AIMS Mathematics, 5(4): 3446–3455.
DOI:10.3934/math.2020223
Received: 25 February 2020
Accepted: 12 March 2020
Published: 07 April 2020

http://www.aimspress.com/journal/Math

Research article

Mathematical modeling of ER-positive breast cancer treatment with AZD9496 and palbociclib

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Abstract: Breast cancer is a heterogeneous disease. Understanding the tumor subtypes can help identify the best option of treatment. Mathematical modeling of tumor growth is a useful tool to understand the observed clinical phenomena. This work is based on a previously published mathematical model of breast cancer in MCF-7 cell line. In this paper, cancer therapy using AZD9496 and palbociclib is incorporated into the mathematical model. Numerical results produced using the mathematical model are compared with those observed in clinical and experimental studies. Numerical simulation shows that monotherapy with AZD9496 can inhibit the growth of a tumor with a restricted tumor size, monotherapy with palbociclib is ineffective, and combination therapy with AZD9496 and palbociclib can produce synergistic effect and control a larger tumor.

Keywords: breast cancer; MCF-7 cell line; cancer treatment; mathematical modeling; mathematical simulation
Mathematics Subject Classification: 37N25, 92B05, 92D25

1. Introduction

Breast cancer is the second most commonly diagnosed cancer in women worldwide. Approximately 75% of breast cancers are estrogen receptor positive (ER+) [1]. Estrogen receptors are activated by estradiol binding leading to tumor growth. Standard treatment for ER+ breast cancer involves the use of endocrine therapy after surgery or chemotherapy [2,3] to reduce the risk of breast cancer relapse and lead to prolonged life. There are two types of Endocrine therapy for breast cancer including drugs that lower estrogen levels and drugs that block ERs on breast cancer cells. The aromatase inhibitors (AIs) inhibit estrogen biosynthesis leading to reduction of estradiol (E2) levels. The selective ER modulators (SERMs) block ERs and reduce ER activity. The best known SERM is tamoxifen which binds to the ER and modulates its function leading to reduction of tumor cell division rate and slows tumor growth.

Tamoxifen has been proven to be effective but most patients eventually develop resistance resulting in tumor recurrence [2–6]. It has been reported that tamoxifen may switch the mode of action from antagonism to agonism promoting turmor growth [7].

Fulvastrant is the first selective ER degrader (SERD), a pure antagonist which blocks and damages ERs, approved by FDA in 2002 [8]. It has been shown that fulvastrant has higher affinity for ERs than tamoxifen [3] and has been proven to be effective in patients with ER+ breast cancer after progression on other endocrine therapies such as tamoxifen or AIs [4, 9]. The maximum feasible dose for fulvestrant is 500 mg given by monthly intramuscular injections [7, 10, 11]. However, fulvestrant gives low bioavailability and a long period of time (3-6 months) to reach steady state plasma concentration [5, 10]. These disadvantages of fulvestrant result in limitations in its clinical benefit. Therefore, there has been a compelling clinical need to develop oral SERDs to overcome these limitations [4, 9].

AZD9496 is a new oral SERD and is a potent antagonist and degrader of ERs with high oral bioavailability, rapid absorption [5, 9, 10]. Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors in combination with endocrine therapy have shown increased progression-free survival in ER+ breast cancer compared with endocrine therapy alone [5, 12, 13]. Experimental study by Weir et al [5] has shown that AZD9496 gives greater tumor growth inhibition compared with fulvestrant. Further study has shown tumor regression in combination therapy using AZD9496 and CDK4/6 [5].

A mathematical model of tumor growth in MCF-7 breast cancer cell line with interaction among the cancer cells and immune cells has been developed by Wei [14]. The model was based on several experimental results using MCF-7 breast cancer cells. Multistability which resembles the 3 E's of cancer immunoediting (elimination, equilibrium, and escape) was observed in the mathematical model. In this study, treatment terms are to be incorporated into the mathematical model for the study of outcome of treatment using combination therapy with AZD9496 and CDK4/6. To provide details, the mathematical model is presented in Section 2. Numerical simulations and discussion are given in Section 3. Finally, a brief conclusion is made in Section 4.

2. Mathematical model

2.1. Formulation of AZD9496 dynamics

A first-in-human study of AZD9496 has reported a mean terminal half-life ($t_{1/2}$) of 1.4 to 5.7 hours and a rapid absorption with a median t_{max}, the time to reach the peak plasma concentration, of 1.33-3.00 hours [9,10]. Let U in mg be the amount of AZD9496 in the body but has not entered the circulation, Z in mg the amount of AZD9496 in the circulation, α_7 the absorption rate constant, and β_7 the elimination rate constant. The dynamics of AZD9496 are described by the following equations:

$$\frac{dU}{dt} = -\alpha_7 U, \tag{2.1}$$

$$\frac{dZ}{dt} = \alpha_7 U - \beta_7 Z. \tag{2.2}$$

The value for β_7 is determined by $\ln 2/t_{1/2}$. If $t_{1/2} = 3.5$, then $\beta_7 = \ln 2/(3.5/24) = 4.7541$. The value for α_7 is obtained by solving Eqs. (2.1) and (2.2) followed by setting $Z'(t_{max}) = 0$ to find α_7. This gives $\alpha_7 = 24.3659$.

2.2. Formulation of palbociclib dynamics

Palbociclib, which has been shown to arrest tumor growth, is a CDK4/6 inhibitor administered orally and absorbed slowly from intestine in 6-12 hours with a median $t_{max} = 5.5$ ranging from 2.0 to 9.8, a terminal terminal half life of 25.9 ± 7.5 (mean±SD) hours, and a bioavailability of 46% [15]. Let P in mg be the amount of palbociclib in the body but has not entered the circulation, Q in mg the amount of palbociclib in the circulation, α_8 the absorption rate constant, and β_8 the elimination rate constant. The dynamics of palbociclib are described by the following equations:

$$\frac{dP}{dt} = -\alpha_8 P, \tag{2.3}$$

$$\frac{dQ}{dt} = k_1\alpha_8 P - \beta_8 Q. \tag{2.4}$$

The parameter values $\alpha_8 = 14.1512$ and $\beta_8 = \ln 2/1.08 = 0.64$ are obtained in a similar way used in Section 2.1. Because the bioavailability of palbociclib is 46%, about half amount of the drug enters the circulation and $k_1 = 0.5$ is used throughout the paper.

2.3. Mathematical model with treatment

Let α_9 and α_{10} be the constants for tumor growth inhibition induced by palbociclib and AZD9496, respectively. The combination treatment using AZD9496 and palbociclib incorporated into the mathematical model proposed by Wei [14] is as follows:

$$\begin{aligned}\frac{dT}{dt} &= T(ae^{-\alpha_9 Q} + \frac{ce^{-\alpha_{10}Z}ET}{1+\alpha_1 E+\beta_1 T^2})(1-T/K) - \frac{p_1 TN^2}{1+\alpha_2 T+\beta_2 N^2} \\ &\quad -\frac{p_6 T^2 L}{1+\alpha_6 T^2+\beta_6 L}.\end{aligned} \tag{2.5}$$

$$\frac{dN}{dt} = eC - fN - p_2 NT + \frac{p_3 NT}{1+\alpha_3 T+\beta_3 N}, \tag{2.6}$$

$$\frac{dC}{dt} = \alpha - \beta C, \tag{2.7}$$

$$\frac{dL}{dt} = (p_4 L_N + \frac{p_5 I}{\alpha_4 + I}L)(1-L/K_L)\frac{T}{\alpha_5+T} - dL, \tag{2.8}$$

$$\frac{dU}{dt} = -\alpha_7 U + \sum_{i=0}^{M_1} s_i\delta(t_{1i}), \quad 0 \le t_{10} < t_{11} < \cdots < t_{1M_1} \tag{2.9}$$

$$\frac{dZ}{dt} = \alpha_7 U - \beta_7 Z, \tag{2.10}$$

$$\frac{dP}{dt} = -\alpha_8 P + \sum_{i=0}^{M_2} v_i\delta(t_{2i}), \quad 0 \le t_{20} < t_{21} < \cdots < t_{2M_2} \tag{2.11}$$

$$\frac{dQ}{dt} = 0.5\alpha_8 P - \beta_8 Q, \tag{2.12}$$

$$E(t) = \tilde{E}(t-n\tau), \quad t \in [n\tau, (n+1)\tau), \quad n = 0, 1, 2, \cdots, \tag{2.13}$$

where $E(t)$ is a periodic function and t is in days. The variables and parameter values are summarized in Table 1. The parameter values α_9 and α_{10} are to be determined using experimental data.

Table 1. Parameter values in Eqs. (2.5)-(2.13).

Parameter/ Variable	Value	Units	Description
T	Variable	Cell	MCF-7 tumor cell population
N	Variable	Cell L^{-1}	NK cell population
C	Variable	Cell L^{-1}	WBC population
L	Variable	Cell L^{-1}	CTL population
E	Variable	pmol L^{-1}	Estradiol in circulation
U	Variable	mg	AZD9496 not in circulation
Z	Variable	mg	AZD9496 in circulation
P	Variable	mg	Palbociclib not in circulation
Q	Variable	mg	Palbociclib in circulation
a	0.066	Day^{-1}	Tumor growth rate
c	0.00147	L $Cell^{-1}$ Day^{-1} $pmol^{-1}$	Tumor growth rate induced by E2
α_1	0.507	L $pmol^{-1}$	Half saturation constant
β_1	7.08×10^{-8}	$Cell^{-2}$	Half saturation constant
K	10^9	Cell	Tumor cell carrying capacity
p_1	8.7×10^{-4}	L^2 $Cell^{-2}$ Day^{-1}	NK induced tumor death
α_2	7×10^6	$Cell^{-1}$	Half saturation constant
β_2	5.4×10^{-5}	L^2 $Cell^{-2}$	Half saturation constant
β	6.3×10^{-3}	Day^{-1}	WBC death rate
α	5×10^7	Cell L^{-1} Day^{-1}	WBC production rate
e	0.00486	Day^{-1}	Fraction of WBCs becoming NK cells
f	0.0693	Day^{-1}	NK cell death rate
p_2	3.42×10^{-6}	Cell Day^{-1}	NK cell inactivation by tumor cells
p_3	1.87×10^{-8}	Cell $^{-1}$ Day^{-1}	NK cell recruitment rate
α_3	1.6×10^{-5}	$Cell^{-1}$	Half saturation constant
β_3	3.27	L $Cell^{-1}$	Half saturation constant
p_6	2.04×10^{-3}	L $Cell^{-2}$ Day^{-1}	CTL induced tumor death
α_6	0.268	$Cell^{-2}$	Half saturation constant
β_6	4343	L $Cell^{-1}$	Half saturation constant
L_N	2.3×10^8	Cell L^{-1}	Naive CTL population
K_L	8×10^8	Cell L^{-1}	CTL carrying capacity
p_4	9×10^{-5}	Day^{-1}	Fraction of naive CTL activated
I	2.3×10^{-11}	g L^{-1}	IL-2 concentration
α_4	2.3×10^{-11}	g L^{-1}	Half saturation constant
p_5	4.14	L $Cell^{-2}$ Day^{-1}	CTL growth rate induced by IL-2
d	0.41	Day^{-1}	CTL death rate
α_5	1000	Cell	Half saturation constant
α_7	24.3659	Day^{-1}	Absorption rate of AZD9496
β_7	4.7541	Day^{-1}	Elimination rate of AZD9496
α_8	14.1512	Day^{-1}	Absorption rate of palbociclib
β_8	0.64	Day^{-1}	Elimination rate of palbociclib
α_9	0.01	mg^{-1}	Tumor growth inhibition by palbociclib
α_{10}	0.2263	mg^{-1}	Tumor growth inhibition by AZD9496
s_i	Varies	mg	AZD9496 treatment dosage at t_{1i}
v_i	Varies	mg	Palbociclib treatment dosage at t_{2i}

A study conducted by Weir et al. [5] used an MCF-7 xenograft model to study in vivo efficacy of AZD9496 which was administered orally once daily (QD) at several selected dosages. In this fitting process, the experimental data are the tumor volumes on day 21 after treatment. Since the mathematical model has been developed for human patients, the dosages in mg/kg are converted into those for a patient of 60 kg throughout the paper. Let x_i, $i = 1, 2, \cdots, 6$ be the dosages of ADZ9496 in Figure 1 and $y_i = T(21)$ is the solution to Eqs. (2.5)-(2.13) with the initial condition

$(T(0), N(0), C(0), L(0), U(0), Z(0), P(0), Q(0)) = (8.72 \times 10^7, 2.5 \times 10^8, 4.3 \times 10^9, 6.6 \times 10^8, 0, 0, 0, 0)$ corresponding to the dosage x_i. Experimental data have shown WBC counts of $(4.3 \pm 0.8) \times 10^3$ cells/μL and lymphocyte counts of $(3.5 \pm 0.6) \times 10^3$ cells/μL of in mice [16]. Berrington et al. [17] have reported that 7% (2-13%) and 19% (13-32%) of lymphocytes are NK cells and CTLs, repectively. Therefore, $C(0) = 4.3 \times 10^9$, $N(0) = 3.5 \times 10^9 \times 0.07 = 2.5 \times 10^8$ and $L(0) = 3.5 \times 10^9 \times 0.19 = 6.6 \times 10^8$ are used in this fitting process. The parameter value for α_{10} is to be determined. It has been found in this work that Eqs. (2.5)-(2.13) with parameter values given in [14] poorly fit the data set. Therefore, parameters a, c, and α_{10} are used as fitting parameters. The result of the fitting process gives $a = 0.066$, $c = 0.00147$, and $\alpha_{10} = 0.2263$. Figure 1 shows the experimental data and the fitting curve.

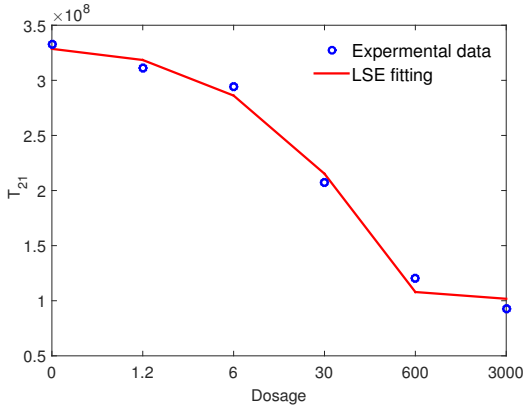

Figure 1. Curve fitting for the parameter values a, c, and α_{10}.

Weir et al. [5] also conducted an experiment to study the efficacy of combination therapy using AZD9496 and palbociclib. The result has shown that a tumor with an initial volume of 0.42 cm^3 (about 10^8 cells) reduced to that with 0.25 cm^3 (about 6×10^7 cells) after 18 days when treated with AZD9496 at 5 mg/kg QD and palbociclib at 50 mg/kg QD. Consider that the maximum tolerated dose (MTD) of palbociclib is 125 mg. The combination doses at 300 mg QD for AZD9496 and 125 mg QD for palbociclib are selected. The parameter value α_9 is determined to satisfy $T(18) = 6 \times 10^7$ by solving Eqs. (2.5)-(2.13) with $T(0) = 10^8$. This results in $\alpha_9 = 0.01003$.

3. Numerical simulation and discussion

3.1. Tumor dynamics without treatment

The system under study has a smaller intrinsic tumor growth rate, a, and a larger factor, c, of tumor growth induced by E2 than those in [14]. Recall that the system using parameter values in [14] exhibits three stable equilibria, and the immune system is able to eliminate or control a tumor smaller than 2 mm in diameter. The system under study exhibits two stable equilibria without treatment (Figure 2). They are tumor free equilibrium and large tumor equilibrium. Figures 2(a) and (b) show that the immune system is able to eliminate a tumor of 10^3 cells ($\approx$ 0.2 mm in diameter) while a tumor of 10^4 cells ($\approx$ 0.43 mm in diameter) grows large with time. Tumor population dynamics depend strongly on tumor cell properties and individual variations.

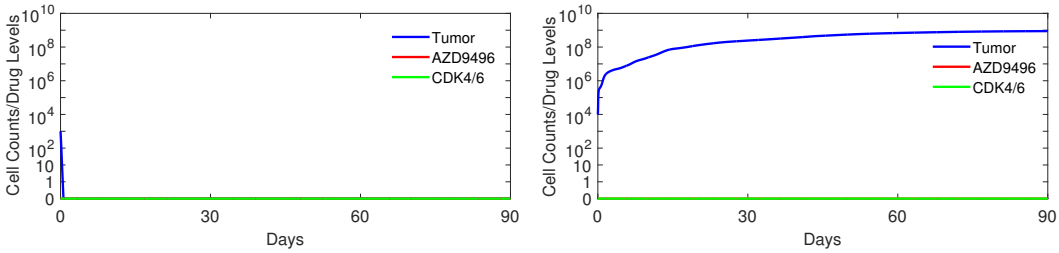

Figure 2. Tumor dynamics with initial conditions (a) $(10^3, 4\times10^8, 8\times10^9, 8\times10^8, 0, 0, 0, 0)$ and (b) $(10^4, 4\times10^8, 8\times10^9, 8\times10^8, 0, 0, 0, 0)$. Parameter values are shown in Table 1.

3.2. Tumor dynamics with monotherapy using AZD9496

Based on an MCF-7 xenograft model in mice treated with AZD9496, it was reported that a dose of 5 mg/kg is the minimum dose required for significant tumor inhibition [9]. A dose $s_i = 300$ QD is selected in the simulation and the results are shown in Figures 3(a)-(c). Figures 3(a)-(c) show that the treatment with AZD9496 at a dose of 300 mg QD is able to eliminate a tumor of 10^6 cells ($\approx$ 2 mm in diameter) and control a tumor of 10^7 cells ($\approx$ 4 mm in diameter) but the treatment fails to control a tumor of 10^8 cells ($\approx$ 9 mm in diameter). Increasing the dose s_i to 3000 mg QD still fails to control a tumor of 10^8 cells (Figure 3(d)). Experimental data [5] have shown little difference in inhibition of tumor growth between AZD9496 doses of 5 mg/kg ($s_i = 300$) and 50 mg/kg ($s_i = 3000$). Similar results have also been observed by [4].

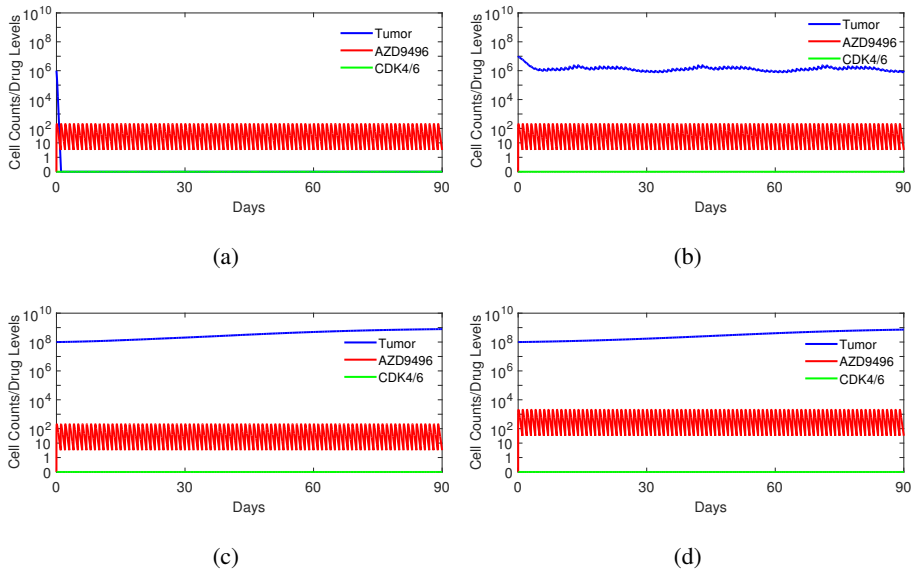

Figure 3. Tumor dynamics of monotherapy using AZD9496 with selected initial tumor cell population levels and dosages. (a) $T(0) = 10^6$ and $s_i = 300$, (b) $T(0) = 10^7$ and $s_i = 300QD$, (c) $T(0) = 10^8$ and $s_i = 300$ QD, and (d) $T(0) = 10^8$ and $s_i = 3000$ QD. Parameter values are shown in Table 1.

3.3. Tumor dynamics with monotherapy using palbociclib

The maximum dose of palbociclib used in an experimental study by Weir et al. [5] is 50 mg/kg ($v_i = 3000$) QD, which is a high dose. Figure 4 shows that monotherapy using palbociclib is ineffective. This agrees with the results in the experimental study by Weir et al. [5].

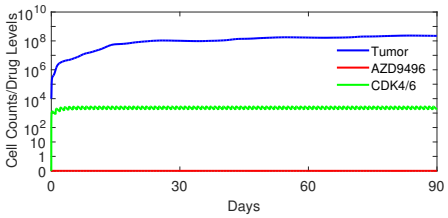

Figure 4. Tumor dynamics of monotherapy using palbociclib with $T(0) = 10^4$ and $v_i = 3000$ QD. Parameter values are shown in Table 1.

3.4. Tumor dynamics with combination therapy

Combination therapy allows the use of lower dosages of each therapy drug to reduce toxicity and overcome resistance. It can also produce synergistic effect and enhance response. In this simulation, doses $s_i = 300$ (AZD9496) QD and $v_i = 125$ (palbociclib) QD are selected. Figure 5 shows that the combination therapy can produce synergistic effect and control a tumor of 10^8 cells which would otherwise grow large when treated with monotherapy using AZD9496 or palbociblib alone.

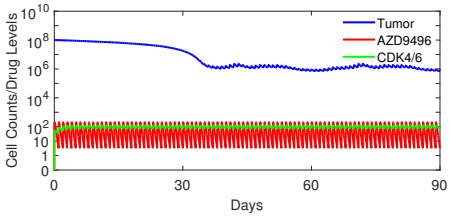

Figure 5. Tumor dynamics of combination therapy using AZD9496 and palbociclib with $T(0) = 10^8$, $s_i = 300$ QD, and $v_i = 125$ QD. Parameter values are shown in Table 1.

3.5. Variation in treatment schedule

First-in-human studies have been conducted to determine safety and tolerability for AZD9496 [9, 10]. Patients received AZD9496 in a dose escalation design with 20 mg QD to 600 mg twice daily (BID). Although the maximum tolerated dose was not reached, Hamilton et al. [9] has recommended the 250 mg BID dose for subsequent AZD9496 study. Figure 6(a) shows that monotherapy using AZD9496 alone at 250 mg BID is able to eliminate a tumor of 10^7 cells. This treatment has a better outcome than that of the treatment at 500 mg QD (Figure 6(b)). Dividing a single daily dose into two smaller doses and administered twice daily can be more effective. Furthermore, Figure 6(c) shows that AZD9496 250 mg BID combined with palbociclib 125 mg QD is able to eliminated a tumor of 10^8 cells.

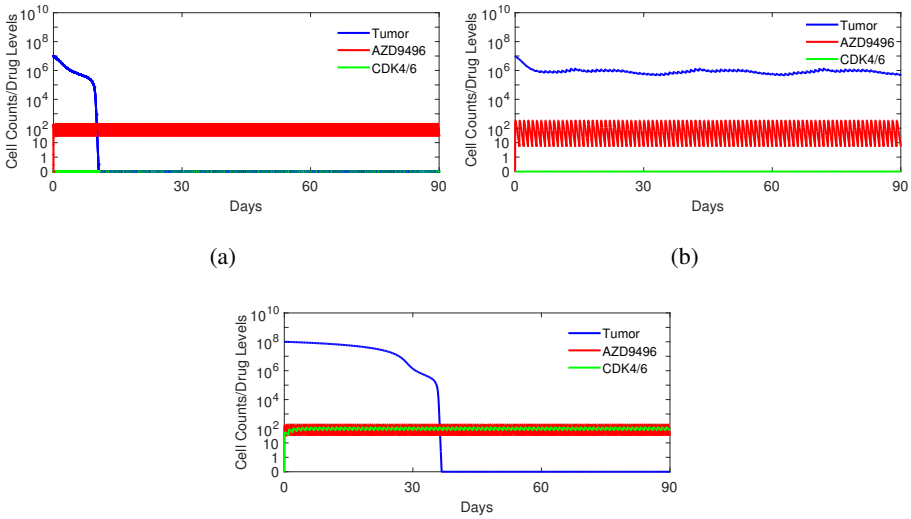

Figure 6. Tumor dynamics of combination therapy using AZD9496 twice daily and palbociclib once daily with (a) $T(0) = 10^7$ and $s_i = 250$ BID, (b) $T(0) = 10^7$ and $s_i = 500$ QD, and (c) $T(0) = 10^8$ and $s_i = 250$ BID, and $v_i = 125$ QD. Parameter values are shown in Table 1.

3.6. Variation in tumor cell proliferation rate

The doubling time of MCF-7 breast cancer cells ranges between 30 hours and several days [18,19]. A doubling time of 30 hours is corresponding to $a = ln2/(30/24) = 0.55$ while that of 10 days is corresponding to $a = ln2/10 = 0.069$. There is a large variation in the intrinsic tumor growth rate a. Assume a breast cancer with $a = 0.2$, where the doubling time is about 3.5 days. Figure 7(a) shows that combination therapy with doses $s_i = 300$ (AZD9496) QD and $v_i = 125$ (palbociclib) QD is not able to control a tumor of 10^8 cells. Increasing the dose of AZD9496 is not effective (figure not shown). Figure 7(b) shows that increasing the dose of palbociclib to 250 mg QD is able to control a tumor of 10^8 cells. However, this dose is beyond the MTD of palbociclib.

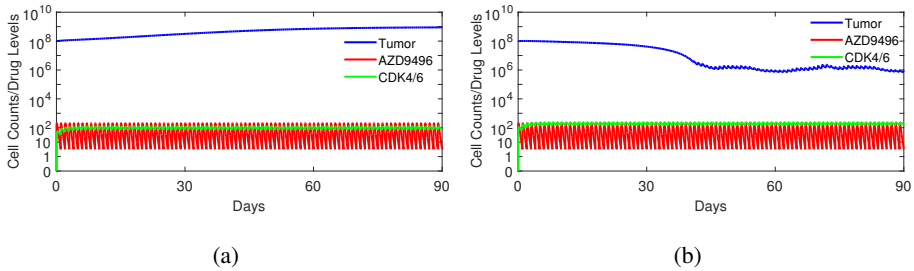

Figure 7. Tumor dynamics of combination therapy using AZD9496 and palbociclib with (a) $T(0) = 10^8$, $s_i = 300$ QD, and $v_i = 125$ QD, and (b) $T(0) = 10^8$, $s_i = 300$ QD, and $v_i = 250$ QD. Parameter values are shown in Table 1 except for $a = 0.2$.

4. Conclusion

This paper, which is based on a previously developed mathematical model [14], studies a combination therapy using AZD9496 as a degrader of ERs and palbociclib as a CDK4/6 inhibitor. Treatment terms are modeled based on clinical and experimental data and information of pharmacokinetic parameters of the above drugs [5, 9, 10, 15].

Numerical simulation shows that monotherapy using AZD9496 alone can help control a tumor with a restricted size while using palbociclib alone is ineffective. This has also been observed in the experimental study conducted by Weir [5] using an MCF-7 xenograft model in mice. A clinical trial has reported that some patients receiving AZD9496 had stable cancer [9]. Combination therapy using AZD9496 and palbociclib can generate synergistic effect and induce tumor regression for a larger tumor, which would otherwise grow large when monotherapy with either AZD9496 or palbociclib is used. This also agrees with the experimental results in [5].

A change in dosing schedule may affect the outcome of a treatment. Dividing a large single dose into two smaller doses may be more effective. Finally, an example with a larger tumor cell proliferation rate is studied. Numerical simulation shows that combination therapy can inhibit tumor growth if a lager dose, which is beyond MTD, of palbociclib is used. It is suggested that triple therapy using immunotherapy and the above two drugs may be able to treat the tumor with safety and efficacy.

Acknowledgments

This research work was supported by the Ministry of Science and Technology of Taiwan under the grant MOST107-2115-M-035-006.

Conflict of interest

The author declares no conflicts of interest in this paper.

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