Using numerical modeling to analyze the behavior of cancer cells after diverse co-treatments

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Abstract: It is important to analyze a variety of treatments for colorectal cancer and the effects of possible co-treatments, in order to find the most efficient ones. Experimental results using cancer cell lines provide valuable information, but in combination with numerical simulations, additional quantitative information can be obtained. In this study, the viability of SW-480 cancer cells was analyzed experimentally after cotreatments of *Phellnus linteus* extract and chemical compound (Cisplatin drug). Numerical simulations are afterward applied to analyze the effect of diverse cotreatments on the numerical parameters of the model that are related to both cell proliferation and cell death. This approach can provide valuable insight into the quantitative effect these considered treatments have on the behavior of cancer cell lines. Similar analyses could be also performed using numerical simulations to predict the values of parameters for diverse cases that were not studied experimentally, and this would be an additional benefit for the exploration of the effects of various possible treatments.

Keywords: numerical model, SW-480 cancer cell line, parameter estimation

1. Introduction

One of the most common cancers with significant mortality rates worldwide is the colorectal carcinoma (CRC). It is therefore very important to analyze a variety of possible treatments and co-treatments, in order to find the most efficient ones. Experimental results using cancer cell lines provide valuable information, but in combination with numerical simulations, additional quantitative information can be obtained, that can be used to additionally analyze the benefits of considered treatments. There are several numerical models proposed in the literature that were applied to

model cancer progression [1,2] and the model proposed by Breward et al. [2] is used within this study.
In this paper, the effect of *P. linteus* extract and chemical compound (Cisplatin drug) in cotreatments was analyzed for a colorectal cancer cell line – SW-480. The viability of cells was measured experimentally after cotreatments, and afterward numerical simulations were performed to analyze the effect of these cotreatments on the numerical parameters related to cell proliferation and cell death.

2. Materials and Methods

In this Section, the experimental setup is explained and information about the numerical model and parameter estimation are provided.

2.1 Experimental setup

Colorectal cancer cell line SW-480 was obtained from ATCC (Manassas, USA), seeded in 96-well plates, and propagated according to standard culturing procedure [3]. *P. linteus* methanol extract was prepared as previously described [3]. Two types of co-treatments were performed: cells were treated with extract which was added simultaneously with cisplatin – 0 h; or the addition of cisplatin was done 6 h after the initial treatment of cells with *P. linteus* extract – 6 h. Either way, the final concentration of cisplatin in wells was 10 μM, and for *P. linteus* extract: 10, 25, 50 and 250 μg/mL. Cytotoxic effects of these co-treatments were evaluated by the MTT method [and obtained results were analyzed 24 or 72 h after treatment.

2.2 Numerical model

The numerical model proposed by Breward et al. [2] was used in this study. Details of the numerical model are provided in the literature [4]. If the concentration of cancer cells is denoted by α and the oxygen concentration is denoted by C, then the change of concentration over time can be described using the following relation:

$$\frac{\partial \alpha}{\partial t} = \frac{(1+s_1)\alpha(1-\alpha)C}{1+s_1C} - \frac{(s_2+s_3C)\alpha}{1+s_4C} \tag{1}$$

The parameters of the model are denoted by s1 (related to cell proliferation) and s2, s3 and s4 (related to dell death).
The change in oxygen concentration within the observed domain can be described using the following relation:

$$\frac{\partial^2 C}{\partial x^2} = \frac{Q\alpha C}{1+Q_1C} \tag{2}$$

The parameters Q and Q1 are related to the oxygen consumption rate.

The incremental-iterative form of eqs. (1) and (2) is solved numerically using the finite element method [5] and the in-house developed software.

2.3 Parameter estimation

As it was discussed in Section 2.2, there are overall 6 parameters of the numerical model - s1, s2, s3, s4, Q and Q1. It was demonstrated in literature [4] that for the considered experimental setup (where the aerobic conditions can be presumed) it can be assumed that unlimited supply of oxygen is available. For this reason, the parameters related to the oxygen consumption rate have almost no influence on the percentage of viable cells and are therefore estimated only for the control cancer cell lines and assumed equal for all considered cotreatments. The remaining 4 parameters vary for each considered cotreatment, so they are estimated for each considered treatment using the experimental data.

The estimation procedure was carried out in Matlab. The minimization function used for the estimation of parameters considers the percentages of cells obtained in experiment and simulation, 24 and 72 hours after treatment. The function can be described using the following relation:

$$SE = \left(V_{24}^{e} - V_{24}^{s}\right)^2 + \left(V_{72}^{e} - V_{72}^{s}\right)^2 \tag{3}$$

3. Results

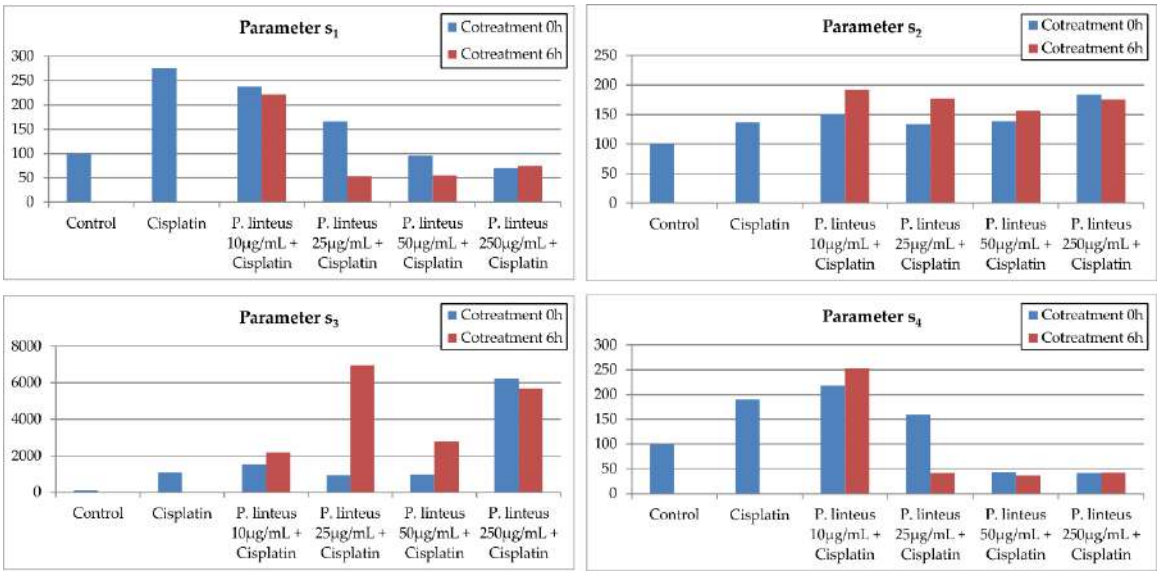

Figure 1. Values of estimated parameters for all considered cotreatments.

Figure 1 shows the results of the parameter estimation. The relative values of parameters are shown in order to ensure easier analysis of the influence of considered cotreatments. As it can be observed, the values of parameter s_1 that is related to cell proliferation decrease when the insertion of P. linteus treatment occurs 6 hours after the treatment with chemical compound. This means that cell proliferation is smaller for these cotreatments. Similarly, the values of parameters s_2 and s_3 related to cell death increase for the cotreatments after 6 hours, indicating that for these cases more cells die. It can be concluded that the cotreatment after 6 hours is more effective than the immediate administration of both treatments.

3. Conclusions

In this study, numerical simulations are applied to analyze the effect of diverse cotreatments of P. linteus extract and chemical compound (Cisplatin drug) on the numerical parameters of the model. This approach can provide valuable insight into the quantitative effect these considered treatments have on the behavior of cancer cell lines. Similar analyses could be also performed using numerical simulations to predict the values of parameters for diverse cases that were not studied experimentally, and this would be an additional benefit for the exploration of the effects of various possible treatments.

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