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Dynamical Analysis and Optimal Control of a Mathematical Model for Breast Cancer Patients

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ABSTRACT

This research studies a mathematical model of breast cancer patient dynamics under intensive chemotherapy treatment. The model has five compartments that represent different stages of breast cancer, recovered individuals, and those who suffered side effects from chemotherapy, especially cardiotoxicity. The equilibrium point and local stability were analyzed, revealing a stable equilibrium under certain conditions. Optimal control strategies incorporating additional treatment and a ketogenic diet were applied to minimize cardiotoxicity and treatment costs. Numerical simulations using MATLAB showed that the additional treatment achieved the goal effectively. These results provide insights for optimizing breast cancer treatment protocols.

Keywords: breast cancer patient dynamics; cancer treatment optimization; chemotherapy-induced cardiotoxicity; mathematical modeling; Pontryagin's minimum principle.

INTRODUCTION

Cancer is a malignant tumor that grows rapidly and abnormally. Globally, cancer ranks first as a cause of death with approximately 10 million cancer deaths in 2020 [1]. Breast, lung, prostate, and colon cancer are the common types of cancer [1]. In 2022, WHO reported that breast cancer is the most common cancer with 670 thousand deaths and 2.3 million new cases [2]. Breast cancer does not only occur in women. Based on the existing cases, around 5-10% of the cases are men [2]. The factors that cause breast cancer are divided into modifiable factors and non-modifiable factors. The modifiable factors are obesity, smoking habits, alcohol consumption, overexposure to artificial light, chemical exposure, intake of processed food, *diethylstilbestrol* consumption, physical activity, and other drug consumption. Whereas, non-modifiable factors are women, advanced age, family history, genetic mutations, race/ethnicity, pregnancy and breastfeeding, breast tissue density, previous history of breast cancer, and radiation therapy [3].

Besides surgical removal of cancer cells, one of the treatments given to breast cancer patients is chemotherapy. Chemotherapy treatment is carried out using cancer cell-killing drugs given by mouth or injections into the patient's blood vessels [4]. Although chemotherapy plays an important role in cancer treatment, this treatment provides side effects such as cardiotoxicity (toxicity that affects the heart) [5]. Based on [6], cardiotoxicity has become the main cause of death

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in malignant cancer. [7] found that 7-27% of deaths due to cardiac dysfunction were cancer patients who suffered cardiotoxicity. In fact, the incidence of cardiac dysfunction is higher in breast cancer patients, at 72.97 per 1000 person-years [7]. Cardiotoxicity can be in the form of heart failure, coronary artery disease, valvular heart disease, and arrhythmias [6]. Cardiotoxicity is caused by exposure to chemical compounds that are toxic and cannot be determined through the dose given [5]. A class of chemotherapy drugs closely associated with cardiotoxicity is *anthracyclines* [6-9]. Anthracycline-induced cardiotoxicity can be permanent due to the death of cardiomyocytes through several biological processes [8]. As a result, although 98% of anthracycline-induced cardiotoxicity is detected within the first year after completing treatment, cardiotoxicity may also manifest months to years after completing chemotherapy [8]. Cardiotoxicity of *doxorubicin*, a type of *anthracycline*, induces apoptosis and necrosis of cardiac myocytes followed by fibrosis of the myocardium [9]. In addition, some drugs that inhibit the growth of cancer cells while giving the side effect of cardiotoxicity include *taxanes*, *alkylating* agents, small molecule *tyrosine kinase* inhibitors, and *trastuzumab* [9]. Based on the description, we know that cardiotoxicity is a problem that needs to be considered, because patients can may experience death even before recovering from cancer. Therefore, preventive measures and treatment are needed. One of the best treatments for cardiotoxicity is to prevent heart injury [10]. According to [9], treatments that can be used to prevent cardiotoxicity are *dexrazoxane*, *statins*, β-blockers, *Angiotensine Converting Enzyme* (ACE) inhibitors, and *neuregulin*-1 (NRG-1).

Cancer treatment itself does not always rely on conventional treatments such as chemotherapy. Cancer patients can also take additional treatments in an effort to improve their quality of life. One popular additional treatment is a ketogenic diet. Based on the Warburg effect, which states that tumor cells mostly obtain energy through glycolysis, several studies have suggested that additional treatment in the form of a ketogenic diet can be helpful in reducing tumor cell growth [11-13]. The ketogenic diet is a calorie-restricted diet with high fat (70%), moderate protein (20%), and low carbohydrate (10%) consumption [12]. The application of a ketogenic diet will result in a decrease in glucose supply as a food source for tumor cells, leading to the process of autophagy [11-12, 15]. In addition, the ketogenic diet can also reduce the secretion of *Tumor Necrosis Factor* (TNF-α) and increase the secretion of *Interleukin*-10 (IL-10), thereby reducing inflammation [12].

Many researchers have constructed mathematical models of cancer to understand how cancer spreads with treatment and thus help in improving healthcare. [16] formulated an anti-tumor, anti-angiogenic, and immune model as the effects of low-dose chemotherapy treatment. Furthermore, [17] analyzed the mathematical model of cancer treatment with radiotherapy followed by chemotherapy. This was done by separating the two treatments into two stages. [18] used a deterministic mathematical model to study the dynamics of cancer cells and healthy cells. Then, [4] built a model to analyze the stages of breast cancer patients. The model considers the side effects of the chemotherapy treatment carried. Different from previous studies, the mathematical model in [4] is at the human population level. In this study, it was concluded that reducing the cardiotoxic rate would improve disease-free conditions. Then, [19] developed a mathematical model to study the interaction between breast cancer cells and immune cell types and their effects when given the drug *rituximab*. Furthermore [20] used the model built by [4] to study the important characteristics of the model using data on breast cancer patients in Saudi Arabia from the years 2004 to 2016.

This research studies the dynamics model of breast cancer patients by [20]. Dynamic analysis is carried out by determining the equilibrium point and its local stability. Furthermore, control variables in the form of additional treatment and ketogenic diet are added to the model. One of the additional treatments that can be applied is *dexrazaxone*. *Dexrazaxone* works by preventing the formation of *anthracycline-iron* which is toxic [9]. The aim of optimal control is to minimize the

number of patients who suffer cardiotoxicity due to chemotherapy treatment and the costs associated with control measures. The optimal control problem is solved using the Pontryagin minimum principle. Furthermore, numerical simulations are performed using the forward-backward sweep method to determine the effect of control.

METHODS

The steps carried out for this research are as follow.

1. Construct a mathematical model based on [20].
2. Determine the equilibrium point of the model.
3. Analysis the local stability of the equilibrium point.
4. Construct a model with controls, including additional treatment and ketogenic diet.
5. Solve the optimal control problem to minimize the number of individuals experiencing cardiotoxicity using the Pontryagin's minimum principle.
6. Perform numerical simulations to support the analytical results using MATLAB software.

RESULTS

Model Construction

The dynamics model of breast cancer patients was constructed based on [20]. Each subpopulation is defined as individuals who receive hospitalization for breast cancer. After diagnosis, individuals with breast cancer are classified into stage 1 to 4 subpopulations. Then, the model has five subpopulations, including the subpopulation of breast cancer patients of stage 1 and 2 ($X(t)$), breast cancer patients of stage 3 ($B(t)$), breast cancer patients of stage 4 ($C(t)$), recovered individuals after chemotherapy treatment ($R(t)$), and the subpopulation of individuals who suffered cardiotoxicity as a side effect of chemotherapy treatment ($E(t)$). The assumptions applied are all breast cancer patients receive chemotherapy treatment and among the patients, some patient have serious conditions, recover temporarily, and suffer cardiotoxicity during the chemotherapy treatment. An illustration of the dynamics of breast cancer patients is given in Figure 1.

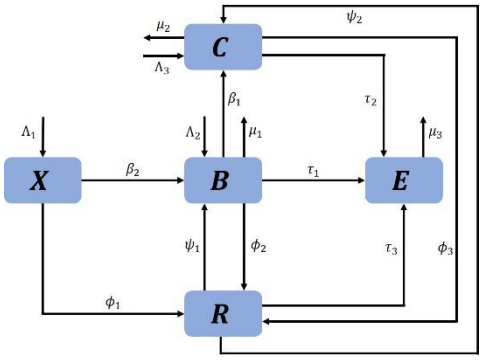


Figure 1. Compartment diagram of breast cancer model.

Individuals identified as stage 1 and 2 breast cancer patients are contained in the subpopulation $X(t)$ with the rate Λ_1. Then, some patients recovered due to chemotherapy at the rate of ϕ_1, while individuals who have worse conditions will become stage 3 breast cancer patients at the rate of β_2. Therefore, the dynamics of stage 1 and 2 breast cancer patients is given by

$$\frac{dX}{dt} = \Lambda_1 - (\phi_1 + \beta_2)X.$$

The subpopulation $B(t)$ represents all individuals identified as stage 3 breast cancer patients, either due to diagnosis at the rate of Λ_2, or because they have a worse condition at the rate of β_2. After chemotherapy treatment, some individuals are cured with rate ϕ_2. However, recovered individuals can relapse back into stage 3 breast cancer patients at the rate of ψ_1. Intensive chemotherapy treatment will cause the patient to suffer cardiotoxicity at the rate of τ_1. Individuals with worse conditions will become stage 4 breast cancer patients at the rate of β_1. There are individuals who experience cancer death at the rate of μ_1. The dynamics of stage 3 breast cancer patients is

$$\frac{dB}{dt} = \Lambda_2 + \beta_2 X + \psi_1 R - (\phi_2 + \beta_1 + \mu_1)B.$$

Individuals identified as stage 4 breast cancer patients due to diagnosis are included in the subpopulation $C(t)$ with rate Λ_3, while individuals identified due to adverse conditions have rate β_1. Some individuals recover after chemotherapy treatment with a rate of ϕ_3. However, cured individuals can return to being stage 4 breast cancer patients with a rate of ψ_2. Intensive chemotherapy treatment will cause patients to have cardiotoxicity at the rate of τ_2. In addition, some individuals experience cancer death at the rate of μ_2. Then, the dynamics of stage 3 breast cancer patients is given by

$$\frac{dC}{dt} = \Lambda_3 + \beta_1 B + \psi_2 R - (\phi_3 + \tau_2 + \mu_2)C.$$

Stage 1 and 2, 3, and 4 cancer patients are cured due to chemotherapy treatment at the rate of ϕ_1, ϕ_2, and ϕ_3 respectively. Some individuals may relapse back to stage 3 and stage 4 breast cancer patients with the rate of ψ_1 and ψ_2 respectively. Then, some individuals with disease-free conditions can experience cardiotoxicity due to chemotherapy treatment at the rate of τ_3. The dynamics of recovered individuals is

$$\frac{dR}{dt} = \phi_1 X + \phi_2 B + \phi_3 C - (\psi_1 + \psi_2 + \tau_3)R.$$

The subpopulation $E(t)$ comes from stage 3 cancer patients, stage 4 cancer patients, and disease-free individuals who receive chemotherapy treatment at the rate of τ_1, τ_2, and τ_3 respectively. In addition, some individuals with cardotoxicity experience death at the rate of μ_3. Therefore, the dynamics of cardiotoxicity patients is given by

$$\frac{dE}{dt} = \tau_1 B + \tau_2 C + \tau_3 R - \mu_3 E.$$

Then, the breast cancer patients dynamic model can be seen in the system (1).

$$\begin{aligned}
\frac{dX}{dt} &= \Lambda_1 - aX, \\
\frac{dB}{dt} &= \Lambda_2 + \beta_2 X + \psi_1 R - bB, \\
\frac{dC}{dt} &= \Lambda_3 + \beta_1 B + \psi_2 R - cC, \\
\frac{dR}{dt} &= \phi_1 X + \phi_2 B + \phi_3 C - dR, \\
\frac{dE}{dt} &= \tau_1 B + \tau_2 C + \tau_3 R - \mu_3 E.
\end{aligned} \tag{1}$$

where

$$\begin{aligned}
a &= \phi_1 + \beta_2, \\
b &= \phi_2 + \beta_1 + \tau_1 + \mu_1, \\
c &= \phi_3 + \tau_2 + \mu_2, \\
d &= \psi_1 + \psi_2 + \tau_3,
\end{aligned}$$

and nonnegative initial condition $X(0) = X_0 \geq 0,\ B(0) = B_0 \geq 0, C(0) = C_0 \geq 0, R(0) = R_0 \geq 0, E(0) = E_0 \geq 0$.

Equilibrium Points and Stability Analysis

The equilibrium point are obtained by equating equation (1) to zero. We denote the equilibrium point by P, i.e.

$$P = (X, B, C, R, E) = \left(\frac{\Lambda_1}{a}, \frac{\sigma_2}{abcd(1-M)}, \frac{\sigma_3}{abcd(1-M)}, \frac{\sigma_1}{abcd(1-M)}, \frac{\tau_1\sigma_2+\tau_2\sigma_3+\tau_3\sigma_1}{\mu_3 abcd(1-M)}\right),$$

where

$$\sigma_1 = (\Lambda_1\beta_2 + \Lambda_2 a)(\beta_1\phi_3 + \phi_2 c) + b(\Lambda_1\phi_1 c + \Lambda_3\phi_3 a),$$
$$\sigma_2 = (\Lambda_1\beta_2 + \Lambda_2 a)(cd - \phi_3\psi_2) + \psi_1(\Lambda_1\phi_1 c + \Lambda_3\phi_3 a),$$
$$\sigma_3 = (\Lambda_1\beta_2 + \Lambda_2 a)(\beta_1 d + \phi_2\psi_2) + \Lambda_1\phi_1(\beta_1\psi_1 + \psi_2 b),$$
$$M = \frac{\phi_2\psi_1}{bd} + \frac{\beta_1\phi_3\psi_1}{bcd} + \frac{\phi_3\psi_2}{cd} = \frac{\phi_2\psi_1 c + \beta_1\phi_3\psi_1 + \phi_3\psi_2 b}{bcd}.$$

We can see that the equlibrium point P exists if it satisfies $M < 1$. Then, the stability of the equilibrium point will be determined through the eigenvalues of the Jacobian matrix of system (1). By linearing the system (1), we have Jacobian matrix

$$J = \begin{bmatrix} -a & 0 & 0 & 0 & 0 \\ -\beta_2 & -b & 0 & -\psi_1 & 0 \\ 0 & -\beta_1 & -c & -\psi_2 & 0 \\ -\phi_1 & -\phi_2 & -\phi_3 & -d & 0 \\ 0 & 0 & 0 & 0 & -\mu_3 \end{bmatrix}.$$

By solving $|J(P) - rI| = 0$, we obtain eigenvalues as follow $r_1 = -a,\ r_2 = -\mu_3$, and $r_{3,4,5}$ that satisfies the equation

$$r^3 + a_1 r^2 + a_2 r + a_3 = 0, \tag{2}$$

where

$$a_1 = b + c + d,$$
$$a_2 = bc + bd + cd - \phi_2\psi_1 - \phi_3\psi_2,$$
$$a_3 = bcd - \beta_1\phi_3\psi_1 - \phi_3\psi_1 c - \phi_3\psi_2 b.$$

The equation (2) has a negative real eigenvalues if its satisfies the Routh-Hurwitz criterion, i.e.

i. $a_1 = b + c + d > 0$,

ii. $a_3 > 0$, i.e.

$$bcd - \beta_1\phi_3\psi_1 - \phi_3\psi_1 c - \phi_3\psi_2 b > 0,$$
$$bcd\left(1 - \left(\frac{\phi_2\psi_1}{bd} + \frac{\beta_1\phi_3\psi_1}{bcd} + \frac{\phi_3\psi_2}{cd}\right)\right) > 0,$$
$$bcd(1 - M) > 0,$$
$$M < 1,$$

iii. $a_1 a_2 - a_3 > 0$, i.e.

$$(b + c + d)(bc + bd + cd - \phi_2\psi_1 - \phi_3\psi_2) - (bcd - \beta_1\phi_3\psi_1 - \phi_3\psi_1 c - \phi_3\psi_2 b) > 0,$$
$$b^2 c + b^2 d + bc^2 + bd^2 + c^2 d + cd^2 + 3bcd - (\phi_2\psi_1 + \phi_3\psi_2)(b + c + d) - bcd(1 - M) > 0,$$
$$b^2(c + d) + c^2(b + d) + d^2(b + c) + bcd(2 + M) > (\phi_2\psi_1 + \phi_3\psi_2)(b + c + d). \tag{3}$$

Since all parameters and a_1 are positive, then P is asymptotically stable if $M < 1$ and inequality (3) are satisfied. To support the results of the analysis, the behavior of the solution will be illustrated through numerical simulations in the next session.

Optimal Control

In this section, a model with control will be built. Based on the previous description, it is known that chemotherapy treatment in cancer patients can cause cardiotoxicity. Therefore, a dynamic model of breast cancer patients with control in the form of additional treatment and a ketogenic diet is created. Additional treatment is added as a form of prevention against cardiotoxicity, while the ketogenic diet is intended to suppress tumor cell growth so that the patient's cancer stage does not increase. The control of additional treatment and ketogenic diet are represented by $u_1(t)$ and $u_2(t)$, respectively. Then, the model with controls applied is

$$\begin{aligned}
\frac{dX}{dt} &= \Lambda_1 - \Big(\phi_1 + \beta_2\big(1-u_2(t)\big)\Big)X,\\
\frac{dB}{dt} &= \Lambda_2 + \beta_2\big(1-u_2(t)\big)X + \psi_1 R - \big(\phi_2 + \beta_1\big(1-u_2(t)\big) + \tau_1\big(1-u_1(t)\big) + \mu_1\big)B,\\
\frac{dC}{dt} &= \Lambda_3 + \beta_1\big(1-u_2(t)\big)B + \psi_2 R - \big(\phi_3 + \tau_2\big(1-u_1(t)\big) + \mu_2\big)C,\\
\frac{dR}{dt} &= \phi_1 X + \phi_2 B + \phi_3 C - \Big(\psi_1 + \psi_2 + \tau_3\big(1-u_1(t)\big)\Big)R,\\
\frac{dE}{dt} &= \tau_1\big(1-u_1(t)\big)B + \tau_2\big(1-u_1(t)\big)C + \tau_3\big(1-u_1(t)\big)R - \mu_3 E.
\end{aligned} \tag{4}$$

This optimal control aims to find the most effective treatment strategy for minimizing the number of patients who suffer cardiotoxicity and the treatment cost. The objective function of the optimal control problem is

$$\mathcal{J} = \int_0^T A_1 E(t) + \tfrac{A_2}{2}u_1(t)^2 + \tfrac{A_3}{2}u_2(t)^2 dt, \tag{5}$$

where A_1, A_2, and A_3 denote the weight of cardiotoxicity patients, additional treatment controls, and ketogenic diet controls respectively.

Based on Pontryagin minimum principle, the system (1), and the objective function (5), the Hamilton function is defined by

$$\begin{aligned}
\mathbb{H} = {} & A_1 + \frac{A_2}{2}u_1(t)^2 + \frac{A_3}{2}u_2(t)^2\\
& + \lambda_1\Big(\Lambda_1 - \Big(\phi_1 + \beta_2\big(1-u_2(t)\big)\Big)X\Big)\\
& + \lambda_2\big(\Lambda_2 + \beta_2\big(1-u_2(t)\big)X + \psi_1 R\\
& \qquad - \big(\phi_2 + \beta_1\big(1-u_2(t)\big) + \tau_1\big(1-u_1(t)\big) + \mu_1\big)B\big)\\
& + \lambda_3\big(\Lambda_3 + \beta_1\big(1-u_2(t)\big)B + \psi_2 R - \big(\phi_3 + \tau_2\big(1-u_1(t)\big) + \mu_2\big)C\big)\\
& + \lambda_4\Big(\phi_1 X + \phi_2 B + \phi_3 C - \Big(\psi_1 + \psi_2 + \tau_3\big(1-u_1(t)\big)\Big)R\Big)\\
& + \lambda_5\big(\tau_1\big(1-u_1(t)\big)B + \tau_2\big(1-u_1(t)\big)C + \tau_3\big(1-u_1(t)\big)R - \mu_3 E\big)
\end{aligned}$$

with λ_i, $i = 1,2,\ldots,5$ are the adjoint variables that satisfy

$$\begin{aligned}
\frac{d\lambda_1}{dt} &= -\frac{\partial \mathbb{H}}{\partial X} = -\big[-\lambda_1\big(\phi_1 + \beta_2(1-u_2(t))\big) + \lambda_2\beta_2(1-u_2(t)) + \lambda_4\phi_1\big],\\
\frac{d\lambda_2}{dt} &= -\frac{\partial \mathbb{H}}{\partial B} = -\big[-\lambda_2\big(\phi_2 + \beta_1\big(1-u_2(t)\big) + \tau_1\big(1-u_1(t)\big) + \mu_1\big)\\
&\qquad + \lambda_3\beta_1\big(1-u_2(t)\big) + \lambda_4\phi_2 + \lambda_5\tau_1\big(1-u_1(t)\big)\big],\\
\frac{d\lambda_3}{dt} &= -\frac{\partial \mathbb{H}}{\partial C} = -\big[-\lambda_3\big(\phi_3 + \tau_2\big(1-u_1(t)\big) + \mu_2\big) + \lambda_4\phi_3 + \lambda_5\tau_2\big(1-u_1(t)\big)\big],\\
\frac{d\lambda_4}{dt} &= -\frac{\partial \mathbb{H}}{\partial R} = -\Big[\lambda_2\psi_1 + \lambda_3\psi_2 - \lambda_4\Big(\psi_1 + \psi_2 + \tau_3\big(1-u_1(t)\big)\Big) + \lambda_5\tau_3\big(1-u_1(t)\big)\Big],\\
\frac{d\lambda_5}{dt} &= -\frac{\partial \mathbb{H}}{\partial E} = -[A_1 - \lambda_5\mu_3],
\end{aligned}$$

where $\lambda_i(T) = 0, i = 1,2,\ldots,5$ are the transversal condition. Then, the optimal control is given by

$$u_1^*(t) = \min\left\{\max\left\{\frac{\tau_1 B(\lambda_5 - \lambda_2) + \tau_2 C(\lambda_5 - \lambda_3) + \tau_3 R(\lambda_5 - \lambda_4)}{A_2}, 1\right\}, 0\right\},$$

$$u_1^*(t) = \min\left\{\max\left\{\frac{\beta_2 X(\lambda_2 - \lambda_1) + \beta_1 B(\lambda_3 - \lambda_2)}{A_3}, 1\right\}, 0\right\}.$$

In the next section, numerical simulations are performed to illustrate the behavior of the model solution when control is applied.

Numerical Simulation

In this section, numerical simulation of the model solution is performed to illustrate the results that has been carried out. Numerical simulation were performed using the Runge-Kutta 4th order method with parameter values in Table 1 and the initial condition $X(0) = 30{,}000, B(0) = 12{,}300, C(0) = 783, R(0) = 334, E(0) = 10$.

Based on parameter values in Table 1, we have $M = 0.090462 < 1$ and the inequality (3) gives $0.401425 > 0.016968$. Then, by using MATLAB software, we can see the behaviour of the model solution in Figure 2. Based on Figure 2, we can see that each compartment goes to $(218{,}750; 17{,}889; 61{,}827; 27{,}050; 475{,}730)$ which is the equilibrium point P. Then, it is proven that equilibrium point P is asymptotically stable.

Table 1. Parameter values.

Description	Symbol	Value (people/time)	Source
Recruitment rate of stage 1 and 2 breast cancer patients	Λ_1	14,000	[18]
Recruitment rate of stage 3 breast cancer patients	Λ_2	80	[18]
Recruitment rate of stage 4 breast cancer patients	Λ_3	90	[18]
Transformation rate of stage 3 breast cancer patients into stage 4	β_1	0.01	[18]
Transformation rate of stage 1 and 2 cancer patients into stage 3	β_2	0.034	[18]
Recovery rate of stage 1 and 2 breast cancer patients due to chemotherapy	ϕ_1	0.03	[18]
Recovery rate of stage 3 breast cancer patients due to chemotherapy	ϕ_2	0.4	[18]
Recovery rate of stage 4 breast cancer patients due to chemotherapy	ϕ_3	0.01	[18]
Relapse-free individual rate for being a stage 3 breast cancer patients	ψ_1	0.03	[18]
Relapse-free individual rate for being a stage 4 breast cancer patient	ψ_2	0.3	[18]
Cardiotoxic rate for stage 3 breast cancer patients due to intensive chemotherapy treatment	τ_1	0.03	[18]
Cardiotoxic rate for stage 4 breast cancer patients due to intensive chemotherapy treatment	τ_2	0.1	[18]
Cardiotoxic rate for recovered individuals due to intensive chemotherapy treatment	τ_3	0.2	[18]
Cancer death rate at stage 3	μ_1	0.0256	[18]
Cancer death rate at stage 4	μ_2	0.0256	[18]
Death rate due to cardiotoxicity	μ_3	0.0256	[18]

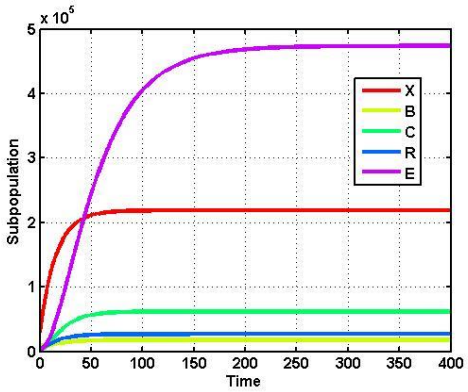
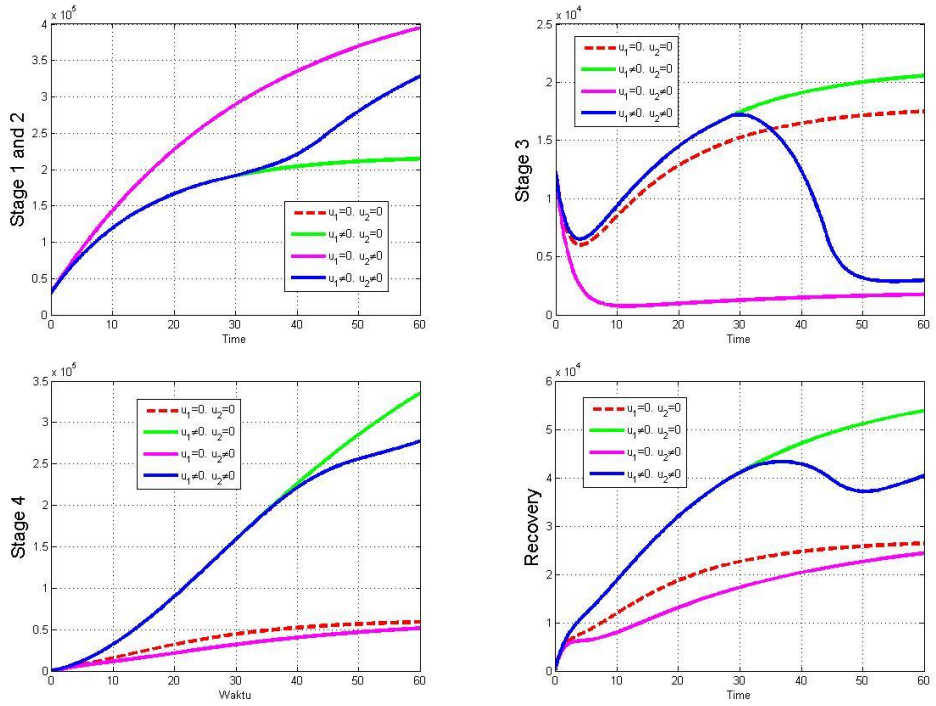


Figure 2. Numerical simulation of *P*.

We use forward-backward sweep method and MATLAB software to illustrate the behavior of solutions with the parameter values in Table 1 and the weighted values $A_1 = 2$, $A_2 = 3$, and $A_3 = 3$. There are two controls in system (4). Thus, the simulation of optimal control are divide into three strategy: only additional treatment (strategy A), only ketogenic diet (strategy B), and the combination of additional treatment and ketogenic diet (strategy C). Numerical simulations are conducted with the same initial condition values.

Figure 3 show the result of numerical simulation when control are applied. It can be seen that applying u_1, the additional treatment, the number of cardiotoxicity subpopulations decreases, while the number of recovered individuals increases. However, the number of stage 3 and 4 breast cancer patients increased. Then applying u_2, ketogenic diet, is good at reducing the number of stage 3 and 4 breast cancer patients. In addition, the number of recovered individuals in this strategy is decreased.



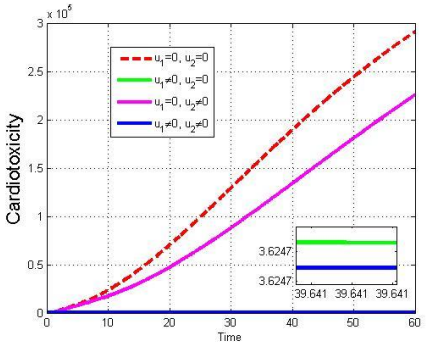


Figure 3. Numerical simulation with control.

The combination of additional treatment and ketogenic diet showed the greatest reduction in the cardiotoxicity subpopulation. However, it can be seen that the recovered individuals decreased slightly at the end. Then, we show the objective function values of each strategy in Tabel 2. This objective function value indicates how well the control strategy is at achieving a goal. Since the goal of the control problem is to minimize individual cardiotoxicity and treatment costs, the smaller the objective function value, the more optimal the treatment strategy. Although the cardiotoxicity subpopulation in strategy B decreases, this strategy is not good enough to reach the goal. This is shown by the objective function value of strategy B (11,548,172.688875) which is quite large compared to other strategies. Based on Table 2, we can also see that the objective function value of strategy C (732.579827) was greater than the objective function value of strategy A (703.043556). As a result, it can be concluded that the most effective strategy in achieving the goal of reducing cardiotoxicity subpopulation and treatment costs is strategy A, which has the smallest objective function value among the other strategies.

Table 2. Objective function values of each strategy.

Objective Function Value (Strategy)		
A	B	C
703.043556	11,548,172.688875	732.579827

DISCUSSION

This study shows the effectiveness of a treatment in breast cancer patients using an optimal control approach. Initially, the dynamic analysis is carried out on the model in the form of a system of ordinary differential equations so that one equilibrium point is obtained that exists and is stable under certain conditions. This result is in compliance with research conducted by [20]. Then, based on previous research, it is known that the side effect of chemotherapy, cardiotoxicity, greatly affects the patient's life as well as the cancer itself. As a result, optimal control was conducted to determine which treatment was most effective among the additional treatment (*dexrazaxone*) and the ketogenic diet. Based on Figure 3, only applying additional treatment or its combination with the ketogenic diet is good in reducing cardiotoxicity. However, only applying the additional treatment was better in improving individual recovery. This also supported by the objective function value of strategy A which has the smallest value compared to other strategies (Table 2). These findings contribute to the development of breast cancer models with cardiotoxicity effects at the patient level. Considering that there is not much research on this topic, further research can be done by exploring treatments related to chemotherapy-induced cardiotoxicity.

CONCLUSIONS

The breast cancer patient dynamics model is a model with five compartments, namely the subpopulation of stage 1 and 2 breast cancer patients ($X(t)$), the subpopulation of stage 3 cancer patients ($B(t)$), the subpopulation of stage 4 cancer patients ($C(t)$), the subpopulation of cured patients ($R(t)$), and the subpopulation of cardiotoxic patients ($E(t)$). In this model, there is one equilibrium point that exists if $M < 1$ and is asymptotically stable under certain conditions. Then, control variables were added to the model in the form of additional treatments and a ketogenic diet. Based on the numerical simulation results, it can be concluded that the additional treatment strategy is the most effective strategy in reducing cardiotoxicity and treatment costs. This is also shown by the objective function value which has the smallest value compared to other strategies. In future research, it is recommended to add parameters that represent the natural death rate, and test the model using actual patient data.

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