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Computational determination of the optimal dose of the cis-platinum to maximize the life time of patients diagnosed with cancer

Abstract In this work, we present the results of our study over the expected lifetime of the patients diagnosed with relapsed squamous cell lung cancer (SCC) treated by cis-platinum. We developed the mathematical model which consist of cells sensitive and resistant to cis-platinum. The performed simulations suggest that the best strategy to prolong the patient lifetime after diagnosis is to keep the sensitive cells subpopulation at the constant level instead of killing all of them.

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Key words and phrases: therapy optimization, cis-platinum, cancer growth, resistance to the drug.

1. Introduction Many mathematical models of cancer growth were proposed in the past years and reviewed by Enderling and A.J. Chaplain(2014). Most of them describe the early cancer development, from a single cell, and only some describe relapsed and late-stage tumor growth [8, 10]. Also, most of the models focus on describing the chemotherapeutic treatment, where the goal is the to cure the patient.

In real cases, in the time of relapse, tumor consists of sensitive and resistant cells, where the vast majority of the cells are sensitive [13]. Moreover, both cancer cell types compete for oxygen and nutrients [3]. Because of that, the less sensitive cells in the cancer cells population are, the more oxygen and nutrients are available for the resistant subpopulation and vice versa.

Following work of [1], we investigate here the tumor progression in the case of the resistant, late-stage tumor. We chose relapsed squamous cell lung cancer (SCC), and modeled progression and chemotherapeutic treatment with

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cisplatin [15]. Here, we focus on modeling SCC patients treatment in the case when cure is impossible, and the goal is to prolong the patient's survival.

2. Methods

Cisplatin resistant cells are growing slower than the cisplatin sensitive ones [5]. To model the growth of cells as well as drug impact on the cancer cells properly, we proposed the following mathematical model:

2.1. Model structure. We constructed the mathematical model under the assumption that a lung cancer patient is diagnosed at an advanced stage with a tumor which is already resistant to cisplatin chemotherapy.

The model is governed by the following assumptions:

- tumor is composed of cisplatin-sensitive and cisplatin-resistant cells,
- at the time of recurrence, tumor is composed of $M_{relapse}$ cells, where $\sigma \cdot M_{relapse}$ cells are cisplatin-resistant and $(1-\sigma)M_{relapse}$ cells are cisplatin-sensitive,
- both types of cells growth are according to continuous Gompertzian growth dynamics with growth rates λ_s and λ_r, respectively,
- the amount of cisplatin-resistant cells is below the detection threshold and thus $\sigma = 0.01$ for nominal parameter values,
- the resources and space are limited,
- a patient dies when tumor burden reaches M_{death} cells,
- cisplatin-sensitive and cisplatin-resistant cells compete with each other for space and resources, and thus they are modeled accordingly with a coefficient of competition advantage, which equals a,
- cisplatin induces death of chemosensitive cells according to Norton-Simon law which states that the rate of tumor regression during chemotherapy is proportional to that of the unperturbed tumor growth [2],
- toxicity constraints are not included in the model.

The second assumption requires a further comment. There are two main mechanisms of resistance to cisplatin in lung cancer: the primary and secondary one [7]. Here, we focus only on the primary drug resistance and thus consider only those lung cancer patients who are cisplatin-resistant at the onset of treatment. Indeed, it is believed that the primary drug resistance in lung cancer is the dominant mechanism of cisplatin resistance in lung cancer [4, 12]. Thus, we modeled cisplatin resistance accordingly as follows. At the diagnosis, there is a small fraction of cisplatin-resistant cells, which is undetectable ($<= 10^9$ cells). It means that abundance of cisplatin-resistant cells is below standard exome or genome sequencing techniques and is detectable only through single-cell measurements such as ultra deep single-cell sequencing [14].

The above assumptions lead to the following system of ordinary differential equations:

$$\begin{aligned} \frac{d}{dt}x_s &= -\lambda_s x_s \ln\left(\frac{x_s+ax_r}{K}\right)(1-C) \\ \frac{d}{dt}x_r &= -\lambda_r x_r \ln\left(\frac{x_r+(1-a)x_s}{K}\right), \end{aligned} \tag{1}$$

where x_s and x_r are the number of cisplatin-sensitive and cisplatin-resistant cells.

Cisplatin concentration (C) is given in a.u. This form of cisplatin introduction allows for proper simulation of the drug doses which are too small to reduce the sensitive cells population growth ($C < 1$). Doses which are high enough to stop the population growth completely ($C = 1$), and finally high enough to to reduce its population size ($C > 1$).

2.2. Model parametrization All model parameters are presented in Table 1. Most of the parameters are taken from previous studies, and the rest are assumed based on the current biological knowledge. Importantly, the growth rates of cisplatin-sensitive and cisplatin-resistant cells are fitted to volumetric data presented in [9], where the doubling time of SCC cells is estimated.

Table 1: Values of parameters of the model described with Eq. (1)

Symbol	Description	Value	Reference
λ_s	growth rate of sensitive cells	0.023[1/day]	taken from [9]
λ_r	growth rate of resistant cells	0.0116[1/day]	assumed
K	carrying capacity	10^{12}	taken from [16]
a	coefficient of competition advantage	0-1	varied
$M_{relapse}$	tumor burden at diagnosis	10^{11}	taken from [9]
M_{death}	lethal tumor burden	$0.5 \cdot 10^{12}$	taken from [10]
σ	fraction of resistant cells at diagnosis	0.01	assumed
C	cisplatin concentration [A.U.]	1	estimated

3. Results. In the case of no drug application ($C = 0$), the system is in the steady state when derivatives from Eq. (1) are equal 0. It is true when x_s and x_r are equal to 0 which gives the trivial solution:

$$\begin{aligned} x_{r0} &= 0 \\ x_{s0} &= 0. \end{aligned} \tag{2}$$

or

$$\begin{aligned} \ln\left(\frac{x_s + a \cdot x_r}{K}\right) &= 0 \\ \ln\left(\frac{x_r + (1-a) \cdot x_s}{K}\right) &= 0, \end{aligned} \tag{3}$$

which means that

$$\begin{aligned} \frac{x_s + a \cdot x_r}{K} &= 1 \\ \frac{x_r + (1-a) \cdot x_s}{K} &= 1. \end{aligned} \tag{4}$$

Calculating x_s from the first line equation and putting it to the second one we may receive formulas for both x_{s0} and x_{r0} in the steady state as follows:

$$\begin{aligned} x_{r0} &= K \cdot \tfrac{a}{a^2-a+1} \\ x_{s0} &= K \cdot \tfrac{1-a}{a^2-a+1}, \end{aligned} \tag{5}$$

since $a \in <0,1>$, $x_{r0} \geq 0$, and $x_{s0} \geq 0$. One can notice that when $a = 0$, $x_{r0} = 0$ and $x_{s0} = K$ and with $a = 1$, $x_{s0} = 0$ and $x_{r0} = K$, thus coefficient a may be considered as the percentage of the resistant cells advantage over the sensitive cells in the access to resources and space [14]. One may notice that with $a = 0.5$ the steady state for both x_{s0} and x_{r0} is equal $\frac{2}{3} \cdot K$, thus $x_{s0} + x_{r0}$ may theoretically be above K but one has to remember that when the total population of cancer cells $x_s + x_r = 0.5 \cdot 10^{12}$ i.e. $\frac{1}{2} \cdot K$ a patient dies and simulation stops. So $x_s + x_r$ is always below K. In the case of the therapy, we have another solution in which $(C = 0)$. In this state, the sensitive cells population is kept at the constant level but as long as it is far from K and a is high enough the resistant cells population grows to the level given by Eq. 5.

From the model structure, one may conclude that the therapy results will depend not only on the drug dose but also on the competition advantage of the resistant cells over the sensitive ones [11]. To illustrate this we simulated our model with various values of C and a and performed heatmap presented in Fig. 1.

For the small doses of C $(C < 1)$ with the growing dosage of cisplatin, the expected time of survival also grows, while the impact of a value is negligible. For such low doses, the cisplatin only slows down the growth rate of the sensitive cells (see Fig. 2 top-right panel), but as a whole cancer population grows rather fast no matter which subpopulation has the competition advantage, thus the short lifetime of the patients ($t < 300$ days).

Surprisingly, for the $C > 1$ and $a \in (0,1)$ one can notice that the higher dose of the drug, the shorter lifetime of the patients. The effect is more visible

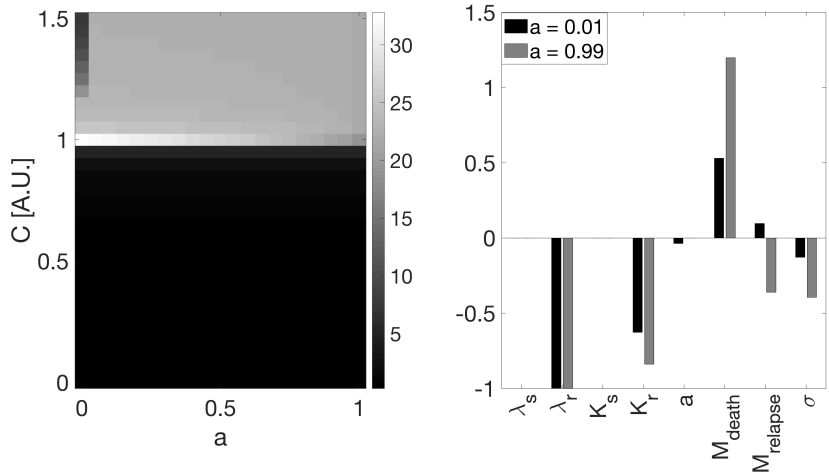

Figure 1: Heat-map of the patient life time after the diagnosis as a function of drug dose C and competition coefficient between the resistant and sensitive cell a (left). The local sensitivity analysis for nominal parameters values (Table 2.2) and two values of the competition (right).

for the lower a, i.e., when sensitive cells have higher competition advantage over the resistant ones (Fig. 3). The higher advantage of one subpopulation, fewer resources and space are available for the second one and thus slower the growth or even shortage of the second subpopulation may be observed. For the $C > 1$ derivative of x_s from Eq. 1 has a negative sign; thus, the sensitive subpopulation shrinks. The shrinking is faster for higher C, which means that more resources and space is available for the growth of resistant cells, and as can be noticed in Eq. 1 the x_r grows faster (Fig. 3 down-right). As a result, the total cancer cells population will reach the death threshold faster, and by that patient's lifetime is shorter with the higher drug doses. One can also notice that with fixed drug dose, for the smaller a, the lifetime is longer (Fig. 2). It is because when sensitive cells have an advantage over the resistant ones, even the small fraction of sensitive cells uses so many resources that the resistant subpopulation grows slower. This effect may also be noticed in the second column of Fig. 2, where simulation stops when the total number of cancer cells reach the given threshold of $0.5 \cdot 10^{12}$ cells, which is the indicator of the patient's death.

Next, we performed a sensitivity analysis to investigate which parameters influence the patient's survival (time interval from relapse to death) by using the following formula to calculate the sensitivity coefficient:

$$S_j \approx= \frac{\partial Y(p_j + \Delta p_j, t) - Y(p_j, t)}{\Delta p_j}, \tag{6}$$

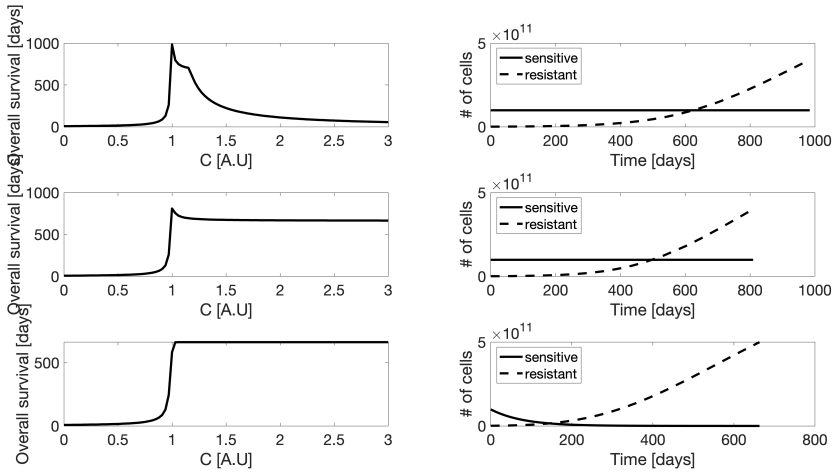

Figure 2: The time life (left column) and cancer subpopulation sizes (right column) of the patients treated with cis-platinum dose of $C = 1a.u.$ for various values of competition coefficient a. First row, $a = 0$, second row $a = 0.5$, third row $a = 1$.

where Y is patient's survival and p_j is j parameter. Interestingly, when a is small, we can observe that by increasing $M_{relapse}$, we can increase the patient's survival. That is, by delaying the chemotherapy, we can improve the patient's survival. However, for high values of a, we observe the intuitive result that the higher the tumor burden at relapse is, the smaller is the chance of patient's survival.

The longest lifetime may be observed for the $C = 1$ and small a (Figs 2 and 3 left column). In fact, when we start with the x_s and x_r such as $x_s + x_r < 0.5 \cdot 10^{12}$, i.e., cancer size is below the death threshold, and sensitive cells use most of the oxygen and nutrients, the best strategy to prolong the patients life is to keep the sensitive cells subpopulation at the constant level. It assures that the resistant subpopulation will keep in check sensitive one, and by that whole cancer will grow as slow as possible. To better understand the results, one should keep in mind that because of the form of Eq. 1 and death threshold which is set at the level of $\frac{1}{2} \cdot K$, it is not possible to completely stop or reverse the resistant subpopulation growth, which is consistent with the medical knowledge.

We can observe the interesting solution for the special cases when $a = 0$ and $a = 1$. For $a = 0$ in the case without the drug and death-related constraint $x_{r0} = 0$ and $x_{s0} = K$, because sensitive subpopulation takes all the resources. In the case with the drug, for C high enough to cause sensitive subpopulation to shrink the x_s goes to 0 and the restrictions over the x_r growth do not hold; thus x_r proliferates rapidly (Fig. 2). The higher cisplatin dose, the faster

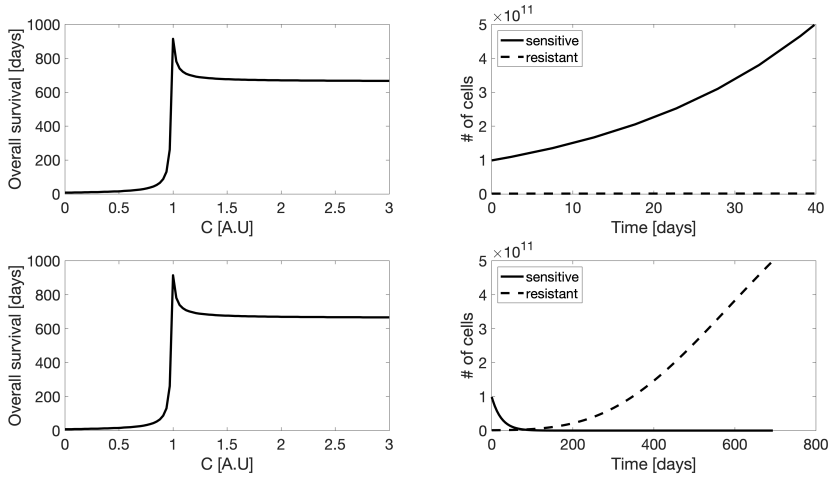

Figure 3: The time life (left column) and cancer subpopulation sizes (right column) of the patients treated with cis-platinum dose of 0.8 a.u. (first row) and 1.2 a.u. (second row) for competition coefficient $a = 0.2$.

shrinking of the x_s and by that the faster growth of x_r thus, we may observe a dramatic shortage of the patient's life. For $a = 1$ all the resources are used by the resistant cells subpopulation so, as long as sensitive cells population do not grow ($C \geq 1$) the patient's lifetime does not depend on the drug dose and is restricted only by the rate of the resistant subpopulation growth.

4. Conclusion. In the presented paper, we showed how the patients lifetime, after the diagnosis of relapsed squamous cell lung cancer, treated with cisplatin, depends on the drug dose. We considered the cancer composition of sensitive and resistant cells, and the competition advantage of resistant cells over sensitive was a key parameter of our model. Our results suggest that the best strategy during the treatment is not to kill all of the sensitive cells but rather keep them at a constant level. It is especially visible in the cases when the sensitive cells have an advantage over the resistant ones in accessing the resources and space. It may be interesting to study how the observed effect depends on the therapy scheduling and cancer composition at the detection time. It will be the subject of further research.

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Wyznaczanie optymalnej dawki cis-platyny w celu maksymalizacji czasu życia pacjentów ze zdiagnozowanym nowotworem.

Streszczenie W niniejszej pracy przedstawiamy wyniki naszych badań nad przewidywanym czasem życia pacjentów ze zdiagnozowanym nawrotowym rakiem płaskonabłonkowym płuc, który jest podtypem niedrobnokomórkowego raka płuc, leczonych cis-platyną. Opracowaliśmy model matematyczny składający się z komórek wrażliwych i odpornych na cis-platynę. Przeprowadzone symulacje sugerują, że najlepszą strategią przedłużenia czasu życia pacjentów jest utrzymanie subpopulacji komórek wrażliwych na stałym poziomie zamiast doprowadzania do śmierci ich wszystkich.

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