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MATHEMATICAL MODEL OF LEUKEMIA WITH CHIMERIC ANTIGEN RECEPTOR (CAR) T CELL THERAPY

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ABSTRACT

Leukemia, a type of blood cancer that originates in the bone marrow, is characterized by the uncontrolled growth of abnormal blood cells, which disrupt the normal functioning of blood cells. Chimeric antigen receptor (CAR) T-cell treatment, a form of immunotherapy, utilizes genetically modified T cells to specifically target and eliminate cancer cells. This treatment has shown promising results for leukemia patients who are unresponsive to chemotherapy or other therapies, as well as those who experience relapses. In this study, we develop a mathematical model of leukemia that incorporates chimeric antigen receptor (CAR) T-cell therapy. The model takes into account the logistic intrinsic growth rate of leukemia cells, which gradually declines over time due to limited resources within the body. There are four compartments in this model: susceptible blood cells, infected blood cells, leukemia cells, and immune cells. We have analyzed the equilibrium points and their local stability, determined the basic reproduction number, and conducted a sensitivity analysis. Through numerical simulations, we observed that prior to treatment, the number of leukemia cells in the blood escalated rapidly towards endemic conditions. However, after receiving CAR T-cell therapy through external infusion, the leukemia cells either became extinct or took a significant amount of time to reach endemic levels in the blood. Sensitivity analysis revealed that the growth rate of cancer cells (r) and the death rate of immune cells (τ) significantly contribute to the increase in the basic reproduction number (R_0).
Keywords: Mathematical Model, Leukemia Treatment, Chimeric Antigen Receptor, CAR T Cells

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PRELIMINARY

Leukemia, also known as blood cancer, is a type of cancer that develops in the bone marrow, identified by an increase in the number of leukocytes in the blood (Y. Dong et al., 2020)(NCI, 2022). According to the Global Cancer Observatory, the number of new cases of leukemia in the world reach 474.519 in 2020, with around 311.594 deaths reported. In the same year, there were approximately 14,979 new cases in Indonesia with 11,530 of death. According to existing data, Leukemia become the sixth highest death rate after

lung cancer, breast cancer, cervical cancer, liver cancer, and nasopharyngeal cancer (Globacan, 2020).

The immune system in the body basically recognizes and eliminates foreign substances that enter the body. The immune system plays a vital role in combating cancer cells by recognizing and eliminating them. However, there are several reasons why the immune system often fails to respond effectively to cancer cells in the body, (1) cancer cells originate from cells in the body, making it challenging for the immune system to identify them as foreign entities and mount a response, (2) the immune system may be insufficient in strength to effectively combat the proliferation of cancer cells, (3) the ability of cancer cells to defend themselves. Therefore, external stimuli is required to enhance the effectiveness of in fighting against cancer cells (Sharma & Samanta, 2016),(Abbott & Ustoyev, 2019). Immunotherapy is a cancer treatment that works by assisting the immune system in detecting, slowing growth, preventing metastases, and destroying cancer cells. CAR T cell therapy is a breakthrough and new opportunity for leukemia patients who have not responded to chemotherapy or other treatments or who have relapsed. This therapy works by manipulating the immune system, in which T cells are genetically engineered and developed in the laboratory to be able to express specific immune receptors (CARs) allowing them to attack and kill leukemia cells (H. Dong & Markovic, 2018), (Raskov et al., 2021).

Mathematical models (Ndii, 2018) regarding the dynamics of leukemia transmission with treatment mechanisms have been studied by several researchers. (Eftimie et al., 2011) give a brief review and analyse Interactions between immune system and cancer. (Agarwal & Bhadauria, 2015) studied a treatment model cancer with immunotherapy, (Sharma & Samanta, 2016) studied dynamic analysis of the tumor and immune system with chemotherapy and immunotherapy. (Moore & Li, 2004), (Dimitriu, 2019), (Valle et al., 2021), and (Karg et al., 2022), proposed and analyzed the dynamical model of chronic myelogenous leukemia. In addition, (Guzev et al., 2022),(Rodrigues et al., 2019), and (Fadaei et al., 2021) formulate and analyse a mathematical model of chronic lymphocytic leukemia with a treatment such as chemotherapy or chemoimmunotherapy.

Studies involving CAR-T in the leukemia model have also been analysed by several researchers (Pérez-García et al., 2021), (Martínez-Rubio et al., 2021), (Barros et al., 2021), (Khatun & Biswas, 2020). (Khatun & Biswas, 2020) investigated the mathematical model of the interaction of leukemia cells and immune cells by administering Chimeric Antigen Receptor (CAR) T cells. In contrast to (Khatun & Biswas, 2020), this study

describes the growth of the leukemia cell population using a logistic equation model. This is due to the fact that leukemia cells have limited resources in the body, and the logistic model provides empirical data to match the growth of the leukemia cell population (Gruber et al., 2019). The model will then be analysed using mathematical theories and simulated using Maple software to determine the interaction of leukemia cells and immune cells by administering Chimeric Antigen Receptor (CAR) T cells.

The next steps in this paper are (i) construct a mathematical model of the interaction of susceptible blood cells, infected blood cells, leukemia cells and immune cells with Chimeric Antigen Receptor (CAR) T cell therapy, (ii) finding the equilibrium point of the model, stability criterion of the equilibrium point, determining the basic reproduction number and sensitivity index, (iii) performing simulations based on the existence and stability conditions and interpreting the result.

MODEL FORMULATION AND ANALYSIS

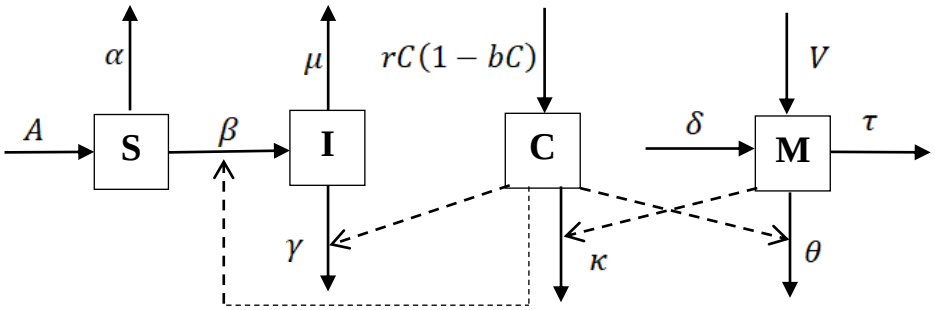
This paper discusses the problem of leukemia in the presence of T-cell Chimeric Antigen Receptor (CAR) therapy. Furthermore, a literature study was conducted to gain an overview of leukemia and mathematical modeling in the form of a system of differential equations. The model was developed and analyzed by determining the equilibrium point of the model, the stability of the equilibrium point using Routh Hurwitz criteria, determining the basic reproduction number using the Next Generation Method, sensitivity analysis, and dynamic simulation using Maple software.

The mathematical model of the interaction of leukemia cells and immune cells in the presence of T-cell Chimeric Antigen Receptor (CAR) therapy involves four compartments, namely susceptible blood cells (S), infected blood cells (I), leukemia cells (C) and immune cells (M). The assumptions used to form the model are as follows:

1. Susceptible blood cell population originates from the bone marrow, lymph nodes and thymus which enter the blood circulation.
2. The growth rate of leukemia cells follows a logistic growth model.
3. The interaction between susceptible blood cells and leukemia cells will increase and move into the infected blood cell population.
4. The interaction between infected blood cells and leukaemic cells causes the infected blood cells to decay.
5. Susceptible blood cell, infected blood cell and immune cell can naturally die.
6. Leukemia cells can trigger the presence of immune cells.

7. Immune cells can destroy leukemia cells.
8. CAR T cells proliferate constantly.

The interaction scheme of the four populations is presented in the compartment diagram in Figure 1.



Description:

⟶ : recruitment, proliferation, transition, reinfusion and death of cell

- - -➢ : affected cells due to cell interaction

Figure 1. Compartment diagram

From Figure 1, the model can be presented in a system of nonlinear differential equations (1)

$$\begin{aligned}
\frac{dS}{dt} &= A - \alpha S - \beta SC \\
\frac{dI}{dt} &= \beta SC - \mu I - \gamma CI \\
\frac{dC}{dt} &= r(1 - bC)C - \kappa CM \\
\frac{dM}{dt} &= V + \delta C - \tau M - \theta MC
\end{aligned} \tag{1}$$

with $S(t) \geq 0, I(t) \geq 0, C(t) \geq 0,$ and $M(t) \geq 0$. The model variables and parameters an are described in Table 1.

Table 1. Variables and parameters description

Variables/ Parameters	Description	Domain	Unit
S	The blood cell population is vulnerable	$S \geq 0$	concentration
I	Infected blood cell population	$I \geq 0$	concentration
C	Leukemia cell population	$C \geq 0$	concentration
M	Immune cell population	$M \geq 0$	concentration
A	Recruitment rate of susceptible blood cells produced from bone marrow, lymph nodes, thymus that enter the blood circulation	$A \geq 0$	$\frac{\text{concentration}}{\text{day}}$
α	The rate of natural death of blood cells is vulnerable	$\alpha > 0$	$\frac{1}{\text{day}}$

Variables/ Parameters	Description	Domain	Unit
β	The rate of change of blood cells susceptible to become infected blood cells	$\beta > 0$	$\frac{1}{\text{concentration} \cdot \text{day}}$
μ	The rate of natural death of infected blood cells	$\mu > 0$	1/day
γ	The rate of decay of infected blood cells as a result of interacting with leukemia cells	$\gamma > 0$	$\frac{1}{\text{concentration} \cdot \text{day}}$
r	Leukemia cell growth rate	$r > 0$	1/day
b	Leukemia cell carrying capacity	$b > 0$	1/concentration
κ	Leukemia cell decay rate as it interacts with immune cells	$\kappa > 0$	$\frac{1}{\text{concentration} \cdot \text{day}}$
V	CAR T-cell external infusion rate	$V > 0$	$\frac{\text{concentration}}{\text{day}}$
δ	Immune cell proliferation rate	$\delta > 0$	1/day
τ	The rate of natural death of immune cells	$\tau > 0$	1/day
θ	The rate of decay of immune cells caused by interactions with leukemia cells	$\theta > 0$	$\frac{1}{\text{concentration} \cdot \text{day}}$

Equilibrium Analysis

1. Equilibrium Point Before CAR T Cell Treatment

A. Cancer-free equilibrium E_1

This equilibrium states a condition when there are no cancer cells in the blood, there are no infected blood cells and no treatment is given to the patient or the condition at the time $C = 0, I = 0$ and $M = 0$.

$$E_1 = \left(\frac{A}{\alpha}, 0,0,0\right) \tag{2}$$

B. Endemic equilibrium with the innate immune response E_2

This equilibrium describes a condition when blood cells are susceptible to infection with leukemia. This case considers a response from the immune system due to natural stimulation in the body. Usually, there is a severe situation in the body because the natural immune system is very weak. The leukemia cells continue to grow unhindered, and the infected cells crowd out the healthy blood cells even more, which makes the patient's clinical condition worse.

$$E_2 = \left(\frac{Abr}{\alpha rb+\beta(r-\kappa M^*)}, \frac{\beta Abr(r-\kappa M^*)}{(\alpha br+\beta(r-\kappa M^*))(\mu rb+\gamma(r-\kappa M^*))}, \frac{(r-\kappa M^*)}{rb}, \frac{\delta\kappa+r(\tau b+\theta)\pm\sqrt{(\delta\kappa+r(\tau b+\theta))^2-2(\theta\kappa)(\delta r)}}{2\theta\kappa}\right) \tag{3}$$

Coexistence condition for E_2 are $r - \kappa M^* > 0$ and $(\delta\kappa + r(\tau b + \theta))^2 - 2(\theta\kappa)(\delta r) \geq 0$.

2. Equilibrium Points After CAR T Cell Treatment

A. Cancer-free equilibrium E_3

This equilibrium represents a condition when there are no cancer cells in the blood and no infected blood cells after CAR T cell treatment, or a condition when $C = 0$ dan $I = 0$.

$$E_3 = \left(\frac{A}{\alpha}, 0, 0, \frac{V}{\tau}\right) \tag{4}$$

B. Endemic equilibrium point after treatment E_4

This state describes the presence of cancer cells in the body even though treatment has been carried out.

$$E_4 = \left(\frac{Arb}{\alpha rb+\beta(r-\kappa\widehat{M})}, \frac{\beta Arb(r-\kappa\widehat{M})}{(\alpha br+\beta(r-\kappa\widehat{M}))(\mu rb+\gamma(r-\kappa\widehat{M}))}, \frac{(r-\kappa\widehat{M})}{rb}, \frac{(\delta\kappa+r(\tau b+\theta))\pm\sqrt{(\delta\kappa+r(\tau b+\theta))^2-4(\theta\kappa)(Vrb)}}{2\theta\kappa}\right) \tag{5}$$

E_4 must meet the conditions of existence $r - \kappa\widehat{M} > 0$and $(\delta\kappa + r(\tau b + \theta))^2 - 4(\theta\kappa)(Vrb) \geq 0$.

Basic Reproduction Number

The equation in system (1) that contributes to the addition of new cases of infection is the differential equation of leukemia cells (C). By using the Next Generation Matrix (NGM) method (Ndii, 2018),, the basic reproduction number is obtained,

$$R_0 = \frac{\tau r}{\kappa V}. \tag{5}$$

Stability Analysis

The stability of the equilibrium point of model (1) can be determined by observing the sign of the real part of the eigenvalues of the Jacobian matrix.

Stability Theorem (Brauer et al., 2019)

If $\bar{\boldsymbol{x}}$ *is equilibrium of the system (1), and if all eigenvalues of the coeficient matrix of the linearization (jacobian matrix) at this equilibrium have negative real part, then the equilibrium* $\bar{\boldsymbol{x}}$ ***is*** *local asymptotically stable*.

The Jacobian matrix of system (1) is

$$J = \begin{bmatrix} -\alpha - \beta C & 0 & -\beta S & 0 \\ \beta C & -\mu - \gamma C & \beta S - \gamma I & 0 \\ 0 & 0 & r - 2rbC - \kappa M & -\kappa C \\ 0 & 0 & \delta - \theta M & -\tau - \theta C \end{bmatrix} \tag{6}$$

1. Stability of cancer-free equilibrium E_1

The eigenvalues derived from the Jacobian matrix (6) evaluated at equilibrium point E_1 are $\lambda_1 = -\alpha, \lambda_2 = -\mu$, $\lambda_3 = r$ and $\lambda_4 = -\tau$. Because λ_3 is positive, then this equilibrium point is unstable.

2. Stability of endemic equilibrium before treatment E_2

The eigenvalues obtained from the Jacobian matrix (6) evaluated at equilibrium point E_2 are $\lambda_1 = -\frac{arb+\beta(r-\kappa M^*)}{rb}$,$\lambda_2 = -\frac{arb+\gamma(r-\kappa M^*)}{rb}$. Meanwhile, λ_3 and λ_4 satisfy a characteristic polynomial $a_2\lambda^2 + a_1\lambda + a_0 = 0$ with $a_2 = rb$, $a_1 = (rb+\theta)(r-\kappa M^*) + \tau rb$, and $a_0 = (r-\kappa M^*)(\tau rb + \theta(r-\kappa M^*) + \delta\kappa - \theta\kappa M^*)$. By using Routh Hurwitz criterion (Brauer et al., 2019), (Khumaeroh et al., 2018), when $a_2 > 0$, $a_1 > 0$, and $a_0 > 0$, then λ_3 and λ_4 is negative. Therefore, the endemic equilibrium point with the natural immune response is locally asymptotically stable if $\tau rb + \theta(r-\kappa M^*) + \delta\kappa > \theta\kappa M^*$.

3. Stability of cancer-free equilibrium after treatment E_3

The eigenvalues obtained from the Jacobian matrix (6) evaluated at equilibrium point E_3 are, $\lambda_1 = -\alpha$, $\lambda_2 = -\mu$, $\lambda_3 = -\frac{V\kappa(1-R_0)}{\tau}$ and $\lambda_4 = -\tau$. Then all eigen values is negative or locally asymptotically stable when $R_0 < 1$.

4. Stability of endemic equilibrium after treatment E_4

The eigenvalues obtained from the Jacobian matrix (6) evaluated at equilibrium point E_4 are $\lambda_1 = -\frac{arb+\beta(r-\kappa\widehat{M})}{rb}$, $\lambda_2 = -\frac{arb+\gamma(r-\kappa\widehat{M})}{rb}$. While λ_3 and λ_4 satisfy $b_2\lambda^2 + b_1\lambda + b_0 = 0$ with $b_2 = rb$, $b_1 = (rb+\theta)(r-\kappa\widehat{M}) + \tau rb$, and $b_0 = (r-\kappa\widehat{M})(\tau rb + \theta(r-\kappa\widehat{M}) + \delta\kappa - \theta\kappa\widehat{M})$. By using Routh Hurwitz criterion, λ_3 and λ_4 is negative when $b_2 > 0$, $b_1 > 0$, and $b_0 > 0$. So that the endemic equilibrium point after treatment is locally asymptotically stable if $\tau rb + \theta(r-\kappa\widehat{M}) + \delta\kappa > \theta\kappa\widehat{M}$.

Numerical Simulation

Numerical simulation of this mathematical model uses Maple software to see an overview of the interaction of leukemia cells and immune cells with Chimeric Antigen Receptor (CAR) T-cell therapy treatment. The simulation process was carried out with initial values $S(0) = 0.95, I(0) = 0.05, C(0) = 0.05, M(0) = 0.01$ and initial time $t(0) = 0$ and $t(t) = 200$ day the parameter values used in the simulation before and treatment of CAR T cells are given in Table 2.

Table 1Parameter Estimation Values (Khatun & Biswas, 2020)**,** (Kurnia & Adi, 2020)

Parameter	Cancer-endemic equilibrium before treatment	Cancer-free equilibrium after treatment	Cancer-endemic equilibrium after treatment
A	1	1	1
α	0.001	0.01	0.001
β	0.00005	0.00001	0.00005
μ	0.0002	0.003	0.0002
γ	0.001	0.001	0.001
r	0.18	0.18	0.18
b	0.001	0.001	0.001
κ	0.005	0.04	0.005
V	0	0.5	1
δ	0.01	0.03	0.01
τ	0.001	0.006	0.05
θ	0.002	0.01	0.002

The following graphic is the dynamic simulation of cancer-endemic equilibrium before treatment

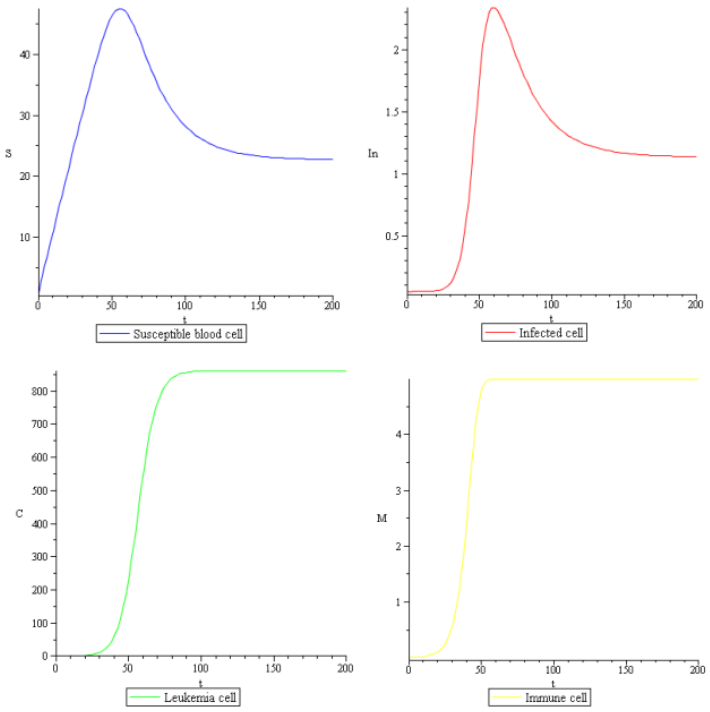


Figure 1Graph of S, I, C, M before treatment (endemic condition)

Figure 2 shows that the population of susceptible blood cell, infected cell, leukemia cell, and immune cells are stable towards their equilibrium points, (S, I, C, M)= (25, 1.2, 900, 5) concentration. In addition, immune cells stabilize faster than other cells. It can be seen in the graph that immune cells have reached stability around day 50. On the other

hand, susceptible cells, infected cells, and cancer cells stabilize around days 150, 150, and 80 respectively. When cancer cells are present in the body, immune cells naturally activate to combat cancer cells when there is no treatment available.

Furthermore, numerical simulation after treatment can be seen in Figures 3 and 4.

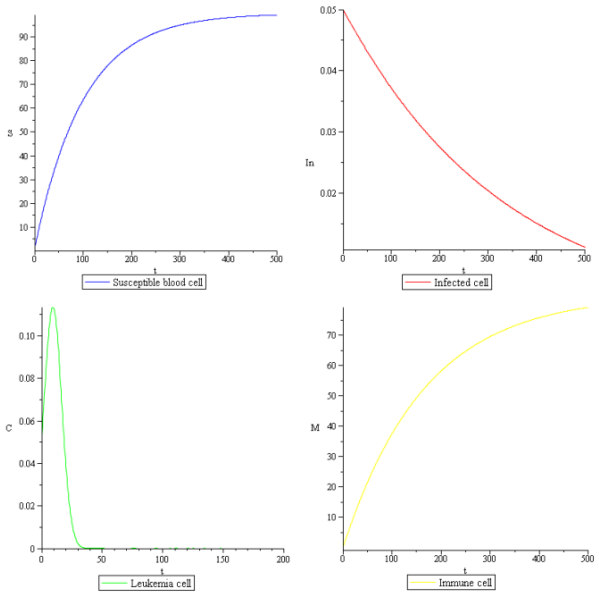


Figure 2Graph of S, I, C, M after Chimeric Antigen Receptor (CAR) T cell therapy (cancer-free condition)

From Figure 3, the population of susceptible blood cell, infected cell, leukemia cell, and immune cells are stable to cancer free equilibrium, (S, I, C, M)≈(100, 0, 0, 80) concentraion. Additionally, it may be observed that cancer cells stabilize more quickly than other cells because, in contrast to susceptible cells, infected blood cells, and immune cells, which require 500 days, cancer cells take only 50 days to stabilize. This condition indicates that providing Chimeric Antigen Receptor (CAR) T-cell infusions aids in the fight against and killing of cancer cells in the body, resulting in a gradual decrease in the quantity of cancer and infected cells in the blood and eventual elimination of cancer.

Meanwhile, based on Figure 4, the population of susceptible blood cell, infected cell, leukemia cell, and immune cells are stable to endemic free equilibrium, (S, I, C, M) ≈ (25, 1.3, 850, 5) concentration. based on the stability time, cancer cells and immune cells reached the equilibrium point faster ($t \approx 100$ days) compared to susceptible and infected blood cells (t≈ 200 days). However, as time passes, the immune cells start to decrease while the cancer cells continue to grow and multiply. Consequently, the cancer cells persistently target susceptible blood cells, resulting in an escalation of the infected cell.

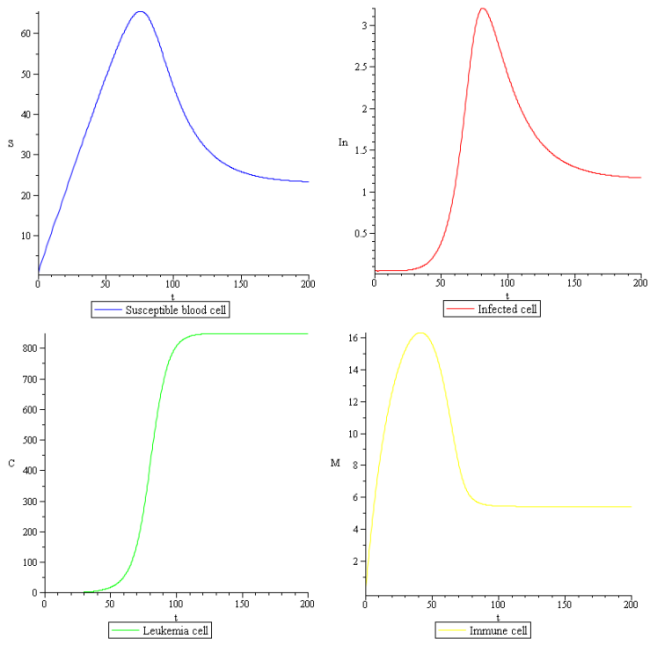


Figure 3Graph of S, I, C, M after Chimeric Antigen Receptor (CAR) T cell therapy (Cancer-endemic condition)

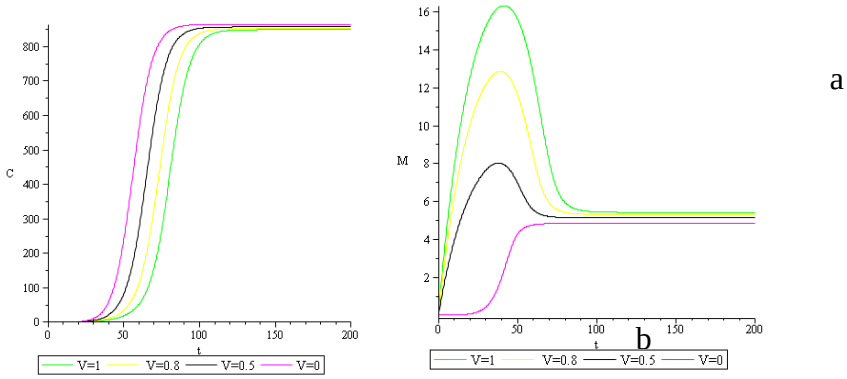


Figure 4. (a) Leukemia cell and (b) Immune Cell for different CAR T cell external reinfusion values (V)

In Figure 5, cancer cells and Immune cells simulation is conducted by varying the parameter of CAR T-cell external infusion (V), while keeping the other parameter values same as the endemic condition after treatment (Table 4). The graph illustrates that in the absence of external infusion of CAR T cells, cancer cells experience uncontrolled and rapid growth towards endemic levels within the body. However, when an external infusion of CAR T cells is injected, the number of immune cells increases, and the progression toward endemic levels becomes slower. This implies that the external infusion of CAR T cells enhances the strength of immune cells in combating cancer cells. Despite the cancer cells are present in the body, CAR T cell treatment impedes the occurrence of cancer cell endemicity and delays the stability of immune cells within the body.

Sensitivity Analysis

Sensitivity analysis is a mathematical modeling technique that evaluates the effects of changes in input variables on the output of a model (Ndii, 2018),(Ilahi & Khumaeroh, 2021),(Khumaeroh et al., 2018). In this study, the normalized sensitivity index is determined by normalizing the effect of changing the parameters values on the basic reproduction number (R_0).

$$S_{\boldsymbol{P}} = \frac{\partial R_0}{\partial \boldsymbol{P}} \cdot \frac{\boldsymbol{P}}{R_0} \tag{6}$$

The sensitivity simulation using endemic parameter values after treatment in Table 2 are shown in Figure 6.

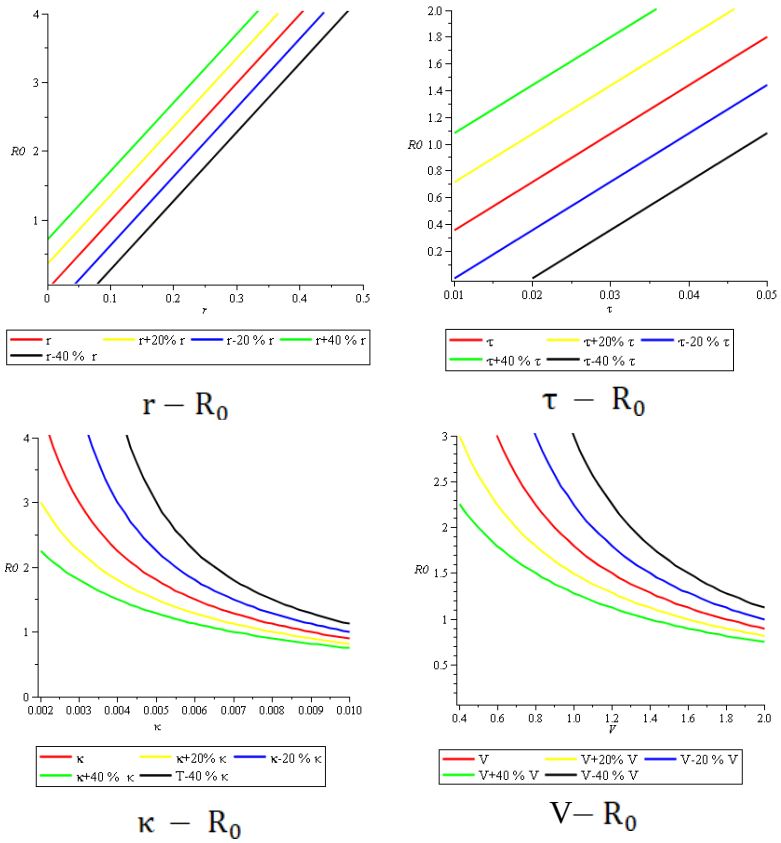


Figure 6. Parameter sensitivity index to Basic Reproduction Number (R_0)

The graphic in Figure 6 demonstrates how the value of R_0 will increase as the growth rate of cancer cells (r) and the death rate of immune cell (τ) each rise. Meanwhile, the value of R_0 is going to decrease as the parameter of cancer cell death due to interaction with immune cells (κ) and the external infusion rate of CAR T cells (V) increases. This result is in line with the previous research by (Khatun & Biswas, 2020), that the spread of leukemia largely depends on the rate of cancer cells or abnormal white blood cells as well

as immune cells. The rate of cancer cells increases when the recruitment rate of abnormal white blood cells increases in the blood. However, as the external infusion of immune cells rises, cancer cells gradually decline.

CONCLUSION

In this study, we developed a leukemia model with the presence of Chimeric Antigen Receptor (CAR) T cells. The analysis results revealed the existence of four equilibrium points, represented as E1, E2, E3, and E4. Stability analysis conducted at each equilibrium point demonstrated that E1 is unstable, whereas the other three equilibrium points, E2, E3, and E4, can be stable under certain conditions. Simulation results indicated that, basically the natural immune system of the body is capable of eliminating leukemia cells. However, over time, these immune cells gradually weaken and become insufficient to combat leukemia. By implementing T-cell Chimeric Antigen Receptor (CAR) therapy, the immune system gains enhanced capabilities to fight leukemia cells, consequently prolonging the time it takes for leukemia cells to establish themselves in the body. Sensitivity analysis revealed that the growth rate of cancer cells (r) and the death rate of immune cells (τ) have a significant effect on increasing the basic reproduction number (R_0).

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