Mathematical Models for Absorption and Efficacy of Ovarian Cancer Treatments*

Jianmin Zou[1] and Stephen Gundry[1] and Emir Ganic[2] and M. Ümit Uyar[1]

Abstract— **The creation of personal and individualized anti-cancer treatments has been a major goal in the progression of cancer discovery as evident by the continuous research efforts in genetics and population based PK/PD studies. In this paper we use our clinical decision support tool, called ChemoDSS, to evaluate the effectiveness of three treatments recommended by the NCCN guidelines for ovarian cancer using pre-clinical data from the literature. In particular, we analyze the treatments of PC (i.e., Paclitaxel and Cispaltin), DC (i.e., Docetaxel and Carboplatin), and PBC (i.e., Paclitaxel, Bevacizumab, and Carboplatin). Our in silico analysis of the ovarian cancer treatments shows that PC was the most effective regimen for treating ovarian cancer compared to DC and PBC, which is consistent with literature findings. We demonstrate that we can successfully evaluate the effectiveness of the selected ovarian cancer treatment regimens using ChemoDSS.**

I. Introduction

Cancer is a disease that typically involves cellular dysfunction, followed by an imbalance in cell proliferation and apoptosis (i.e., programmed cell death) causing abnormal cell growth, metastasis, and eventually death if not treated. It is the second leading cause of death among diseases worldwide [1]. The large degree of variability among the types of cancers and the genetic variability in cancer patients make the selection of cancer treatment complicated. Further complications are caused by the type of care (e.g. curative or palliative) that is chosen for the individual patient. Hence, oncologists are faced with the difficult decision of selecting a treatment that maximizes the effect against cancerous cells while minimizing the toxicity to the overall health of the patient. To aid practitioners worldwide, the National Comprehensive Cancer Network (NCCN) publishes clinical practice guidelines in oncology [2]. These regularly updated guidelines include treatment regimens that have been most successful in treating large groups of patients for a particular type of cancer.

To better understand tumor response to chemotherapies, tumor growth, pharmacokinetic (PK), and pharmacodynamic (PD) models are collectively used. Complicated and correlated processes of tumor growth can be modeled either empirically or functionally. Empirical models use mathematical equations to describe the tumor growth and in doing so treat the tumor cell population as a whole. On the other hand, functional models reflect the heterogeneity within tumor cell population and are based on a set of assumptions about their biological growth [3]. PK models portray the way drugs are dispersed throughout the body from the time they are absorbed until they are metabolised or excreted (i.e., PK defines exposure to the drug). PD models describe the occurrence of biological processes and the consequent effects caused by the presence of the drug concentration in the body. Characterizing the effects of anticancer drugs and relating their effects to the tumor response may be possible when tumor growth, PK, and PD models are combined [4].

In our previous work we studied tumor growth, drug metabolism, and the effectiveness of anticancer drugs as they apply to HER2+ breast cancer in pre-clinical settings [5]. In this paper, we use our decision support software, called ChemoDSS, for in silico evaluation of ovarian cancer treatments. Specifically, we evaluate three treatments recommended by the NCCN guidelines for ovarian cancer by using pre-clinical data from the literature for A2780 human ovarian cancer xenografts in athymic mice. The chemotherapies we selected were PC (i.e., Paclitaxel and Cispaltin), DC (i.e., Docetaxel and Carboplatin), and PBC (i.e., Paclitaxel, Bevacizumab, and Carboplatin). In our analysis, the exponential-linear tumor growth model was selected to define the tumor progression. Multicompartment PK models were used to define drug absorption, and the effectiveness of treatment was characterized by the signal transduction PD model. Model parameters were taken from the literature. When these parameters were not explicitly available for the models used in our analysis, they were computed from literature data using methods from our previous research in bio-inspired artificial intelligence computation techniques such as genetic algorithms and others [6]–[8]. Our in-silico analysis of the NCCN guidelines for ovarian cancer is consistent with literature findings [2].

II. PK and PD Models

A. Pharmacokinetic models

In our clinical decision support tool ChemoDSS, we use multicompartment PK models to represent the dynamics of the anti-cancer drugs moving throughout the body of the patient [5]. Different PK models can have one, two, and three compartments. The PK parameters for Cisplatin, Docetaxel, and Paclitaxel were obtained from [9]. To obtain the PK parameters from Bevacizumab [10] and Carboplatin [11], we

*The initial research used in this work was supported by U.S. Army Communications-Electronics RD&E Center contracts W15P7T-09-CS021 and W15P7T-06-C-P217, and by the National Science Foundation grants ECCS-0421159, CNS-0619577 and IIP-1265265. The contents of this document represent the views of the authors and are not necessarily the official views of, or are endorsed by, the U.S. Government, Department of Defense, Department of the Army or the U.S. Army Communications-Electronics RD&E Center.

[1]Department of Electrical Engineering, The City College of New York
[2]Department of Computer Science, The Graduate Center of the City University of New York

978-1-4244-7929-0/14/$26.00 ©2014 IEEE

evaluated concentration curves from pre-clinical data with bio-inspired artificial intelligence computation techniques established in our previous research [6]–[8]. In our in silico analysis, the drug Docetaxel was modeled using a three compartment PK model, whereas the remaining drugs were modeled using two compartment models.

B. Tumor Growth model

In our analysis we represent the tumor growth by the exponential-linear model studied in [12]. This model is useful for portraying tumor growth in pre-clinical settings since the tumor size never reaches the plateau population which is usually evident in other types of empirical models. The exponential-linear tumor growth model can be defined as follows:

$$\begin{aligned} \frac{dw(t)}{dt} &= \lambda_0 \cdot w(t) \qquad w(t) \leq w_{th} \\ \frac{dw(t)}{dt} &= \lambda_1 \qquad\quad w(t) > w_{th} \\ w(0) &= w_0 \end{aligned} \tag{1}$$

where w_0 represents the weight of the initial tumor, λ_0 is the exponential growth rate, and λ_1 is the linear rate. The variable w_{th} is a threshold of the tumor weight where the growth switches from exponential to linear.

C. Pharmacodynamic models

For our in silico analysis, the transit compartment model for signal transduction [9] was used to represent the process of drug effects on the tumor. The model has four compartments (namely, x_1, x_2, x_3, and x_4), which describe the delay between the drug intake and tumor cell death as shown in Fig. 1(a). As illustrated in Fig. 1(a), a coefficient called α is used to account for the interactions that occur when multiple drugs are administered together. At any given time, the tumor weight is distributed through the four compartments, where compartment x_1 only contains reproducing tumor cells, and remaining compartments contain the dying ones. The rate the cells move from compartment x_2 through x_4 is represented by k_1, while k_2 is the measure of drug effect for killing cancer cells. Using a set of ordinary differential equations, the entire model can be expressed as follows:

$$\frac{dx_1(t)}{dt} = \frac{\lambda_0 \cdot x_1(t)}{\left[1 + \left(\frac{\lambda_0}{\lambda_1} \cdot w(t)\right)^{\psi}\right]^{\frac{1}{\psi}}} - \alpha \cdot PK(t) \cdot x_1(t) \tag{2}$$

$$\frac{dx_2(t)}{dt} = \alpha \cdot PK(t) \cdot x_1(t) - k_1 \cdot x_2(t) \tag{3}$$

$$\frac{dx_3(t)}{dt} = k_1 \cdot [x_2(t) - x_3(t)] \tag{4}$$

$$\frac{dx_4(t)}{dt} = k_1 \cdot [x_3(t) - x_4(t)] \tag{5}$$

In Eq. (2) the tumor weight, $w(t)$, is defined as:

$$w(t) = x_1(t) + x_2(t) + x_3(t) + x_4(t) \tag{6}$$

$PK(t)$ represents the amount of cells that will be damaged from anticancer drugs as depicted in Fig. 1(b), which can be expressed as:

$$PK(t) = k_{2A} \cdot c_A(t) + k_{2B} \cdot c_B(t) + k_{2C} \cdot c_C(t) \tag{7}$$

where $c_A(t)$, $c_B(t)$ and $c_C(t)$ represent each of the drug concentrations which are computed with the appropriate PK model. Also, note that the tumor growth function in Eq. (2) (i.e., the first term in Eq. (2)) is represented by a continuous function which is equivalent to the piecewise function in Eq. (1) for large values of Ψ [9].

TABLE I
DOSING SCHEDULES FOR CHEMOTHERAPY REGIMENS

Chemotherapy	Drug	Dose	Administration Day
PC	Paclitaxel	135 mg/m^2	day 1
	Cisplatin	90 mg/m^2	day 2
	Paclitaxel	60 mg/m^2	day 8
DC	Docetaxel	70 mg/m^2	day 1
	Carboplatin	AUC 6	day 1
PBC	Paclitaxel	175 mg/m^2	day 1
	Bevacizumab	7.5 mg/kg	day 1
	Carboplatin	AUC 6	day 1

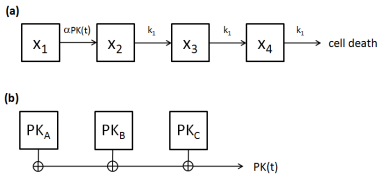

Fig. 1. Example of (a) transit four-compartment PK/PD model and (b) concentration of a multi-drug chemotherapy treatment

III. Decision Support System Software: ChemoDSS

In our Bio-Inspired Computational Laboratory at the City College of CUNY, we developed a decision support system software to study tumor growth and PK/PD models [5]. In this software system, called ChemoDSS, the artificial intelligence algorithms, mathematical models, visualization of data and the graphical user interfaces (GUI) are implemented in Java programming language.

A. Chemotherapy Management Console

Chemotherapy Management Console (CM) allows the user to enter chemotherapy treatments and anti-cancer drug related information. The GUI for the CM is illustrated in Fig. 2. CM has multiple panels allowing the user to enter specific drug parameters. *Drug Administration Panel* is in the center of the console for the users to enter the duration of the cycle, the total number of cycles, and the type of drug administration. *Drug Delivery Panel*, located on the right side of the console, will display the number of days for that cycle when the user selects the duration of the cycle.

In ChemoDSS different combinations of anti-cancer drugs can be chosen by the users, and the PK/PD parameters for each drug can be adjusted as needed. In PK *Model Panel*, various parameters can be entered, including the model type, the rate at which the drug is excreted from the body, the rate at which the drug is distributed within the body, and the volume of drug distribution. Depending on the PD model

chosen in *Tumor Response Console*, relevant PD parameters will be displayed in PD *Model Panel* of CM as shown in Fig. 2.

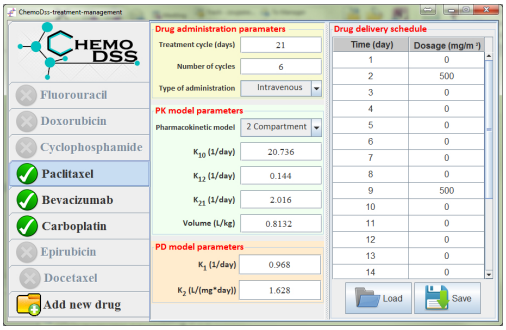

Fig. 2. GUI for Chemotherapy Management Console

B. Tumor Response Console

Using the *Tumor Response Console* (TR), the tumor growth, PK, and PD parameters can be analyzed. As shown in Fig. 3, the users can enter the exponential and linear growth rate parameters, and the initial size of the tumor for the chosen tumor growth model selected in *Tumor Growth Panel* on the top left corner. In addition, the users can choose the PD model and the drug treatment to be analyzed for *Tumor Response Panel* in the center left of the TR console. The response of the tumor and the concentration of the drug can be observed on the right-hand panel of ChemoDSS. In the TR console, users have the option of stopping the assessment at any time and can change parameters related to the existing treatment. A report with the model parameters, drug concentrations, and the tumor response graphs are produced automatically when the evaluation is completed.

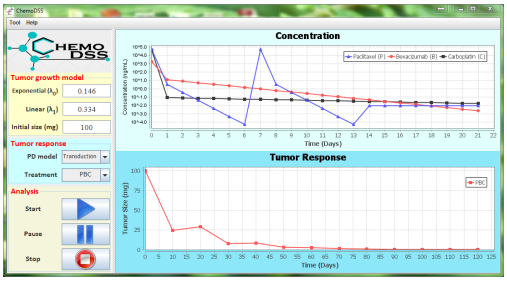

Fig. 3. GUI for Tumor Response Console

IV. In Silico Analysis

ChemoDSS evaluated the effectiveness of three treatments recommended by the NCCN guidelines for ovarian cancer. We generated multi-drug response from the drug combination of PC, DC and PBC using experimental drug response data for cell-line A2780 ovarian cancer tumors that were xenografted onto athymic mice reported in [12]. The tumor growth was modeled using an exponential-linear function as described in Sec. II. Based on the experimental data in [12], the exponential and linear growth constants and the initial tumor size were determined as $\lambda_0 = 0.146\ 1/day$, $\lambda_1 = 0.334\ g/day$, and 100 mg respectively.

TABLE II
PK/PD PARAMETERS

Type	Parameters	Pac	Cis	Doc	Car	Bev
PK	k_{10}	20.736	106.008	47.04	147.331	0.1839
	k_{12}	0.144	108.552	49.152	123.465	1.5380
	k_{21}	2.016	47.304	57.72	134.64	1.9115
	k_{13}	-	-	7.68	-	-
	k_{31}	-	-	2.736	-	-
PD	k_2	0.6288	6.36	6.648	0.2629	0.0013

The values for the PK and PD parameters used in our analysis are shown in Table II. The unit for PK parameters is $1/days$ representing the rates with which the drugs flow throughout the body. The PD values, representing the drug effectiveness, have the units $L/(mg \times days)$. The drug names where abbreviated as Pac (Paclitaxel), Cis (Cisplatin), Doc (Docetaxel), Car (Carboplatin), and Bev (Bevacizumab) in Table II.

The administered treatments of PC, DC, and PBC were analyzed using the schedules described in Table I. The anti-cancer drugs in the treatments are absorbed, dispersed, metabolised, and excreted at different rates as can be seen in Figs. 4 through 6. Figure 4 shows the drug concentration for the PC treatment in an athymic mouse for one cycle of therapy. We can observe that there are significant differences in the length of time that different drugs remain in the body. For example, the concentration of Paclitaxel reduces from 10^4 ng/mL to 10^{-2} ng/mL in approximately 4 days while Cisplatin leaves the body much quicker, in approximately one day.

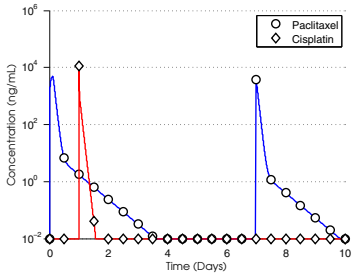

Fig. 4. Drug concentrations for PC in a preclinical mouse model

In Fig. 5 we can see the drug concentration for the treatment of DC in an athymic mouse for one cycle. The peak concentrations occur for Docetaxel and Carboplatin at approximately 10^3 ng/mL and 10^4 ng/mL, respectively. Although the peak concentration of Carboplatin is higher, it exits the body quicker than Docetaxel, in approximately 4 hours. It takes about 36 hours for the concentration of Docetaxel to leave the body which makes the total drug absorbed by the body (i.e., AUC) for these two drugs similar.

We can see in Fig. 6 the concentration values for the targeted and cytotoxic therapy combination of PBC metabo-

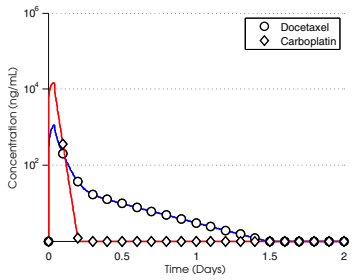

Fig. 5. Drug concentrations for DC in a preclinical mouse model

lized in an athymic mouse for one cycle of treatment. The figure demonstrates that there is a great deal of variability in the AUC of these drugs. We observe that concentration of Bevacizumab peaks at about 10^5 ng/mL and stays in the body for the duration of the whole cycle at a high concentration, slightly falling below 10^4 ng/mL. On the other hand, the concentrations of Paclitaxel and Carboplatin peak at a lower concentration and exit the body much earlier, at approximately 4 days and 8 hours, respectively.

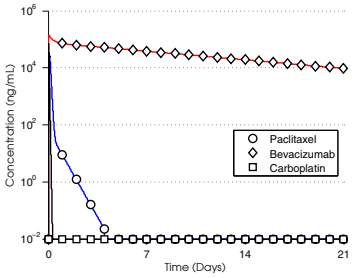

Fig. 6. Drug concentrations for PBC in a preclinical mouse model

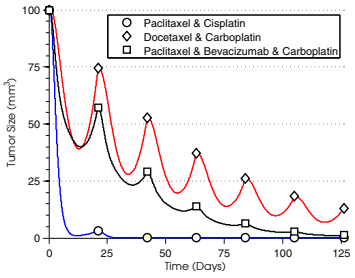

Fig. 7. Tumor response to PBC, PC and DC for ovarian cancer cells in a preclinical mouse model

Figure 7 shows the tumor response of PC, DC, and PBC after 6 cycles of treatment. We can observe that the tumor size has been reduced from 100 to 0.1 mm^3 for chemotherapy treatments of PC and PBC, while DC only reduces the tumor size to 12 mm^3. These results match with literature findings and demonstrate the regimens from NCCN guidelines for PBC, PC, and DC are effective anti-cancer treatments [2]. However, tumor response in PC appears to be preferable to PBC and DC. The tumor size decreases at the beginning of each treatment cycle for PBC and DC due to the administration of anticancer drugs. As soon as the drug concentration leaves the body, the tumor starts to grow in size for the rest of the treatment cycle. The ability for the tumor to regrow after the drugs have left the body appears to be greater for DC than it is for PBC. For PC, the tumor size decreases dramatically after a single cycle of treatment and tumor size is almost equal to zero after 28 days of treatment, where it remains until the end of the analysis.

V. Conclusions

In this paper, using our clinical decision support tool, called ChemoDSS, we evaluate the effectiveness of three treatments recommended by the NCCN guidelines for ovarian cancer with pre-clinical data from the literature. In particular, we analyzed PC, DC, and PBC. Our in silico analysis of the ovarian cancer treatments shows that PC was the most effective regimen for treating ovarian cancer compared to DC and PBC, which is consistent with literature for ovarian cancer treatments. The results of our evaluation demonstrate that we can evaluate NCCN guidelines for ovarian cancer with the help of our software tool ChemoDSS. Future versions of ChemoDSS are expected to be used with personal clinical data to aid oncologists in making treatment decisions.

References

[1] J. Harrold, R.Parker, Clinically relevant cancer chemotherapy dose scheduling via mixed-integer optimization, Computers & Chemical Engineering 33 (12) (2009) 2042–2054.

[2] Clinical practice guidelines in oncology: Ovarian cancer, National Comprehensive Cancer Network, http://www.nccn.org.

[3] P. Magni, M. Simeoni, I. Poggesi, et al., A mathematical model to study the effects of drugs administration on tumor growth dynamics, Mathematical Biosciences 200 (2) (2006) 127 – 151.

[4] P. H. Van Der Graaf, J. Gabrielsson, Pharmacokinetic-pharmacodynamic reasoning in drug discovery and early development, Future Medicinal Chemistry 1 (8) (2009) 1371–1374.

[5] E. Ganic, S. Gundry, J. Zou, M. U. Uyar, Evaluation of anti-cancer therapy using in silico analysis of treatments for HER2+ breast cancer, in: IEEE Intl. Symposium on Medical Measurements and Applications (MeMeA 2014), Lisbon, Portugal, June, 2014.

[6] S. Gundry, J. Zou, E. Urrea, C. Sahin, J. Kusyk, M. Uyar, Analysis of emergent behavior for ga-based topology control mechanism for self-spreading nodes in MANETs, in: Advances in Intelligent Modelling and Simulation, Vol. 422 of Studies in Computational Intelligence, Springer Berlin Heidelberg, 2012, pp. 155–183.

[7] C. S. Sahin, S. Gundry, M. U. Uyar, Markov chain analysis of self-organizing mobile nodes, Journal of Intelligent and Robotic Systems 67 (2012) 133–153.

[8] J. Kusyk, C. Sahin, M. Uyar, E. Urrea, S. Gundry, Self organization of nodes in mobile ad hoc networks using evolutionary games and genetic algorithms, Journal of Advanced Research (2011) 253 – 264.

[9] M. Rocchetti, M. Simeoni, E. Pesenti, et al., Predicting the active doses in humans from animal studies: A novel approach in oncology, European Journal of Cancer 43 (12) (2007) 1862 – 1868.

[10] D. K. Shah, J. Veith, R. J. Bernacki, J. P. Balthasar, Evaluation of combined bevacizumab and intraperitoneal carboplatin or paclitaxel therapy in a mouse model of ovarian cancer, Cancer chemotherapy and pharmacology 68 (4) (2011) 951–958.

[11] H. Wang, M. Li, J. J. Rinehart, R. Zhang, Pretreatment with dexamethasone increases antitumor activity of carboplatin and gemcitabine in mice bearing human cancer xenografts in vivo activity, pharmacokinetics, and clinical implications for cancer chemotherapy, Clinical cancer research 10 (5) (2004) 1633–1644.

[12] M. Simeoni, P. Magni, C. Cammia, et al., Predictive pharmacokinetic pharmacodynamic modeling of tumor growth kinetics in xenograft models after administration of anticancer agents, Cancer Research 64 (2004) 1094–1101.