are $\lambda_1 = -0{,}010077$, $\lambda_2 = -0{,}01074$, $\lambda_3 = -0{,}051209$, $dan\ \lambda_4 = -6{,}456771$. Since λ_1, λ_2, λ_3, and λ_4 are real negative, therefore the endemic equilibrium is asymptotically stable.

4.6. Sensitivity analysis

Sensitivity analysis is performed to investigate some parameters' impact on the basic reproduction number, γ_0 and later impact of such parameters on the leukaemia growth model on equation (1) to (4). To perform, we compute the normalized forward sensitivity index of γ_0 and these indices measure the relative change in a γ_0 for the relative change in its parameters (Table 1).

Definition 3. The normalized forward sensitivity index of a function, $F(x_1, x_2, \cdots, x_n)$, for $x_i (1 \le i \le n)$, is defined as:

$$\Gamma_{x_i}^F = \frac{\partial F}{\partial x_i} \times \frac{x_i}{F}$$

To obtain the sensitivity of γ_0, we take the parameters A, β, a_0, β_0, and β_1 as γ_0 is the functions of these parameters. We obtain:

Table 2. Sensitivity index of γ_0 against the parameter

Parameters	A	β	a_0	β_0	β_1
Sensitivity index	1	1	-1	-0.375	-0.625

From Table 2, the sensitivity index shows that parameters A, β are positive. It means that an increment of 10% in one of the parameters, either A or β will cause γ_0 increased by 10%, while an increment of 10% in β_0 will cause γ_0 decreased by 3.75%. We can see that the most sensitive parameters which has positive impact on γ_0 are the source for susceptible blood cells (A) and Infection rate of susceptible blood cells due to cancer cells (β).

5. NUMERICAL SIMULATION

We simulate the SICW model by using python. The initial values used in simulation are $S(0) = 149.7118, I(0) = 1.182, C(0) = 1.5971, W(0) = 252.26$ taken from [12] and [10]. The parameters are used in Table 1. Simulation is done within the final time of 730 days (two years of therapy).

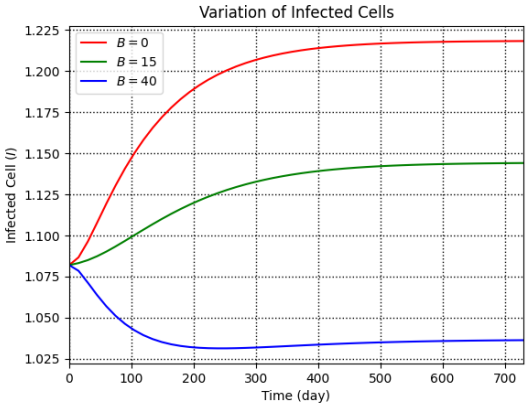

Figure 2 Variation of infected cells within two years of treatment for different external re-infusion (B).

First, we investigate the variation of infected cells by setting up different values for the external reinfusion rate of immune cells, $B = 0$, $B = 15$, and $B = 40$. By letting all values of the test parameters as in Table 1, we obtain the result presented in figure 2. We observe that when the immunotherapy is not present, the number of infected blood cells tends to increase as the B grows over time. The lower the B, the slower the number of infected cells stabilise. When we set the reinfusion rate to 40, the infected cells decrease over time.

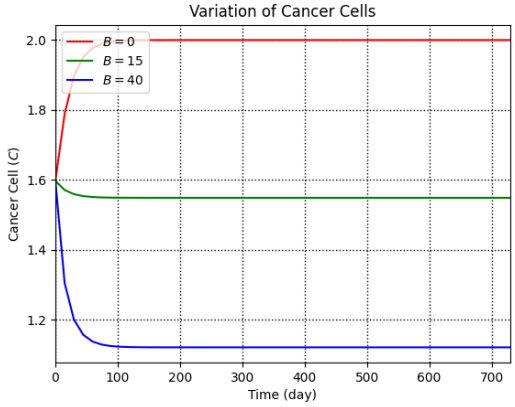

Figure 3 Variation of cancer cells within two years of treatment for different external re-infusion (B).

Next, we set up different values for external re-infusion, $B = 0$, $B = 15$, and $B = 23$ as presented in figure 3. We can see that without any re-infusion or any immunotherapy applied, the number of cancer cells is more significant than the immunotherapy applied. Over the same period, the higher external re-infusion made the cancer cells lower than the lower external re-infusion.

6. CONCLUSION

The numerical simulation results show that the growth of leukaemia cells varies on the rate of infected cells and immune cells. When immunotherapy is not present in cells, $B = 0$, the amount of infected cells and cancer cells are in their potent. Nonetheless, when immunotherapy is present, the quantity of infected cells and cancer cells decline in the bloodstream, and the quantity of immune cells is low. When immunotherapy is present, the quantity of immune cells rises in the bloodstream so that the number of infected cells and cancer cells decrease because the external re-infusion rate of immune cells growth in the bloodstream, and the quantity of infected cells decreases due to the interaction between cancer cells and immune cells.

AUTHORS' CONTRIBUTIONS

Dimas: concept, method and drafting manuscript. Yusuf Fuad & Ayunin Sofro: Review and editing of manuscript; and Hery TS Evitia: data curation, data visualization and editing.

ACKNOWLEDGMENTS

The authors want to thank Institute of Research and Community Service Universitas Negeri Surabaya for the research grant no. B/35396/UN38.3/LT.02/2021.

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