International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

The Analysis of the Effects of an Adoptive T - Cells Therapy on the Growth of Chronic Lymphocytic and Acute Myeloid Leukemia Coexistence Using Caputo's Fractional Differential Sense

Anthony Kwarteng[1], Eric Neebo Wiah[2], Henry Otoo[3]

[1]Mathematics and Statistics Department, Ghana Communication Technology University, Accra, Ghana.
[1,2,3]Mathematical Sciences Department, University of Mines and Technology, Tarkwa, Ghana

ABSTRACT
A malignant disease that affects the blood's lymphoid and myeloid components is termed as a leukemia. It is a cancer that poses serious problems for individuals, families and the healthcare systems around the world. The study sought to examine how the immunotherapy of adoptive T cells affects the growth of coexistence of chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML) cells. The compartmental system of ordinary differential equations and Caputo's fractional differential sense were developed to analyze the coexistence of CLL and AML in a single patient. The study showed that disease free and endemic equilibrium points were proved to be globally asymptotically stable. Numerical simulations were also performed to support the analyses. The studies showed that the concentration levels of both types of leukemia cells were very high before the introduction of immunotherapy of the adoptive T cells.

Keywords: Lymphocytic, Myeloid, Leukemia, Reproduction Number, immunotherapy.

1. Introduction

The parts of the immune system that fight against bacteria, viruses and germs are the White Blood Cells (WBC). A decreased in the number of WBC (leucocytes) in the blood is referred to in Medical terms as Leukopenia. Leukopenia can be more serious since it can increase one's risk of developing potentially life – threatening infections [1, 2].

A malignant disease that affects the blood's lymphoid and myeloid components is termed as a leukemia. It is a malignant disease which is characterized by a rapid and uncontrolled proliferation and growth of premature WBCs [3]. The rapid increase in the number of premature cells inhibit the mature WBCs production [4]. The indolent B-cell lymphoproliferative neoplasm that normally occurs in adults is the chronic lymphocytic leukemia (CLL). It has favorable survival rate of 5 years [5]. There are a lot of clinical case studies that confirmed the CLL and AML coexistence in a single patient [5, 6, 7]. The studies revealed that the coexistence of AML and CLL in a single patient is usually caused by the methods of treatments [5].

There has been an extensive work on how to treat or control the spread of leukemia cells in the recent years. A thorough review of the difficulties, advancements, and potential uses of chimeric antigen receptor (CAR) T cell therapy in the treatment of acute myeloid leukemia (AML) was presented in [8, 9, 10]. The comprehensive evaluations covered the body of research, data from clinical trials, and professional advice on CAR T cell treatment and AML. According to the study, adding more receptors or the right cytokines could enhance CAR therapy. The study in [10] suggested identifying the best clinical conditions, such as minimal residual disease (MRD), low-burden disease, and early salvage, for the application of immunotherapies. The study [11] confirmed the efficacy of unselected donor lymphocyte infusions, or DLIs, in the post-allogeneic treatment of AML and T-ALL patients.

In addition to the many clinical trials, there have been other extensive works on mathematical models that examined the progression and control of leukemia cells. In [12, 13], mathematical models were developed to distinguish between the sensitivity of normal and mutant stem cells of bone marrow microenvironment. Three different equilibria corresponding to the normal hematopoietic state, chronic state and the accelerated-acute phase of the disease were predicted. The studies [14 - 16] also developed different classical and fractional differential systems to describe the dynamic of myeloid leukemia. The Lyapunov functions were developed in [14] to perform the global stability of both the endemic and disease-free equilibrium points. An ordinary differential system was formulated in [17, 18] to determine the impact of genetically modified patient T lymphocytes against leukemia cells. The outcome demonstrated that the concentration of leukemia cells and infected cells in the blood is decreased by external infusion of T- cells, or immune cells. The appropriate Lyapunov functions was developed to prove the global stability of the disease-free equilibrium and endemic equilibrium [14]. In [17, 18] the researchers investigated the effects of engineered patient's T- cells on the spread of leukemia using classical differential models. The adoptive T - cell therapy was found to be more effective in controlling the concentration of leukemia cells.

The researchers were motivated by the work in [17, 18] and decided to extend it to the coexistence of CLL and AML in a single patient. The classical differential system has also been extended to the Caputo's fractional differential sense in the study.

2. Materials and Methods

In this session, the researchers reviewed the models in [17, 18] which served as the bases for the study. They also developed the classical differential models and the Caputo's fractional differential systems. Some basic of properties of Fractional Calculus were also reviewed.

2.1. Mathematical Model Development

The models in [17] were modified by Khatum and Biswas in [18] by adding β_1 as a new parameter to indicate the infected cells' rate of decay. The concentrations of susceptible cells, infected cells, leukemic cells, and white blood cells are denoted by the state variables s, i, c, and w respectively. Figure 1 below shows the schematic transfer of the leukemia cells from Khatum and Biswas.

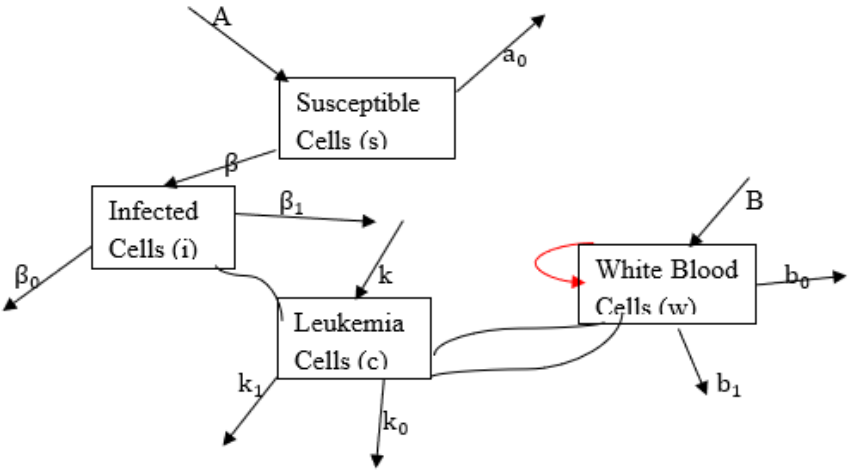

Figure 1: Transmission Diagram of Leukemia in the Patients

From the schematic diagram, Figure 1, they came out with the modified models as given below:

$$\frac{ds}{dt} = A - a_0 s - \beta sc$$
$$\frac{dy}{dt} = \beta sc - \beta_0 y - \beta_1 ci \quad (1)$$
$$\frac{dc}{dt} = k - k_0 c - k_1 cw$$
$$\frac{dw}{dt} = B + bc - b_0 w - b_1 wc$$

The other parameters in (1) have the same meaning as in [18].

2.2. The Modification of the Model

The researchers extended the work in [18] to cover the progression of CLL and AML coexistence in a single patient. So the models in [17, 18] were modified by introducing a new compartment in order to get two leukemic cells compartments, one for CLL and other for AML. The two parameters, φ *and* γ were also introduced to represent the transfer rates of infected cells from infested compartment to CLL and AML compartments respectively base on the type of infected cells as shown in the schematic diagram, fig.2 below

Below is the schematic transmission diagram of leukemic cells.

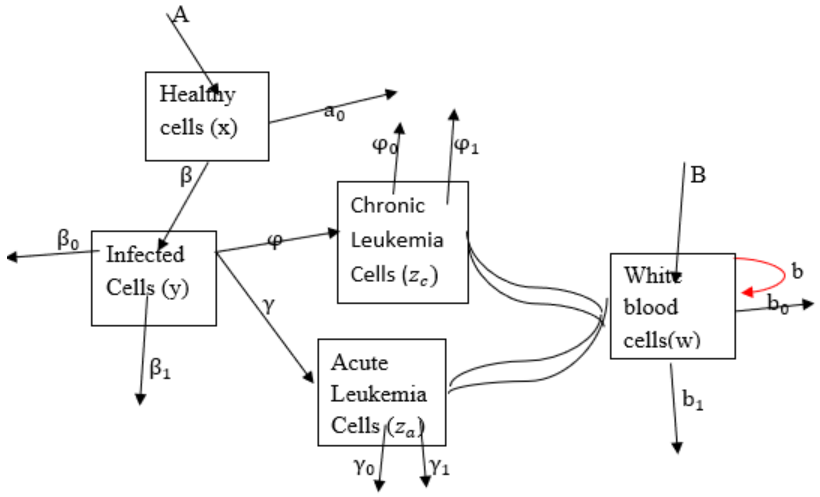

Figure 2: The Modified Transmission Diagram of Leukemia in the Patients

From Figure 2 above, the red arrows indicate the white blood cell self-renewal rates as a result of the leukemia relapse, whereas the curves without arrows indicate the interactions between the cells of the various compartments. The state variables x, y, z_a, z_c *and* w represent the concentration levels of the healthy cells, the infected cells, AML, CLL and white blood cells respectively. The classical models are given below:

$$\frac{dx}{dt} = A - a_0x - \beta xy$$
$$\frac{dy}{dt} = \beta xy - \beta_0 y - \gamma y - \varphi y - \beta_1 y(z_a + z_c)$$
$$\frac{dz_a}{dt} = \gamma y - \gamma_0 z_a - \gamma_1 z_a w \quad (2)$$
$$\frac{dz_c}{dt} = \varphi y - \varphi_0 z_c - \varphi_1 z_c w$$
$$\frac{dw}{dt} = B + b(z_a + z_c) - b_0 w - b_1 w(z_a + z_c)$$

The table below gives the descriptions of the parameters and values used the above models.

Table 1: Summary of Notations

Notations	Definition
A	The constant rate of susceptible blood cells recruitment
a_0	Natural death rate of susceptible cells
β	Rate of infection of healthy cells
β_0	Natural death rate of infected cells
β_1	Decay rate of infected cells
γ	Transfer rate of infected cells to AML compartment
γ_0	Natural death rate of acute leukemic cells
γ_1	Decay rate of AML cells due its interaction with immune system
φ	The transfer rate of infected cells to CLL compartment
φ_0	Natural death rate of chronic leukemic cells
φ_1	Decay rate of CLL cells due its interaction with immune system
B	External reinfusion rate of T – Cells
b	Proliferation rate of white blood cells
b_0	Natural death rate of white blood cells
b_1	Decay rate of immune system due to its interaction with leukemic cells

2.3. The Fractional Calculus

The models (2) was extended to Caputo's Fractional derivative sense as shown (3) below. Some of the important properties of fractional derivatives that are applied to the study throughout are presented below, [15], [16].

Property 1.

Given a function f(t) in the interval C[0, T], the Riemann - Liouville derivative ${}_0^C\mathbb{D}_t^{-\alpha} f(t)$ of order $\alpha > 0$ is given by

$$RL_0\mathbb{D}_t^{\alpha} f(t) = \begin{cases} \frac{1}{\Gamma(n-q)} \frac{d^n}{dt^n} \int_0^t \frac{f(t)}{(t-s)^{\alpha-n+1}} ds, & n-1 < \alpha < n, n \in N \\ \frac{d^n}{dt^n}, & n = q,\ n \in N \end{cases}$$

Property 2,

Taking the Laplace transform $D^{\alpha}f(t)$, we have

$\mathcal{L}\left(D^{\alpha}f(t)\right) = S^{\alpha}F(s) - \sum_{k=0}^{n-1} f^{k}(0)\, S^{\alpha-k-1}$

where F(s) is the Laplace transform of f (t).

If k = 0, then Laplace transform of Caputo fractional derivative become:

$\mathcal{L}\left(D^{\alpha}f(t)\right) = S^{\alpha}F(s) - S^{\alpha-1}f(0)$

Property 3

Mittag - Leffler function with two parameters α, β where α > 0 and β > 0, is given by $E_{\alpha,\beta}(z) = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(\alpha k+\beta)} = zE_{\alpha,\alpha+\beta}(z) + \frac{1}{\Gamma(\beta)}$, for $\alpha, \beta > 0\ z \in \mathbb{C}$

For $\beta = 1$, then Mittag - Leffler function becomes

$E_{\alpha,}(z) = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(\alpha k+1)}$, $z \in \mathbb{C}$

Moreover, Mittag - Leffler function is simply an exponential function exp(z) when $\alpha = \beta = 1$.

Property 4

Given a Mittag function, $f(t) = t^{\beta-1}E_{\alpha,\beta}(\pm at^{\alpha})$, then Laplace transform of f(t) is given by

$\mathcal{L}\left(f(t)\right) = \frac{s^{\alpha}}{s^{\alpha} \pm a}$, for Re(S) > $|a|^{\frac{1}{\alpha}}$ and Re(β) > 0.

2.3.1. The Fractional Derivative Model

The researchers extended the developed models (2) to the Caputo's Fractional derivative sense in order to apply the Fractional Derivative techniques to perform the stability test of the system (1). The Fractional derivative form of the models (3) are given as

$$\begin{aligned}
{}_0^C\mathbb{D}_t^{\alpha} x(t) &= A - a_0 x - \beta xy \\
{}_0^C\mathbb{D}_t^{\alpha} y(t) &= \beta xy - \beta_0 y - \gamma y - \varphi y - \beta_1 y(z_a + z_c) \\
{}_0^C\mathbb{D}_t^{\alpha} z_a(t) &= \gamma y - \gamma_0 z_a - \gamma_1 z_a w \\
{}_0^C\mathbb{D}_t^{\alpha} z_c(t) &= \varphi y - \varphi_0 z_c - \varphi_1 z_c w \\
{}_0^C\mathbb{D}_t^{\alpha} w(t) &= B + bz_a + bz_c - b_0 w - b_1 w z_a - b_1 w z_c
\end{aligned} \qquad (3)$$

Subject to the initial condition

$x_0 \geq 0,\ y_0 \geq 0, z_{a(0)} \geq 0, z_{c(0)} \geq 0\ and\ w_0 \geq 0$

Whereas the operator, ${}_0^C\mathbb{D}_t^{\alpha}$ represents the Caputo's fractional derivative of order $0 < \alpha \leq 1$

All the models' parameters are assumed to be non-negatives. The functions $x(t)$, $y(t)$, $z_a(t)$, $z_c(t)$ and $w(t)$ are also continuous functions.

3. The Model Analysis

3.1. Positivity Solutions of the System

The system (3) is defined as:

$\Lambda+ = \{(x, y, z_a, z_c, w) \in R^5 : x(t), y(t), z_a(t), z_c(t), w(t) \geq 0\}$. Suppose that, $(x_0, y_0, z_{a(0)}, z_{c(0)}, w_0) \in$ x(t)-axis $= \{(x(t), 0, 0, 0, 0) : x(t) \geq 0\}$.

Appling property 4 above to system (3) along the vector x(t) axis, the system (3) becomes:

$$\mathcal{L}\left({}_0^{C}\mathbb{D}_t^{\alpha} x(t)\right) = \mathcal{L}(A - a_0 x)$$

$$S^{\alpha}X(s) - S^{\alpha-1}x(0) = \frac{A}{S} - a_0 X(s)$$

$$S^{\alpha}X(s) + a_0 X(s) = \frac{A}{S} + S^{\alpha-1}x(0)$$

$$X(s)(S^{\alpha} + a_0) = \frac{A}{S} + S^{\alpha-1}x(0)$$

$$X(s) = \frac{A}{S(S^{\alpha}+a_0)} + \frac{(S^{\alpha-1}x(0)}{(S^{\alpha}+a_0)} = \frac{AS^{\alpha-(\alpha+1)}}{S^{\alpha}+a_0} + \frac{S^{\alpha-1}x(0)}{S^{\alpha}+a_0} \quad (4)$$

The inverse Laplace transform of (4) is given as:

$$x(t) = At^{\alpha}E_{\alpha,(\alpha+1)}(-a_0 t^{\alpha}) + x(0)E_{\alpha,1}(-a_0 t^{\alpha}) \quad (5)$$

Hence, system (3) along the x(t) axis, yields

$\{(x, y, z_a, z_c, w) = \{(At^{\alpha}E_{\alpha,(1+\alpha)}(-a_0 t^{\alpha}) + x(0)E_{\alpha,1}(-a_0 t^{\alpha}), 0, 0, 0, 0): x(t) \geq 0\}$

Similarly system (3) along the vectors y(t), $z_a(t)$, $z_c(t)$ and w(t) axes also resulted in the following points:

$(x, y, z_c, z_a, w) = (0, y(0)E_{\alpha,1}(-\beta_0)t^{\alpha}), 0, 0,) \in$ y(t)-axis;

$(x, y, z_a, z_c, w) = (0, 0, z_a(0)E_{\alpha,1}(-\gamma_0)t^{\alpha}), 0, 0,) \in z_a(t)$-axis;.

$(x, y, z_a, z_c, w) = (0, 0, 0, z_c(0)E_{\alpha,1}(-\varphi_0)t^{\alpha}) 0,) \in z_c(t)$-axis and

$(x, y, z_a, z_c, w) = (0, 0, 0, 0, Bt^{\alpha}E_{\alpha,\ \alpha+1}((-b_0)t^{\alpha}) + w(0)E_{\alpha,1}(-b_0)t^{\alpha})) \in$w(t)-axis respectively.

The above points show that $x(t), y(t), z_a(t), z_c(t)$ and $w(t)$ are solutions of the system and positive invariants sets and hence, $\Lambda+$ is a positive invariants set.

3.2. The Uniqueness of the Solution

Lemma 1

Assume that $\Phi(t, u(t))$ satisfies the following:

1. Φ is a continuous function with respect to t for all $u(t) \in R^n$,
2. Φ and $\frac{\partial \Phi}{\partial u}$ are continuous functions with respect to $u(t) \in R^n$,
3. $\|\Phi\| \leq a_1 + a_2\|u\|$ for all $u \in R^n$, and all $a_1, a_2 > 0$.

Then, system (3) possesses a unique solution on $[0, +\infty)$, [19].

Theorem 1.

The System (3) attains unique solution on $[0, +\infty)$ and remains non-negative and bounded for all $t \geq 0$.

Proof.

According to [19], the system, (3) can be reformulated into a Caputo fractional derivative system of order $0 < \alpha \leq 1$, as follows:

${}_{0}^{C}\mathbb{D}_{t}^{\alpha}u(t) = \Phi(t, u(t))$, for, $t \geq 0$, with $u(0) = u_0 \in \mathbb{R}_+^5$, (6)

where $\Phi : \mathbb{R}_+ \times \mathbb{R}^5 \rightarrow \mathbb{R}$, $\Phi(t, u(t)) = v + Au(t) + \bar{u}(t)Bu(t)$, $u(t) = (x(t), y(t), z_a(t), z_c(t), w(t))^T$,
$V = (A\ 0\ 0\ 0\ B)^T$, $v = IV$, $u_0 = (x_0, y_0, z_{a(0)}, z_{c(0)}, w_0)^T$
where $\bar{u}$ represents not u on the row,

$$A = \begin{pmatrix} -a_0 & 0 & 0 & 0 & 0 \\ 0 & -\beta_0 & 0 & 0 & 0 \\ 0 & 0 & -\gamma_0 & 0 & 0 \\ 0 & 0 & 0 & -k_0 & 0 \\ 0 & 0 & b & b & -b_0 \end{pmatrix}$$

$$B = \begin{pmatrix} 0 & -\beta & 0 & 0 & 0 \\ \beta & 0 & -(\gamma + \beta_1) & -(\varphi + \beta_1) & 0 \\ 0 & \gamma & 0 & 0 & -\gamma_1 \\ 0 & (\varphi) & 0 & 0 & -\varphi_1 \\ 0 & 0 & -b_1 & -b_1 & 0 \end{pmatrix}$$

It could be seen that both $\frac{\partial \Phi}{\partial u}$ and Φ are continuous functions and hence the conditions 1 and 2 of Lemma 1 above are satisfied by the function u(t).
The system (3), can be expressed as

$$\left\| {}_{0}^{C}\mathbb{D}_{t}^{\alpha}u(t) \right\| \leq \|v\| + (\|Au(t)\| + \|\bar{u}(t)\|\|B(t)\|)\|u(t)\| \quad (7)$$

The norm, (7), is also used to confirm the condition 3 of lemma (1) above. Hence, (3) has a unique solution on $(0, +\infty)$.

3.3. Basic Reproduction Number

The average number of secondary infections caused by a single primary infection in a susceptible population is called the basic reproduction number (R_0) [18].
The Next - Generation method was used to determine R_0 for the system (3) as shown below:
Let $U = (y, z_a, z_c, x, w)^T$. The system (3) is then expressed as $\frac{du}{dt} = F(U) - V(U)$, where

$$\mathcal{F} = \begin{pmatrix} \beta xy \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \text{ and } \mathcal{V} = \begin{pmatrix} -\beta_0 y - \gamma y - \varphi y - \beta_1 y(z_a + z_c) \\ \gamma y - \gamma_0 z_a - \gamma_1 z_a w \\ \varphi y - \varphi_0 z_a - \varphi_1 z_a w \\ A - a_0 x - \beta xy \\ B + bz_a + bz_c - b_0 w - b_1 w z_a - b_1 w z_c \end{pmatrix}$$

The Jacobean matrices $\mathcal{F}$ and $\mathcal{V}$ with respect to the infected, acute leukemic and chronic cells at the DFEP, $E = (\frac{A}{a_0}, 0, 0, 0, 0)$ are shown below:

$$F = \begin{pmatrix} \frac{\beta A}{a_0} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad V = \begin{pmatrix} -\beta_0 - \gamma - \varphi & 0 & 0 \\ \gamma & -\gamma_0 & 0 \\ \varphi & 0 & -\varphi_0 \end{pmatrix}$$

The inverse (V^{-1}) of the Jacobean matrix, V is given as

$$V^{-1} = \begin{pmatrix} \frac{1}{\beta_0+\gamma+\varphi} & 0 & 0 \\ \frac{\gamma}{\gamma_0(\beta_0+\gamma+\varphi)} & \frac{1}{\gamma_0} & 0 \\ \frac{\varphi}{\varphi_0(\beta_0+\gamma+\varphi)} & 0 & \frac{1}{\varphi_0} \end{pmatrix}$$

$$FV^{-1} = \begin{pmatrix} \frac{\beta A}{a_0(\beta_0+\gamma+\varphi)} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

The eigenvalue of FV^{-1} is given as $|FV^{-1} - I\lambda| = 0$

$$\begin{vmatrix} \frac{\beta A}{a_0(\beta_0+\gamma+\varphi)} - \lambda & 0 & 0 \\ 0 & 0-\lambda & 0 \\ 0 & 0 & 0-\lambda \end{vmatrix} = 0$$

The basic reproduction number, R_0 is the maximum eigenvalue (i.e. max ($|\lambda|$))

Hence, $R_0 = \frac{\beta A}{a_0(\beta_0+\gamma+\varphi)}$ (8)

The DFEP would be locally asymptotically stable if $R_0 < 1$. That is, the concentration of the leukemia cells would be decreasing until the entire cells are eliminated. On the other hand, it would be unstable if $R_0 > 1$

3.4. The Equilibrium Points

The system (3) has two distinct equilibrium points namely disease-free equilibrium point (DFEP) and endemic equilibrium, point, (EEP).

At the DFEP, all infected cells, acute cells, chronic as well as white blood due to the infusion of adoptive T- cells are absent and hence set to zero, (i.e. $y = z_a = z_c = w = 0$).

The EEPs are the steady state situations where the disease persist in the population [18].

To solve for both equilibria, all the derivatives are set to zero and the resulted equations are solved. Hence the DFEP is, $E^0 = \left(\frac{A}{a_0}, 0, 0, 0, 0\right)$ and EEEP is given by $E^*(x^*, y^*, z_a{}^*, z_c{}^*, w^*)$,

where:

$$x^* = \frac{A}{a_0 R_0} + \frac{\beta_1 z^*}{\beta}; \quad y^* = \frac{a_0\mu_1(R_0-1) - a_0\beta_1 z^*)}{\beta(\mu_1 + \beta_1 z^*)}; \quad z_a{}^* = \frac{a_0\gamma\mu_1(R_0-1) - a_0\beta_1\gamma z^*)(b_0 + b_1 z^*)}{((\gamma_0 b_0 + \gamma_0 b_1 z^*) + (B + bz^*)\gamma_1)(\beta_0\beta + \gamma + \varphi + \beta_1\beta z^*)};$$

$$z_c{}^* = \frac{a_0\varphi\mu_1(R_0-1) - a_0\beta_1\gamma z^*)(b_0 + b_1 z^*)}{(\omega_0 b_0 + \varphi_0 b_1 z^*) + (B + bz^*)\varphi_1)(\beta_0\beta + \gamma + \varphi + \beta_1\beta z^*)} \quad \text{and} \quad w^* = \frac{B + bz^*}{b_0 + b_1 z^*};$$

Note that, $z = z_a + z_c$, $z_c = z - z_a$ and $\mu_1 = \beta_0 + \gamma + \varphi$.

3.5. Local Stability at Disease Free Equilibrium Point (DFEP)

Lemma 1

Assume that $\alpha \in [0, 1)$ for the fractional differential system (3), then the following condition holds: the DFEP $E^0 = (\frac{A}{a_0}, 0, 0, 0, 0)$ is locally asymptotically stable if all the eigenvalues are negative.

Theorem 1

The DFEP, $E^0 = (\frac{A}{a_0}, 0, 0, 0, 0)$ is said to be asymptotically stable if $R_0 < 1$

Proof.

The eigenvalue of the Jacobian matrix $J(E^0)$ of (3) evaluated at DFE is given by the characteristic equation, $|J(E_0) - \lambda I| = 0$.

$$|J(E^0) - \lambda I| = \begin{vmatrix} -a_0 - \lambda & -\frac{\beta A}{a_0} & 0 & 0 & 0 \\ 0 & \mu_1(R_0 - 1) - \lambda & 0 & 0 & 0 \\ 0 & \gamma & -\gamma_0 - \lambda & 0 & 0 \\ 0 & \varphi & 0 & -\varphi_0 - \lambda & 0 \\ 0 & 0 & b & b & -b_0 - \lambda \end{vmatrix} = 0$$

The characteristic equation can be expressed as,

$$(-a_0 - \lambda)[(\beta_0 + \gamma + \varphi)(R_0 - 1) - \lambda](-\gamma_0 - \lambda)(-\varphi_0 - \lambda)(-b_0 - \lambda) = 0$$

Hence, the eigenvalues are, $\lambda_1 = -a_0$, $\lambda_2 = \mu_1(R_0 - 1)$, $\lambda_3 = -\gamma_0$, $\lambda_4 = -\varphi_0$ and $\lambda_5 = -b_0$

4 It could be clearly seen that all the eigenvalues are negative when $R_0 < 1$. That means that theorem 1 and lemma 1 are proved. Hence DFE, E^0 is asymptotically stable.

3.6. Local Stability at Endemic Equilibrium Point (EEP), E^*

Theorem 2

The EEP of system (3) is said to be asymptotically stable if $R_0 > 1$.

Lemma 2

Assume that $\alpha \in [0, 1)$ for the fractional differential system (3), then the following conditions hold: if the determinants of all Hurwitz matrices (H_j) of the characteristic equations are greater than zero, then the real part of all the eigenvalues of $J(E^*)$ are negative.

Proof:

The eigenvalues of Jacobian matrix, J at EEP is given by $|J(E^*) - \lambda| = 0$.

$$|J(E^*)| = \begin{vmatrix} T_1 - \lambda & -\beta x^* & 0 & 0 & 0 \\ \beta y^* & T_2 - \lambda & -\beta_1 y^* & -\beta_1 y^* & 0 \\ 0 & \gamma & T_3 - \lambda & 0 & -\gamma_1 z_a{}^* \\ 0 & \varphi & 0 & T_4 - \lambda & -\varphi_1 z_c{}^* \\ 0 & 0 & T_6 & T_6 & T_5 - \lambda \end{vmatrix} = 0$$

Where,

$T_1 = -a_0 - \beta y^*$, $T_2 = \beta x^* - \beta_0 - \gamma - \varphi - \beta_1(z_a{}^* + z_c{}^*)$, $T_3 = -\gamma_0 \gamma_1 w^*$,

$T_4 = -\varphi_0 - \varphi_1 w^*$, $T_5 = b_0 + b_1 z^*$, $T_6 = b - b_1 w^*$

The characteristic equation can be expressed as,

$$k_0 \lambda^5 + k_1 \lambda^4 + k_2 \lambda^3 + k_3 \lambda^2 + k_4 \lambda + k_5 = 0 \quad (9)$$

The determinants of Hurwitz's matrices $|H_j|$ of the above characteristic equation, for j = 1, 2, 3, 4, 5, are given below:

$|H_1| = k_1$; $|H_2| = k_1k_2 - k_3$; $|H_3| = (k_1k_5 + k_1k_2k_3) - (k_1^2k_4 + k_3^2)$;

$|H_4| = (k_1k_2k_3k_4 + 2k_1k_4k_5 + k_2k_3k_5) - (k_2^2k_1k_5 + k_1^2k_4^2 + k_3^2k_4)$ and

$|H_5| = (k_1k_2k_3k_4k_5 + 2k_1k_4k_5^2 + k_2k_3k_5^2) - (k_5^3 + k_1k_2^2k_5^2 + k_1^2k_4^2k_5 + k_3^2k_4k_5)$

For $|H_j| > 0$, then the following inequalities should hold:

$k_1 > 0$; $k_1k_2 > k_3$; $(k_1k_5 + k_1k_2k_3) > (k_1^2k_4 + k_3^2)$; $(k_1k_2k_3k_4 + 2k_1k_4k_5 + k_2k_3k_5) > (k_2^2k_1k_5 + k_1^2k_4^2 + k_3^2k_4)$ and $(k_1k_2k_3k_4k_5 + 2k_1k_4k_5^2 + k_2k_3k_5^2) > (k_5^3 + k_1k_2^2a_5^2 + k_1^2k_4^2k_5 + k_3^2k_4k_5)$

Based on Hurwitz's stability criterion, if the above inequalities are met, then the endemic equilibrium point, E^* is asymptotically stable and hence, $R_0 > 1$.

3.7. Global Stability of Disease Free Equilibrium Point, E^0.

Lemma 3

Let $\Phi(\omega(t)) \in R_+$ be a continuous and differentiable function. Then, for any time, $t \geq t_0$, the extended Volterra-type Lyapunov function,

$$_0^C\mathbb{D}_t^\alpha \Phi[\omega(t) - \omega^0 - \frac{\omega^0 \ln w(t)}{\omega^0}] \leq \left(1 - \frac{\omega^0}{\omega}\right) {}_0^C\mathbb{D}_t^\alpha \omega(t), \ \omega^0 \in R^+ \text{ for } \alpha \in (0,1). \quad (10)$$

Theorem 3

If $\alpha \in (0,1)$, then the disease-free equilibrium point, E^0 is globally asymptotically stable when $R_0 \leq 1$

Proof:

The Lyapunov function, U which is nonnegative at the DFE point, E^0 and a global minimum is constructed as $U : \Omega \to R$, where U is given by,

$$U(t) = \Phi(x(t)) + y(t) + \frac{\beta_0 + \gamma + \varphi}{\gamma} z_a + \frac{\beta_0 + \gamma + \varphi}{\varphi} z_c + w(t) \quad (11)$$

By applying the extended Volterra-type Lyapunov inequality (10) to the function (11), then it becomes:

$$_0^C\mathbb{D}_t^\alpha U(t) = {}_0^C\mathbb{D}_t^\alpha \Phi\left(x(t)\right) + {}_0^C\mathbb{D}_t^\alpha y(t) + \frac{\beta A}{a_0 \gamma R_0} {}_0^C\mathbb{D}_t^\alpha z_a(t) + \frac{\beta A}{a_0 \varphi R_0} {}_0^C\mathbb{D}_t^\alpha z_c(t) + \mathbb{D}_t^\alpha w(t)\Big]$$

$$\leq \left(1 - \frac{x^0}{x(t)}\right) {}_0^C\mathbb{D}_t^\alpha x(t) + {}_0^C\mathbb{D}_t^\alpha y(t) + \frac{\beta A}{a_0 \gamma R_0} {}_0^C\mathbb{D}_t^\alpha z_a(t) + \frac{\beta A}{a_0 \varphi R_0} {}_0^C\mathbb{D}_t^\alpha z_c(t) + \mathbb{D}_t^\alpha w(t) \quad (12)$$

By substituting the system (3) into (12) and simplifying, it becomes

$$_0^C\mathbb{D}_t^\alpha U(t) \leq -(a_0x^0 - \rho x y R_0)\frac{(x - x^0)^2}{x x^0} - \rho x y R_0 \left(\frac{x - x^0}{x^0} - 1\right) - (\beta_1 z - \mu_1)y - (\gamma_0 + \gamma_1 w)\frac{z_a \mu_1}{\gamma} - (\varphi_0 + \varphi_1 w)\frac{z_c \mu_1}{\varphi} - (b_0 + b_1 z)w + (B + bz)$$

Where $\beta = \frac{\mu_1 R_0}{x^0}$; $\rho = \frac{\mu_1}{x^0}$; $A = a_0x^0$ and $\frac{\beta x y (x - x^0)}{x} = -\frac{\beta x y (x - x^0)^2}{x x^0} + \frac{\beta x y (x - x^0)}{x^0}$

It could be seen that the inequality ${}_0^C\mathbb{D}_t^\alpha U(t) \leq 0$ may not hold when $R_0 \leq 1$, at the DFEP. For DFEP to be globally asymptotically stable, then the following conditions need to be satisfied when $R_0 \leq 1$: $a_0x^0 \geq \rho xy;\ x \leq 2x^0;\ \beta_1 z \geq \mu_1;\ B + bz \leq 0;$

3.8. Global Stability of Endemic Equilibrium Point (EEP)

Lemma 4

Let $\xi(\omega(t)) \in R_+$ be a continuous and differentiable function. Then, for any time, $t \geq t_0$, the extended Volterra-type Lyapunov function,

$${}_0^C\mathbb{D}_t^\alpha \xi[\omega(t) - \omega^* - \frac{\omega^* \ln \omega(t)}{\omega^*} \leq \left(1 - \frac{\omega^*}{\omega}\right) {}_0^C\mathbb{D}_t^\alpha \omega(t),\ \omega^* \in R^+ \text{ and } \alpha \in (0,1). \quad (13)$$

Theorem 4

If $\alpha \in (0,1)$, then the EEP is globally asymptotically stabl when $R_0 > 1$

Proof:

Similar to the global stability proof of DFEP, the Lyapunov's function, V which is nonnegative at the endemic equilibrium point, E^* and has a global minimum of T^* is construted as $V: \Omega \to R$, where V is given by

$$V(t) = \xi(x(t)) + \xi(y(t)) + \frac{\beta_0+\gamma+\varphi}{\gamma}\xi(z_a(t)) + \frac{\beta_0+\gamma+\varphi}{\varphi}\xi(z_c(t)) + \xi(w(t)) \quad (14)$$

By applying the extended Volterra-type Lyapunov inequality (13) to the function (14), it becomes:

$${}_0^C\mathbb{D}_t^\alpha V(t) = {}_0^C\mathbb{D}_t^\alpha \xi(x(t)) + {}_0^C\mathbb{D}_t^\alpha \xi(y(t)) + \frac{\mu_1}{\gamma}{}_0^C\mathbb{D}_t^\alpha \xi(z_a(t)) + \frac{\mu_1}{\varphi}{}_0^C\mathbb{D}_t^\alpha \xi(z_c(t)) + {}_0^C\mathbb{D}_t^\alpha \xi(w(t)) \leq$$
$$(1 - \frac{x^*}{x(t)}){}_0^C\mathbb{D}_t^\alpha x(t) + (1 - \frac{y^*}{y(t)}){}_0^C\mathbb{D}_t^\alpha y(t) + \frac{\mu_1}{\gamma}\left(1 - \frac{z_a{}^*}{z_a(t)}\right){}_0^C\mathbb{D}_t^\alpha + \frac{\mu_1}{\varphi}(1 -$$
$$\frac{z_c{}^*}{z_c(t)}){}_0^C\mathbb{D}_t^\alpha z_c + \left(1 - \frac{w^*}{w(t)}\right){}_0^C\mathbb{D}_t^\alpha w(t) \quad (15)$$

By substituting the system (3) and $A = a_0x^* + \beta x^*y^*$; $B = -bz^* + b_0w^* + b_1w^*z^*$, the inequality (15) becomes,

$${}_0^C\mathbb{D}_t^\alpha V(t) \leq (1 - \frac{x^*}{x(t)})(a_0x^* + \beta y^*x^* - a_0x - \beta xy) + (1 - \frac{y^*}{y(t)})(\beta xy - \beta_0 y - \gamma y - \varphi y$$
$$- \beta_1 yz) + (\frac{\mu_1}{\gamma}(1 - \frac{z_a{}^*}{z_a(t)})(\gamma y - \gamma_0 z_a - \gamma_1 z_a w) + \frac{\mu_1}{\varphi}(1 - \frac{z_c{}^*}{z_c(t)})(\varphi y$$
$$- \varphi_0 z_c - \varphi_1 z_c w)$$
$$+ \left(1 - \frac{w^*}{w(t)}\right)(-bz^* + b_0w^* + b_1z^*w^* + bz - b_0w - b_1wz) \quad (16)$$

By equating, $\beta x^*y^*\frac{(x(t)-x^*)}{x(t)} = -\beta x^*y^*\frac{(x(t)-x^*)^2}{x^*x(t)} + \beta x^*y^*\frac{(x(t)-x^*)}{x^*}$ and

$b_1z^*w^*\frac{(w(t)-w^*)}{w(t)} = -b_1z^*w^*\frac{(w(t)-w^*)^2}{w^*w(t)} + b_1z^*w^*\frac{(w(t)-w^*)}{w^*}$,

the inequality (13) is simplified as;

$${}_0^C\mathbb{D}_t^\alpha V(t) \leq -(a_0 + \beta y^*)\frac{(x(t)-x^*)^2}{x(t)} - (b_0 + b_1z^*)\frac{(w(t)-w^*)^2}{w(t)} - \beta(y - y^*)(x - x^*) - \Big(\beta_1 z -$$
$$\beta x + \frac{\beta A}{a_0R_0}\Big)(y - y^*) + \beta Ay\frac{(z_a(t)-z_a{}^*)}{a_0z_aR_0} - (\gamma_0 + \gamma_1 w)\frac{\beta A(z_a(t)-z_a{}^*)}{a_0\gamma R_0} + \beta Ay\frac{(z_c(t)-z_c{}^*)}{a_0z_cR_0} -$$
$$(\varphi_0 + \varphi_1 w)\frac{\beta A(z_c(t)-z_c{}^*)}{a_0\varphi R_0} + b_1z^*w^*\frac{(w(t)-w^*)}{w(t)} - b_1z(w - w^*) + \frac{b(z - z^*)(w(t)-w^*)}{w(t)} \quad (17)$$

It could be seen that for inequality ${}_0^C\mathbb{D}_t^{\alpha}V(t) \leq 0$ to hold when R > 1, then the following conditions need to be satisfied: $x \geq x^*$; $y \geq y^*$; $z_a \geq z_a{}^*$; $z_c \geq z_c{}^*$; $z \geq z^*$; $w \geq w^*$; $\beta Ay(z_a - z_a{}^*) \leq 0$ and $\beta Ay(z_c - z_c{}^*) \leq 0$.
Hence the endemic equilibrium point would then be globally stable.

4. Results and Discussion

Effects of Adoptive T cells on Growth of CLL and AML

Case 1: When the immune response is neglected (i.e. w = 0)
In the situation when the immune system is so weak in such a way that its response, w to the cancer cells is zero, then the endemic equilibrium values of system (3) becomes:

$$x^* = \frac{\mu_1+\beta_1 z^*}{\beta};\quad y^* = \frac{\beta A - a_0\mu_1 - a_0\beta_1 z^*}{\beta(\mu_1+\beta_1 z^*)};\quad z_a{}^* = \frac{\gamma y^*}{\gamma_0};\quad z_c{}^* = \frac{\varphi y^*}{\varphi_0};\quad w^* = 0 \qquad (18)$$

Its observed from (18) that, the level of concentration of both cancer cells, (i. e. z_a and z_c) are only controlled by the natural death. This could enable the cancer cells to grow out of bound leading to worsening of clinical condition of the patient.
Case 2: When there is no dormant membrane or immune response activation cells
(i.e. b = 0):
The immune response activator, b activates the immune system or produces the required number of white blood cells when the cancer cells relapse. So we want to consider immunotherapy by assuming that there is no immune response activation from professional antigen presenting cells. In that case the endemic equilibrium points of (3) becomes:

$$x^* = \frac{\mu_1+\beta_1 z^*}{\beta};\ y^* = \frac{\beta A - a_0\mu_1 - a_0\beta_1 z^*}{\beta(\mu_1+\beta_1 z^*}; w^* = \frac{B}{b_0+b_1 z^*};\ z_a{}^* = \frac{(\frac{\gamma}{\gamma_0})y^*}{(1+\frac{\frac{\gamma_1}{\gamma_0}B}{b_0+b_1 z^*})}; z_c{}^* = \frac{(\frac{\varphi}{\varphi_0})y^*}{(1+\frac{\frac{\varphi_1}{\varphi_0}B}{b_0+b_1 z^*})} \qquad (19)$$

It could be seen that the level of concentrations of both cancer cells (i.e. z_a, z_c) are also checked by the immune response activation as a result of infusion of adoptive T – cells, B in the blood. In view of that the equilibrium values of both cancer cells in (19) are lesser than that of (18). It implies that immunotherapy by engineered T - cells has effects on the growth of cancer cells in the blood even when no antigenicity due to cancer cells is present.
Case 3: When there no engineered T – cells Therapy (B = 0)
We want to consider a situation when the external engineered adoptive T – cell is not applied to the leukemia patient. In that case, the endemic equilibrium values of (3) are as follows:

$$x^* = \frac{\mu_1+\beta_1 z^*}{\beta};\quad y^* = \frac{\beta A - a_0\mu_1 - a_0\beta_1 z^*}{\beta(\mu_1+\beta_1 z^*)};\quad w^* = \frac{bz^*}{b_0+b_1 z^*};\ z_a{}^* = \frac{(\frac{\gamma}{\gamma_0})y^*}{(1+\frac{\frac{\gamma_1}{\gamma_0}b_1 z}{b_0+b_1 z^*})};\ z_c{}^* = \frac{(\frac{\varphi}{\varphi_0})y^*}{(1+\frac{\frac{\varphi_1}{\varphi_0}b_1 z}{b_0+b_1 z^*})} \qquad (20)$$

It's observed that the population of leukemia cells in (18) is greater than that of (20) due to the present of white blood cells. According to [19], the equilibrium value of immune cells due to external infusion of engineered T cells is normally greater than the case without immunotherapy.

5. Conclusion:

The findings show that the levels of concentrations of both AML and CML during the immunotherapy of external infusion of engineered adoptive - T cells are less than when immunotherapy engineered adoptive T – cells was not introduced. This implies that the immunotherapy of engineered adoptive T- cells has

impact on the concentration level of dual AML and CLL and hence can be applied in controlling the growth of both AML and CML.

Based on the findings, it is recommended that there should be further studies that will incorporate genetic mutations and environmental factors to provide a more comprehensive understanding of leukemia progression and treatment responses. The recommendations aim to contribute to the ongoing efforts to improve the understanding and management of leukemia, ultimately benefiting individuals affected by the disease and the broader healthcare community.

REFERENCES:

1. J. Selade-Schulman and M. Soliman What is Leukopenia or Low Blood Cell Count. Healthline Media LLC, (2023); https://www.healthline.com>health
2. Anon., Low White Blood Cell Count, Healthgrade Editorial Staff. https://www.healthgrades.com/right-care/blood-conditions/low-white-blood-cell-count, (2018). Access: June 1, 2020
3. N. Brent, A Mathematical Model of Chronic Myelogenous Leukemia", University College, Oxford University, (2000)
4. A. Manju, and S. B. Archana,, Mathematical Modeling and Analysis of Leukemia: Effect of External Engineered T Cells Infusion, Applications and Applied Mathematics, an International Journal (AAM), Issue 1, (2015), vol.10, pp. 249 – 266. Access: November 19, 2019.
5. Y. Wu, S. Liu, D. Wang, X. Yao, Acute Myeloid Leukemia Secondary to Chronic Lymphocytic Leukemia After Prolonged Chlorambucil Therapy: A Case Report Pharmacogenomics and Personalized Medicine 2023:16, pp. 401–405
6. T. Muta, T. Okamura, Y. Niho, Acute myelogenous leukemia concurrent with untreated chronic lymphocytic leukemia, int j Hematol, (2002);75, pp. 180-190. https://doi.org/10.1007/BF02982026
7. S. Ito, S. Fujiwara, K. Mashima, K. Umino, D. Minakata, H. Nakano Development of acute myeloid leukemia in patient with untreated chronic lymphocytic leukemia. Ann Hematol 2017, pp. 719-724
8. S. Garg, W. Ni, J. D. Griffin, M. Sattler, M., Chimeric Antigen Receptor T Cell Therapy in Acute Myeloid Leukemia: Trials and Tribulations, Hematol. Rep. 2023, 15, 608-626. https://doi.org/10.3390/hematolrep15040063
9. M.,Fan, L. Gao, S. Geng, J. Wang, Y. Wang, Z. Yang, L. Yu, Chimeric antigen receptors for adoptive T cell therapy in acute myeloid leukemia, Journal of Hematology & Oncology, 10:151, DOI 10.1186/s13045-017-0519-7
10. Daver, A. S. Alotaibi, V. Bücklein, M. Subklewe, T – Cell – based immunotherapy of acute myeloid leukemia: curreent concepts and future developments. Leukemia. 2021 July;35(7):1843-1863.Doi:10.1038/s41375-021-01253-x
11. P. D. Lulla, M. Mamonkin, M. K. Brenner, (2019), Adoptive Cell Therapy for Acute Myeloid Leukemia and T- cell Acute Lymphoblastic Leukemia, The Cancer Journal 25(3): p 199 - 207, 5/6 2019. | DOI: 10.1097/PPO.0000000000000376
12. G. P. Lorand, P. Radu, A. B. Eduard, T. Ciprian, A Mathematical Model of the Transition from Normal Hematopoiesis to the Chronic and Accelerated-Acute Stages in Myeloid Leukemia, http://www.mdpi.com/journal/mathematics. Access: March 11, 2020
13. F. Michor, T. P. Hughes, Y. Iwasa, S. Branford, N. P Shah, C. PL Sawyersand, M. A. Nowak, Dynamic of chronic myeloid leukemia, *Nature 435*, (2005),

14. H. Mohamed, A. Mostafa, L. Abdelkader, P. M. Laurent, Analysis of Mathematical model of leukemia, ITM Web of Conferences 4, 01005, (2015), http:// dx.doi.org/10.1051/itmconf/ 20150401005
15. B. Youcef, H. Mohamed, V. Ezio, Mathematical analysis of a B-cell chronic lymphocytic leukemia model with immune response, Applied Mathematics and Nonlinear Sciences: vol. 4, No. 2, (2019) pp. 551.
16. L. Boujallal, Stability Analysis of a Fractional Order Mathematical Model of Leukemia, International Journal of Mathematical Modelling&Computations,Vol.11,No.01. (2021)
17. M. Agarwal, A. S. Bhadauria, (2015), Mathematical modeling and analysis leukemia:effect of external engineered T cells infusion. Appl Appl Math., 10(1), (2015) pp. 249-266.
18. S. Khatun and H. A. Biwas, Modeling the effect of adoptive T cell therapy for the treatment of leukemia wileyonlinelibrary.com/journal/cmm4 © 2019 John Wiley & Sons, Ltd
19. A. Nabti, B. Ghanbari, Global stability analysis of a fractional SVEIR epidemic model. Math Meth Appl Sci. 2021;1–21. https://doi.org/10.1002/mma.7285.