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ORIGINAL RESEARCH
ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ

Relationships between linear-quadratic parameters for cells irradiated in the presence and absence of cisplatin

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Abstract. *Relevance*. According to experimental data, administration of the drug cisplatin into the tumor during radiation therapy can increase its effectiveness. To date, there is no model that can predict the effectiveness of such therapy. The development of such a model is an important task for planning therapy. The goal of this work is to find analytical relationships for the survival of cells exposed to the combined effect of radiation and cisplatin in vitro. *Materials and methods*. Based on digitized experimental data on cell survival from a number of publicly published works, the corresponding linear-quadratic (LQ) approximation coefficients for survival were found for irradiation without the drug α_R, β_R, and for combined exposure to radiation and cisplatin α_{RC}, β_{RC}. Next, a regression analysis of the resulting set of coefficients and cell survival when exposed to cisplatin alone S_C was performed. *Results and Discussion*. α_{RC} was found to be statistically dependent on α_R, β_R and S_C. This dependence could be described by several models, the best of which in terms of a number of indicators was $\alpha_{RC} = \alpha_R + a\beta_R \ln S_C$, where $a = -4.27 \pm 0.57$ is a parameter that is the same for all cell types and experimental conditions. It was found that β_{RC} is statistically dependent on β_R. No signs of dependence of β_{RC} on α_R and S_C were found. The best model for β_{RC} was $\beta_{RC} = \beta_R$. These models are simple, but they allow predicting the value of cell survival under the combined effect of radiation and cisplatin S_{RC} from the values α_R, β_R and S_C only approximately. The obtained models are collated with kinetic equations and a mechanistic interpretation is given, which is based on the hypothesis of a decrease in the rate of recovery of cells from potentially lethal lesions r_+ with an increase in the radiation dose and cisplatin concentration. *Conclusion*. The type of statistical dependence of LQ coefficients α_{RC} and β_{RC} on α_R, β_R and S_C has been found. In the case of high toxicity of cisplatin (low values of S_C), the combination of the above-mentioned models for α_{RC} and β_{RC} allows to make a useful for practical application prediction of cell survival S_{RC}.

The results of this work will help for the future construction of more complex models of the combined effects of radiation and cisplatin, and may also have practical application in the case mentioned above.

Keywords: cisplatin, LQ approximation of cell survival, photon beam therapy, regression analysis, kinetic models of cell survival

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Introduction

For several decades, cisplatin has been used to treat various cancers [1, 2]. The presence of side effects during treatment [3] leads to the need of developing complex therapy that would increase the effectiveness of the drug and reduce the dose required for treatment. One of the options for such therapy may be the use of the drug in combination with radiation. A large number of *in vitro* experiments have shown the potential effectiveness of this method, revealing that cisplatin can serve as a radiosensitizer (see, for example, [4–6]).

To plan therapy with the combined effects of radiation and cisplatin, a model is needed that can predict the fraction of surviving cells after exposure to a given dose of drug and radiation [7]. To date, such a model does not exist. In our opinion, the first step towards its construction is to obtain simple empirical relationships for cell survival *in vitro*. In the future, based on them, it will be possible to build more complex models that take into account in more detail the conditions of the experiment. Further, if necessary, on the basis of such models it will be possible to build mechanistic models of cell survival that contain the most relevant scientific knowledge about the internal processes occurring in cells during therapy.

The purpose of this work is to find analytical relationships for the survival of cells exposed to the combined effects of radiation and cisplatin *in vitro*.

Materials and methods

The main idea of the work

It is known that, over a wide range of doses, experimental data on cell survival during irradiation *in vitro* are almost always well described by a linear-quadratic (LQ) function of the form:

$$S_R = e^{-\alpha_R D - \beta_R D^2}, \qquad (1)$$

where S_R — cell survival, D — deposited dose, α_R and β_R — coefficients selected using regression analysis methods [8, 9]. α_R and β_R depend on cell type, type of radiation and a number of additional experimental conditions. A more general form of expression (1) is applicable to describe cell survival in the presence of cisplatin:

$$\frac{S_{RC}}{S_C} = e^{-\alpha_{RC} D - \beta_{RC} D^2}, \quad (2)$$

where S_{RC} — cell survival under combined exposure to cisplatin and radiation; S_C — cell survival in the presence of cisplatin but without irradiation; α_{RC} and β_{RC} — coefficients similar in meaning to α_R and β_R. Experimental conditions for S_C and S_{RC} must be equivalent, including the use of the same concentration of cisplatin and time of incubation with cells.

Thus, α_R and β_R characterize the response of cells to radiation, and S_C — to the presence of cisplatin. It is logical to assume that, knowing the response of cells to radiation and cisplatin separately, it is possible to predict it for the case of their combined action, that is, knowing α_R, β_R and S_C, to predict α_{RC} and β_{RC}. Mathematically, this hypothesis can be written in the form of relations:

$$\alpha_{RC} = f_{\alpha_{RC}}\left(\alpha_R, \beta_R, S_C, \vec{a}_{\alpha_{RC}}\right) + \varepsilon_{\alpha_{RC}}, \quad (3)$$

$$\beta_{RC} = f_{\beta_{RC}}\left(\alpha_R, \beta_R, S_C, \vec{a}_{\beta_{RC}}\right) + \varepsilon_{\beta_{RC}}, \quad (4)$$

where $f_{\alpha_{RC}}$ and $f_{\beta_{RC}}$ — unknown functions of variables α_R, β_R and S_C; $\vec{a}_{\alpha_{RC}}$ and $\vec{a}_{\beta_{RC}}$ — vectors with parameters that are the same for all cell types, types of photon sources, cisplatin concentrations, times of incubation of cells with cisplatin and other factors; $\varepsilon_{\alpha_{RC}}$ and $\varepsilon_{\beta_{RC}}$ — Gaussian errors. To date, experimental data on the combined effect of radiation and cisplatin are quite small, which is why it is possible to consider only the simplest types of functions $f_{\alpha_{RC}}$ and $f_{\beta_{RC}}$, containing no more than two parameters each. In view of this, we will consider functions of a simpler form:

$$\alpha_{RC} = \alpha_R + f_{\alpha_{RC}}\left(\beta_R, S_C, \vec{a}_{\alpha_{RC}}\right) + \varepsilon_{\alpha_{RC}}, \quad (5)$$

$$\beta_{RC} = \beta_R + f_{\beta_{RC}}\left(\alpha_R, S_C, \vec{a}_{\beta_{RC}}\right) + \varepsilon_{\beta_{RC}}, \quad (6)$$

where we have redefined functions $f_{\alpha_{RC}}$ and $f_{\beta_{RC}}$ and errors $\varepsilon_{\alpha_{RC}}$ and $\varepsilon_{\beta_{RC}}$ from expressions (3) and (4) so as not to introduce too much notation; expressions (3) and (4) will not be used further.

Finding functions $f_{\alpha_{RC}}$ and $f_{\beta_{RC}}$ and their inaccuracies is a regression analysis problem in which expressions (5) and (6) are regression models.

The parameters of models (5) and (6) can be interpreted mechanistically by proposing a new kinetic model of the dynamics of lethal and potentially lethal events occurring in cells during irradiation and administration of cisplatin.

Selection of experimental data

Experimental data were extracted from published articles mainly by digitizing the graphs presented in them. We only used articles that met a number of requirements:

— the article must explicitly indicate: photon source (for example, ^{60}Co or 200 kV), cell type, incubation times of cells with cisplatin during measurement of S_C and S_{RC} (these times must match);

— the dose rate should not significantly exceed the range of usual values used in this kind of experiments (approximately from 0.5 to 5 Gy / min);

— cells should not be exposed to obviously extreme conditions such as hypoxia or hyperthermia;

— the experiment must not involve manipulation of the cell cycle.

A sufficient amount of data was extracted from articles [10–15] to find the parameters of regression models of simple form (5) and (6), containing no more than two parameters, with satisfactory accuracy, namely 25 sets of values $\hat{\alpha}_R$, $\hat{\beta}_R$, $\hat{S}_C$, $\hat{\alpha}_{RC}$, $\hat{\beta}_{RC}$, where the cap above the value means that it represents an estimate based on the experimental data of the article (that is, based on a sample), rather than its true value (within the framework of the frequentist approach to mathematical statistics). Thus, we did not consider all the existing experimental data, but only part of it, due to the fact that a larger amount of data would not significantly improve the quality of the regression analysis results for their practical application.

In the experimental data retrieved from articles, the dose rates ranged from approximately 0.6 to 1.5 Gy/ min. The incubation times of cells with cisplatin varied from 1 to 24 hours. Cells were irradiated either before incubation with the drug or after it (differently in different experiments). 11 types of cells were irradiated with 5 types of photon sources.

Data on the SCC-25 cell line from the article [14] were excluded from consideration as outliers: at a dose of 1 Gy in the presence of cisplatin, an increase in cell survival was observed in them, which did not occur in other experiments.

Regression analysis of experimental data

Unfortunately, we were unable to extract standard errors for all measurements from the articles, so they were not used in our calculations.

If the article did not explicitly indicate the values of $\hat{S}_C$, then they were found by interpolating the presented data. First, we tried interpolation with the Hill function [16]:

$$S_C = \frac{1}{1+\left(\frac{C}{IC_{50}}\right)^n}, \qquad (7)$$

where C — drug concentration, IC_{50} and n — parameters. However, in a number of cases it turned out to be unsatisfactory, which is why linear interpolation between the nearest values was used to obtain values of $\hat{S}_C$.

LQ parameter values $\hat{\alpha}_R$, $\hat{\beta}_R$, $\hat{\alpha}_{RC}$ and $\hat{\beta}_{RC}$ were found using the least squares method (LS) for the functions:

$$f_R = -\frac{\ln \hat{S}_R}{D} = \hat{\alpha}_R + \hat{\beta}_R D, \qquad (8)$$

$$f_{RC} = -\frac{\ln \frac{\hat{S}_{RC}}{\hat{S}_C}}{D} = \hat{\alpha}_{RC} + \hat{\beta}_{RC} D, \qquad (9)$$

where $\hat{S}_R$ and $\hat{S}_{RC}$ — estimations of functions (1) and (2) based on experimental samples. It should be noted that the obtained parameter values cannot be considered the result of solving a standard linear regression problem

$$f'_R = -\frac{\ln S_R}{D} = \alpha_R + \beta_R D + \varepsilon_R, \qquad (10)$$

$$f'_{RC} = -\frac{\ln \frac{S_{RC}}{S_C}}{D} = \alpha_{RC} + \beta_{RC} D + \varepsilon_{RC}, \qquad (11)$$

where ε_R and ε_{RC} — Gaussian errors. The point is that the sizes of the samples relevant to $\hat{S}_R$ and $\hat{S}_{RC}$ are too small (in some cases they have only one degree of freedom) to provide meaningful arguments about the validity of the models (10) and (11). In other words, it cannot be stated that the quantities ε_R and ε_{RC} are random variables having a normal distribution. In view of this, in order to avoid gross errors in further calculations, we assumed that the values of $\hat{\alpha}_R$, $\hat{\beta}_R$, $\hat{\alpha}_{RC}$ and $\hat{\beta}_{RC}$ obtained by this method represent single measurements of the corresponding quantities.

Since it is known that the LQ approximation (1) is not applicable for low doses [17], when selecting parameters, points with a dose value of less than 0.9 Gy were excluded from consideration.

The resulting set of values of $\hat{\alpha}_R$, $\hat{\beta}_R$, $\hat{\alpha}_{RC}$ and $\hat{\beta}_{RC}$ was used to solve regression problems (5) and (6), that is, finding model parameters, their inaccuracies and accompanying statistical criteria.

In total, more than 100 types of functions $f_{\alpha_{RC}}$ and $f_{\beta_{RC}}$ were considered, containing no more than two parameters, from the simplest type to the more complex. Consideration of such a large number of functions was necessary because we were not based on any already published model, so the type of functions was not known in advance and had to be found by enumerating options.

The amount of experimental data was too small to prove the validity of models (5) and (6), but it was possible to provide significant arguments in favor of this based on statistical criteria. To do this, we used the Shapiro-Wilk test, which is considered one of the most powerful tests for testing data for normality [18] and the one-sample t-test for the mean [19]. Based on these criteria, we drew conclusions about the possibility of considering that the quantities $\varepsilon_{\alpha_{RC}}$ and $\varepsilon_{\beta_{RC}}$ have a normal distribution with zero mathematical expectation. It should be noted that for samples of finite size, the use of these criteria is an approximation and assumes that the functions $f_{\alpha_{RC}}$ и $f_{\beta_{RC}}$ with true parameter values are not far from their sample estimates. Despite this rough approximation, this method allows one to track models with highly non-Gaussian errors.

The values of the model parameters and their uncertainties were found in two ways, depending on the type of $f_{\alpha_{RC}}$ and $f_{\beta_{RC}}$. For functions linear in parameters, analytical relations were used [20]. For non-linear functions, one of the bootstrapping methods was used [21]: regression residuals were modeled randomly and for each case the parameter values were found using LS. For each function, a set of one million parameter values was calculated. With such an amount, the inaccuracy of this method was less than 1%, and in the problem under consideration it could be neglected. This method could also be used for linear functions, since it gives the same results as analytical relations, but the calculation required much more time, which is why it was applied only to non-linear cases.

Results and discussion

Figure 1 shows examples of approximation of experimental data by functions (1) and (2), whose parameters were found using (8) and (9), as described in materials and methods. The approximation described the data well in all 25 cases of combined exposure to radiation and cisplatin and, thus, the validity of (2) was not in doubt. The mean value of the coefficient of variation for function (9) was 0.127.

Diamonds indicate experimental data, a solid line of the same color indicates their approximation. Cisplatin concentrations are shown in the legend. a) Data from [10] for CHO cells irradiated with photons from a ^{137}Cs source at a cell incubation time with cisplatin of 1 hour. At a concentration of 8 μg / ml, the authors of the work examined separately the case of cell irradiation after incubation with

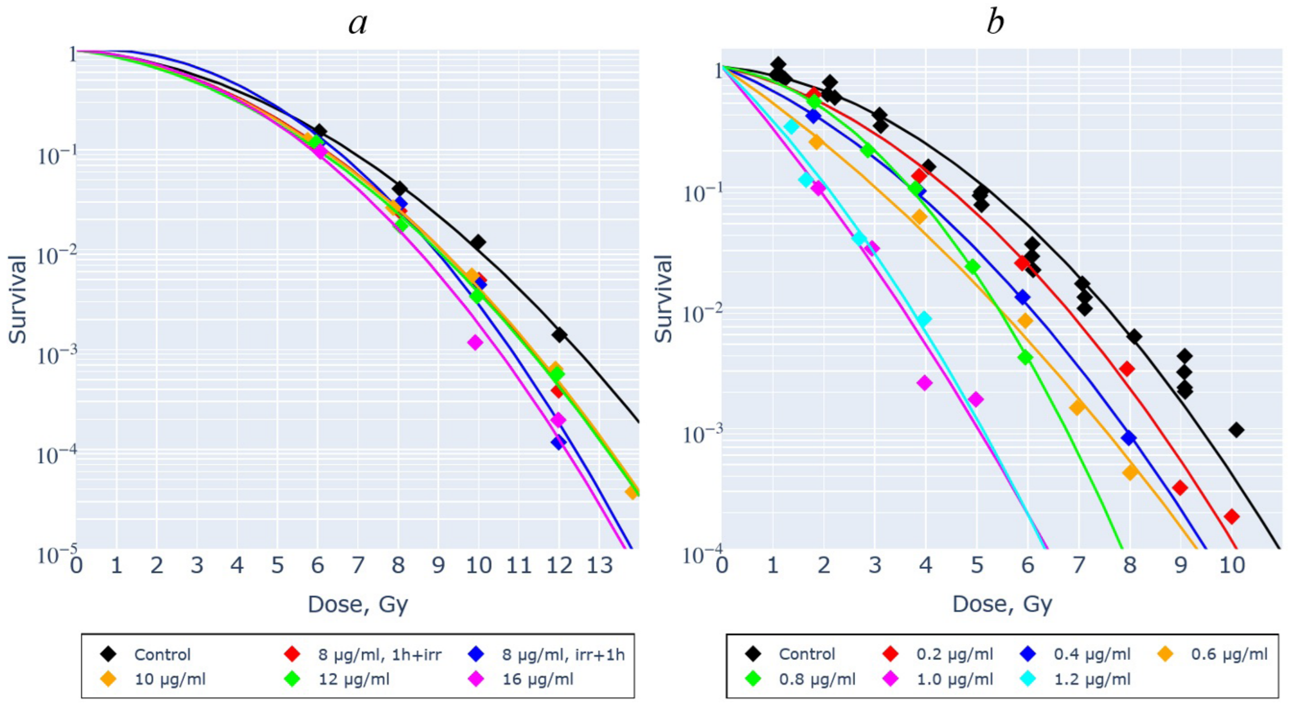

Fig. 1. Examples of approximation of experimental data by LQ functions (1) and (2)

cisplatin (1h + irr) and before incubation (irr + 1h), without finding a significant difference between the data. b) Data from [11] for RIF1 cells irradiated with 200 kV photons at a cell incubation time with cisplatin of 1 hour.

In Table 1 and Table 2 the resulting models (5) and (6) for α_{RC} and β_{RC} are presented, which are most worthy of mention (there are more than 100 models in total). For α_{RC}, by the latter, we mean several of the best models in terms of statistical indicators and simplicity, as well as several models that characterize the methods and results of regression analysis of this work. For β_{RC}, models are presented that have the same form as models for α_{RC}. We found that α_{RC} is statistically dependent on α_R, β_R and S_C, and β_{RC} is dependent on β_R. We found no evidence of a statistical dependence of β_{RC} on α_R and S_C. The results of the regression analysis did not allow us to clearly identify the best model for α_{RC}. Thus, based on statistical indicators, several models could be used as such. In such a situation, we conditionally chose model number 8 as the best one, since among the models with the best performance it had the simplest form. The approximation of experimental data by this model is shown in Figure 2. Unlike α_{RC}, the best model for β_{RC} could be chosen unambiguously and this was model number 2.

Table 1

Models of LQ coefficient α_{RC} for combined exposure to radiation and cisplatin

α_{RC}, Gy^{-1}							
#	Model	a	b	RSD	Shapiro-Wilk p-value	One-sample t-testp-value	R^2
1	a	0.234 ±0.062	-	0.312	4.49 × 10⁻⁵	1.00	-
2	α_R	-	-	0.288	7.31 × 10⁻⁶	0.0166	-
3	$\alpha_R + a$	0.148 ±0.058	-	0.288	7.31 × 10⁻⁶	1.00	-
4	$\alpha_R + a\beta_R^2$	99.0 ±17.6	-	0.214	0.190	0.835	0.569
5	$\alpha_R + a\ln S_C$	-0.237 ±0.040	-	0.206	0.799	0.515	0.599
6	$\alpha_R + a\ln^2 S_C$	0.118 ±0.018	-	0.195	0.0803	0.602	0.642
7	$\alpha_R + a(-\ln S_C)^b$	0.118 ±0.063	2.00 ±0.85	0.199	0.0845	0.592	-
8	$\alpha_R + a\beta_R\ln S_C$	-4.27 ±0.57	-	0.177	0.119	0.844	0.703
9	$\alpha_R + a\beta_R\ln^2 S_C$	1.91 ±0.26	-	0.178	0.0573	0.415	0.699
10	$\alpha_R + a\beta_R(-\ln S_C)^b$	3.43 ±1.22	1.30 ±0.54	0.180	0.0343	0.867	-

Note: α_R is expressed in Gy^{-1}, β_R in Gy^{-2}, S_C is dimensionless. The table shows sample parameter estimates and their standard errors, separated from the former by ±. Parameter a has different dimensions depending on the model, and parameter b is dimensionless. RSD — residual standard deviation. The p-value for Shapiro-Wilk test is indicated for the null hypothesis that the sample is drawn from a population with a normal distribution. The p- value for one-sample t-test for the mean is indicated for the null hypothesis that the sample is drawn from a population with an expected value of zero (see “Materials and methods” section). Coefficient of determination R^2 is indicated only for cases of linear regression, where it can be interpreted in a standard way.

Table 2

Models of LQ coefficient β_{RC} for combined exposure to radiation and cisplatin

β_{RC}, Gy^{-2}							
№	Model	a × 10²	b	RSD×10²	Shapiro -Wilk p-value×10²	One -sample t-testp-value	R²×10²
1	a	3.25 ± 0.65	-	3.25	0.577	1.00	-
2	β_R	-	-	1.94	6.44	0.786	-
3	$\beta_R + a$	0.106 ± 0.387	-	1.94	6.44	1.00	-
4	$\beta_R + a\alpha_R{}^2$	-8.0 ± 16.5	-	1.93	4.51	0.590	0.984
5	$\beta_R + a\ln S_C$	-0.229 ± 0.370	-	1.92	8.32	0.872	1.57
6	$\beta_R + a\ln^2 S_C$	0.137 ± 0.178	-	1.92	9.19	0.915	2.41
7	$\beta_R + a\left(-\ln S_C\right)^b$	0.125 ± 0.409	-0.10 ±1.45	1.98	6.22	0.937	-
8	$\beta_R + a\alpha_R \ln S_C$	0.20 ± 3.65	-	1.94	6.13	0.757	0.0129
9	$\beta_R + a\alpha_R \ln^2 S_C$	0.92 ± 1.93	-	1.93	8.08	0.978	0.939
10	$\beta_R + a\alpha_R\left(-\ln S_C\right)^b$	-1.37 ± 3.71	0.33 ±1.53	1.98	4.80	0.591	-

Note: The table data format is similar to Table 1.

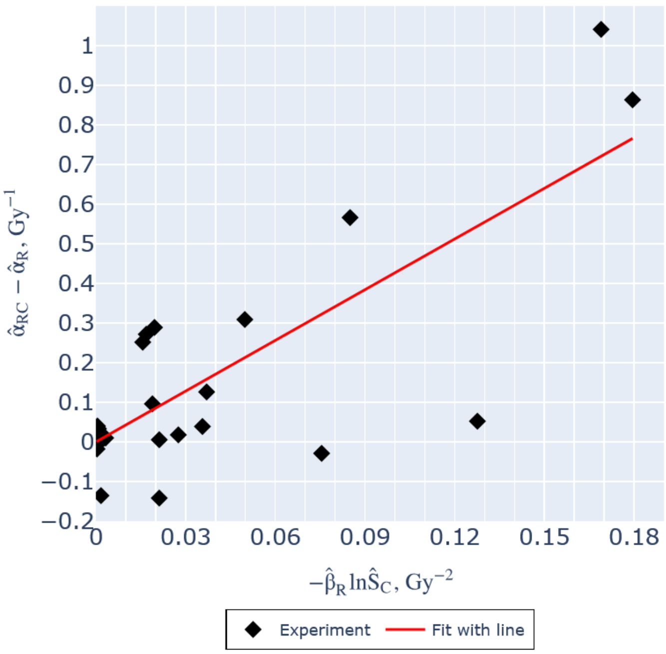

Fig. 2. Approximation of experimental values of LQ coefficient for combined exposure to radiation and cisplatin α_{RC} by linear model 8 from Table 1. R^2 = 0.703

Thus, the best model of cell survival under the combined effects of radiation and cisplatin in this work was considered to be function S_{RC} from (2) with LQ parameters corresponding to models 8 and 2 from Table 1 and Table 2, respectively:

$$\alpha_{RC} = \alpha_R + a\beta_R \ln S_C, \qquad (12)$$

$$\beta_{RC} = \beta_R, \qquad (13)$$

Figure 3 shows this model's description of the experimental data from Figure 1.

Figure 4 shows part of the data from Figure 3 with a constructed 95% prediction interval that predicts the outcome of individual experimental values and thus includes random error (not to be confused with a 95% confidence interval). As can be seen from Figure 4*a*, in some cases the prediction interval is too wide, and then the model's predictions may be useless for practical use. Unfortunately, for the vast majority of experimental data considered in this work, the situation in this regard is similar to Figure 4*a*.

It should be noted that in the experimental data considered there was only one case of high incubation time of cells with cisplatin — 24 hours, much longer than the others (1 hour and 2 hours). According to statistical indicators, this experiment did not stand out in any way from the general trends of the considered models.

According to model (12), α_{RC} can be considered linearly dependent on β_R and ln S_C, however, this result is the average indicator for the 11 types of cells considered in the work, 5 types of photon sources, a wide range of times of incubation of cells with cisplatin and other factors. To use this model to predict the results of an individual experiment, it is necessary to take into account the random error (RSD from Table 1), as it is done in Fig. 4. Due to high RSD values, in some

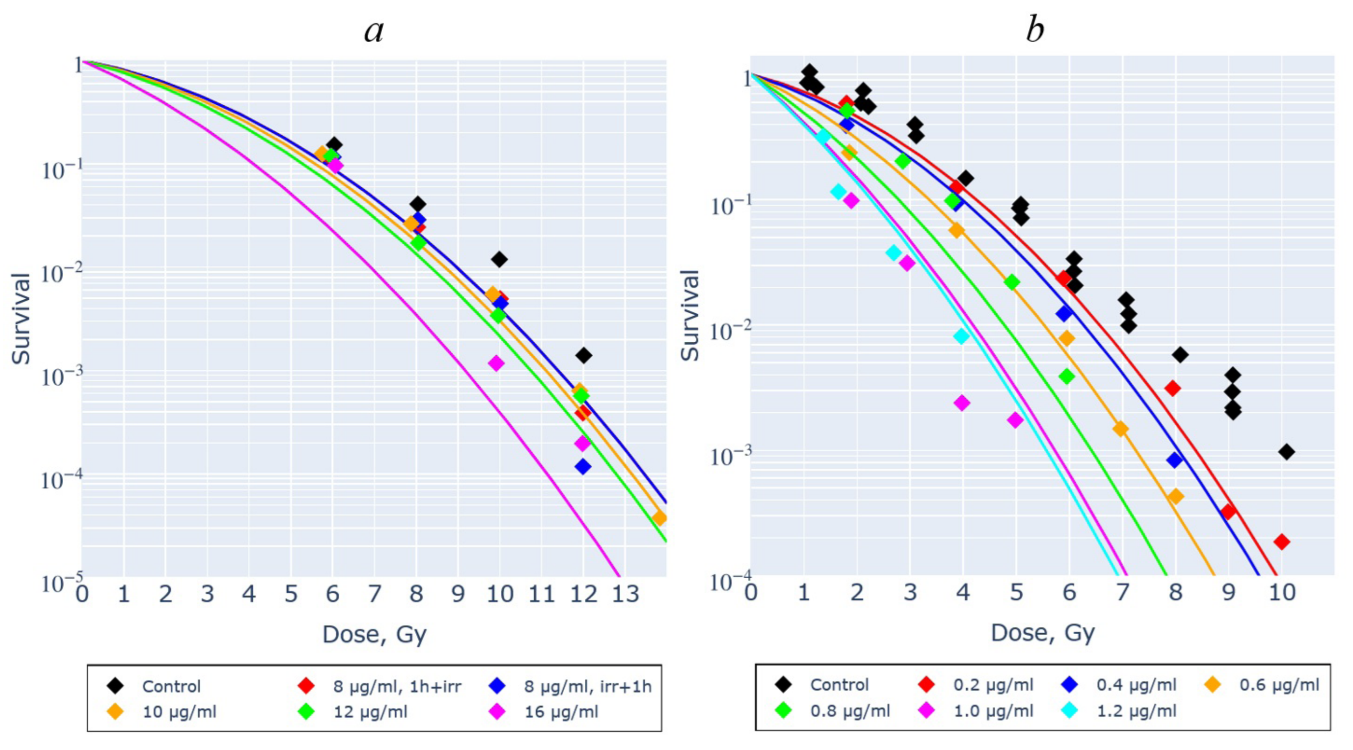

Fig. 3. Description of experimental data on cell survival under combined exposure to radiation and cisplatin from Fig. 1 by models (12) and (13): ***a*** – $\hat{\alpha}_R$ = 0.0819 Gy^{-1}, $\hat{\beta}_R$ = 0.0380 Gy^{-2}. $\hat{S}_C$ are equal to 0.573, 0.484, 0.392 and 0.137 for concentrations of 8, 10, 12 and 16 µg / ml, respectively; ***b*** – $\hat{\alpha}_R$ = 0.0923 Gy^{-1}, $\hat{\beta}_R$ = 0.0686 Gy^{-2}. $\hat{S}_C$ are equal to 0.583, 0.484, 0.290, 0.156, 0.0851 and 0.0731 for concentrations of 0.2, 0.4, 0.6, 0.8, 1.0 and 1.2 µg / ml, respectively

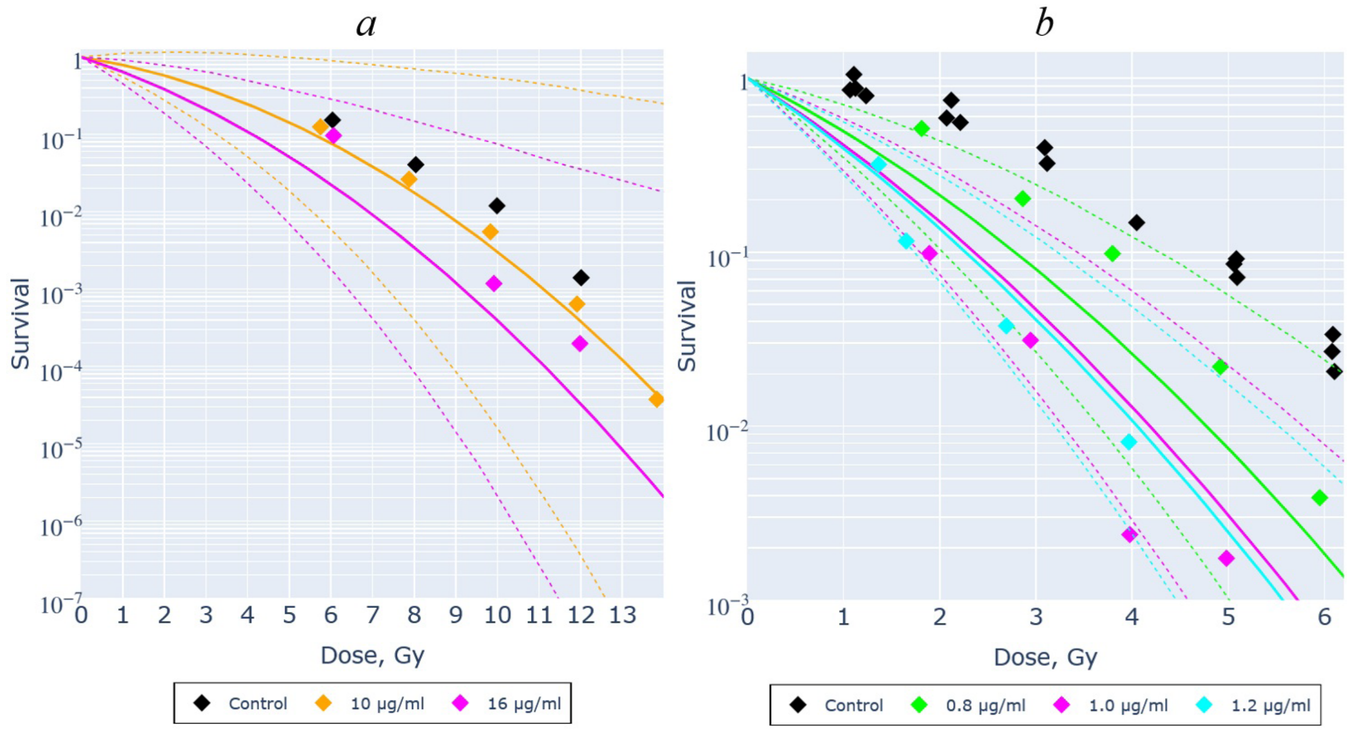

Fig. 4. Description of experimental data on cell survival under combined exposure to radiation and cisplatin from Fig. 1 by models (12) and (13), with a constructed 95% prediction interval (dashed line)

series of experiments there may not be an increase in the value of $\hat{\alpha}_{RC}$ when cisplatin is administered and even a decrease may be observed. According to model (12), one can state that $\hat{\alpha}_{RC}$ clearly increases only at sufficiently high values of $\hat{\beta}_R$ and $|\ln \hat{S}_C|$ (see Fig. 4b, in which $\hat{\beta}_R$ is equal to 0.0686, and $\hat{S}_C$ varies from 0.0731 to 0.156). Just as with the model for α_{RC}, the equality of β_{RC} and β_R (see model (13)) has a high random error, so the value of $\hat{\beta}_{RC}$ can differ significantly from $\hat{\beta}_R$ in individual experiments.

The obtained models (12) and (13) in most cases cannot provide a useful prediction of α_{RC} and β_{RC} based on the values of $\hat{\alpha}_R$, $\hat{\beta}_R$ and $\hat{S}_C$ due to the prediction intervals being too wide. To increase the accuracy of the prediction, we assumed that such a width of the intervals is due to the fact that the parameters of the models should depend on the cell type and the time of incubation of cells with cisplatin, and their obtained values are averaged over these factors. It is known that there are a number of kinetic models that claim to describe cell survival after irradiation (in the absence of drugs in the cells): MKM, LPL, RMR and others [22–24]. Such models are based on kinetic equations, the solution of which allows to express cell survival through a set of parameters that depend on the cell type and radiation. Thus, the expressions (12) and (13) should be solutions (possibly approximate ones) of such equations, generalized to the case of the presence of cisplatin in cells.

Let us create a system of kinetic equations. We will assume that damage to cells as a result of their irradiation and exposure to cisplatin can be divided into two groups: potentially lethal and lethal. By lethal we mean any events that are guaranteed to lead to the death of a cell or the loss of its reproductive functions. By potentially lethal we mean the averaged set of events that with some probability can lead to cell death or loss of reproductive functions (i.e. become lethal). Such events include various types of DNA damage, damage to cell organelles, and increase in level of oxidative stress.

Let us consider the simplest, approximate version of kinetic equations. We will assume that cisplatin was introduced into the cells before the instantaneous irradiation, and all potentially lethal events produced by it can be considered either successfully eliminated by cellular mechanisms or became lethal at the time of irradiation. Then the system of equations can be written as follows:

$$\begin{cases} \dfrac{dU(t)}{dt} = -r_+U(t) - r_-U(t), \quad U(0) = \kappa D \\ \dfrac{dL(t)}{dt} = r_-U(t), \quad L(0) = \eta D - \ln S_C \end{cases}, \qquad (14)$$

where $U(t)$ is the average number of potentially lethal events per cell at time t, $L(t)$ is the average number of lethal events per cell at time t, r_+ is the rate of disappearance of potentially lethal events as a result of successful cell recovery, r_- is the rate of transition of potentially lethal events to lethal ones as a result of unsuccessful recovery, κ is the average number of potentially lethal events per cell, produced by radiation per one Gy, η is the average number of lethal events per cell produced by radiation per one Gy, D is deposited dose. The term $-\ln S_C$ represents the average number of lethal events produced by cisplatin and takes into account the assumption that they are distributed over cells according to Poisson distribution. t = 0 corresponds to the time immediately after irradiation.

Let us assume that r_+ depends on the dose and the presence of cisplatin as follows:

$$r_+ = \frac{1}{A_1 + A_2\left(a_0 \ln S_C + D\right)}, \qquad (15)$$

where A_1, A_2 and a_0 are parameters that do not depend on the dose and concentration of cisplatin. Thus, we assume that the cellular recovery system from potentially lethal events is weakened by increasing radiation dose and cisplatin concentration, which is in agreement with existing data (see, e.g., [25] and [26]). Let us assume that $r_+ >> r_-$ by analogy with [22]. This approximation means that the vast majority of potentially lethal events are successfully eliminated and do not become lethal. Then the system of equations takes the form:

$$\begin{cases} \dfrac{dU(t)}{dt} = -\dfrac{U(t)}{A_1 + A_2\left(a_0 \ln S_C + D\right)}, \quad U(0) = \kappa D \\ \dfrac{dL(t)}{dt} = r_-U(t), \quad L(0) = \eta D - \ln S_C \end{cases}, \qquad (16)$$

This system has an analytical solution:

$$U(t) = \kappa D e^{-\frac{t}{A_1 + A_2\left(a_0 \ln S_C + D\right)}}, \qquad (17)$$

$$L(t) = \eta D - \ln S_C + \\ + r_-\kappa D\left(A_1 + A_2\left(a_0 \ln S_C + D\right)\right)\left(1 - e^{-\frac{t}{A_1 + A_2\left(a_0 \ln S_C + D\right)}}\right), \qquad (18)$$

For large times t, taking into account the Poisson distribution of lethal events across cells, we obtain the LQ dependence for survival:

$$S_{RC} = e^{-L(\infty)} = \\ = S_C e^{-\left(\eta D + r_-\kappa D\left(A_1 + A_2\left(a_0 \ln\left(S_C(C)\right) + D\right)\right)\right)} = S_C e^{-\left(\alpha_{RC} D + \beta_{RC} D^2\right)}, \qquad (19)$$

where

$$\alpha_{RC} = \eta + r_-\kappa\left(A_1 + A_2 a_0 \ln S_C\right), \qquad (20)$$

$$\beta_{RC} = r_-\kappa A_2, \qquad (21)$$

In the absence of cisplatin $\ln S_C = 0$, then:

$$\alpha_R = \eta + r_-\kappa A_1, \qquad (22)$$

$$\beta_R = r_-\kappa A_2 = \beta_{RC}, \qquad (23)$$

Expressing $a\kappa$ through β_R, we find:

$$\alpha_{RC} = \alpha_R + a_0\beta_R \ln S_C, \qquad (24)$$

The obtained relations for α_{RC} and β_{RC} are fully consistent with models (12) and (13) provided that $a = a_0$.

With the approximations made, the case of irradiation of cells before the administration of cisplatin is no different from the case of irradiation after, provided that cisplatin is administered into the cells immediately after irradiation.

Figure 5 and Figure 6 show approximations of the experimental data from Figure1 using models (23) and (24) by analogy with Figure 3 and Figure 4. When approximating, deviations of the experimental values of $\frac{\ln \hat{S}_{RC}}{D}$ from the mentioned models were considered as a Gaussian error. As can be seen from the comparison of Figures 3–6, the model predictions have improved significantly in case a) and remained approximately the same in case b). This difference in predictions is due to the large scatter of experimental data and the sharply changing "shoulder" $\hat{\beta}_{RC}$ in one direction or the other when changing the concentration of cisplatin in the latter case (see Figure 1).

Thus, in a number of cases, approximation of cell survival based on kinetic equations (14) predicts experimental data significantly better than relations (12) and (13). However, it should be noted that such an approximation requires experimental data on the survival during irradiation of a given cell type in the presence of cisplatin, while they are not needed to use relations (12) and (13). That is, it is necessary to know not only $\hat{\alpha}_R$, $\hat{\beta}_R$ and $\hat{S}_C$, but also a number of values of $\hat{S}_{RC}$, which is a serious drawback.

It should be noted that some parameters of the system (14) may be dependent on each other. At the moment, this is the subject of further research and is not addressed in this work.

As described above, system (14) is approximate, since in reality the irradiation of cells is not instantaneous, and potentially lethal events created by cisplatin exist simultaneously with those created by irradiation. However, this case is much more complex and is not considered in this paper.

Significant deviations of individual experimental values of survival from the LQ function approximating them, which in this work were interpreted as random errors, are a serious obstacle to the development of a model of cell survival, since even in cases where the model can very accurately predict the average survival value, variation in the prediction of individual survival values may be too large and have no practical

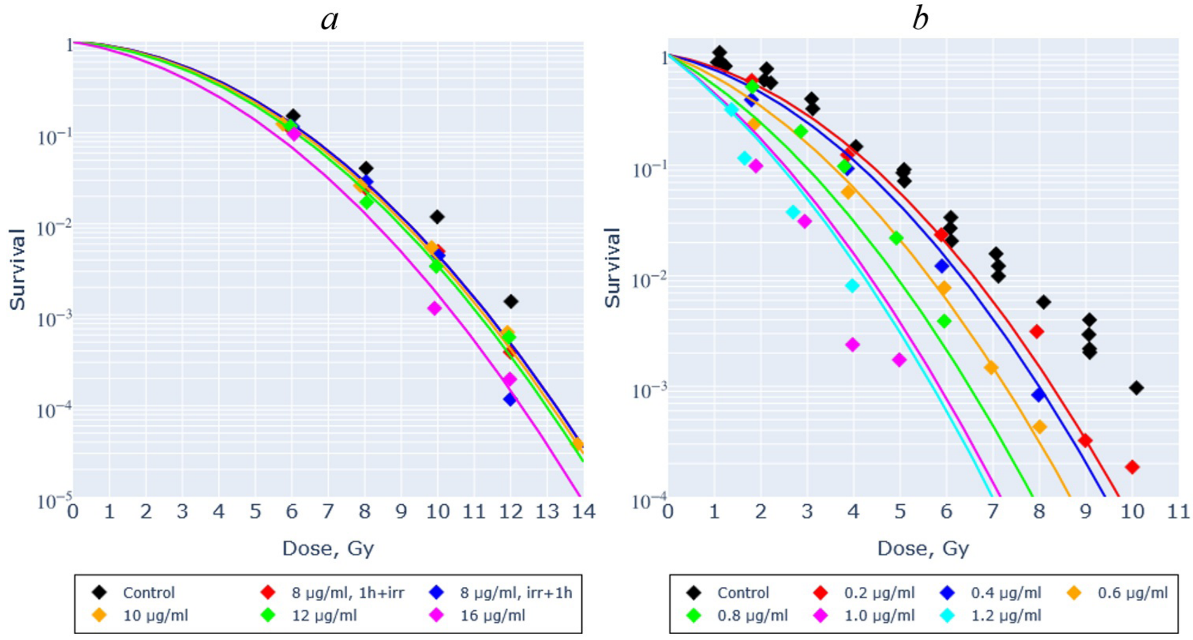

Fig. 5. Description of experimental data on cell survival under combined exposure to radiation and cisplatin from Fig. 1 by models (23) and (24): ***a*** – a_0 = –1.442 ± 0.319, α_R = 0.0175 ± 0.0327, β_R = 0.0483 ± 0.0033; ***b*** – a_0 = –3.555 ± 0.478, α_R = 0.0302 ± 0.0639, β_R = 0.0789 ± 0.0099

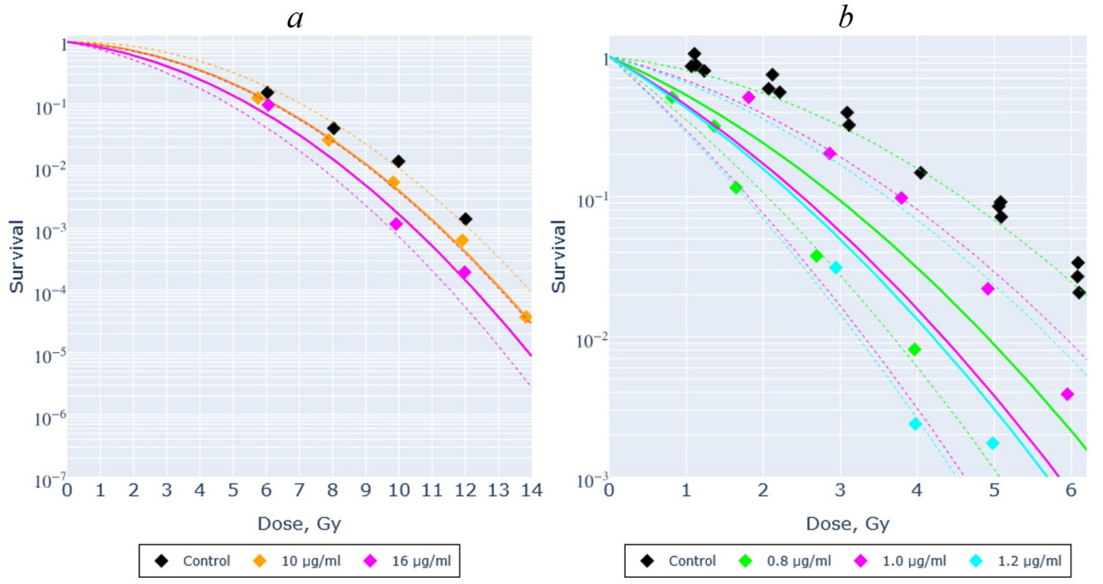

Fig. 6. Description of experimental data on cell survival under combined exposure to radiation and cisplatin from Fig. 1 by models (23) and (24), with a constructed 95% prediction interval (dashed line). In case ***a)*** one of the interval boundaries practically coincides with the solid line, which is why it is not clearly visible

application (the prediction interval constructed from the model is too wide). This makes it relevant to use a more accurate model than LQ to approximate survival data, as well as to investigate random errors in measuring cell survival, for example, whether deviations from LQ are really random errors or regular behavior and whether a significant difference in measured survival values can be avoided when the experiment is repeated (the problem of reproducibility of experimental data).

The experimental data in Fig. 1b cast doubt on the possibility of constructing a useful general cell survival model for practical application based only on the values of $\hat{S}_{RC}$ due to the sharply changing "shoulder" of $\hat{\beta}_{RC}$, first in one direction and then in the other, when the concentration of cisplatin changes. It is likely that to build such a model it is necessary to use microscopic characteristics of cells along with (or instead of) $\hat{S}_{RC}$ as input data.

Conclusion

As a result of statistical processing of experimental data, it was found that α_{RC} is statistically dependent on α_R, β_R and S_C. This dependence can be described by several models, the best of which in terms of a number of indicators is (12). It was found that β_{RC} is statistically dependent on β_R. No signs of dependence of β_{RC} on α_R and S_C were observed. The best model for β_{RC} is (13).

A new kinetic model is proposed. Its innovation is the hypothesis that the rate of recovery of cells from potentially lethal events r_+ decreases with increasing radiation dose and cisplatin concentration. This model in some cases allows to increase the accuracy of the prediction of S_{RC} in comparison with models (12) and (13), but requires the availability of a number of experimental values of $\hat{S}_{RC}$ for the same type of cells and radiation for which the prediction is made.

The results of this work will help for the future construction of more complex models of the combined effects of radiation and cisplatin, and may also have practical application for prediction of cell survival S_{RC} in the case of high toxicity of cisplatin (low values of S_C).

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Соотношения между линейно-квадратичными параметрами при облучении клеток в присутствии и отсутствии цисплатина

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Аннотация. *Актуальность*. Согласно экспериментальным данным введение препарата цисплатин в опухоль при лучевой терапии может повысить ее эффективность. На сегодняшний день не существует модели, способной предсказывать эффективность такой терапии. Разработка такой модели является важной задачей для планирования терапии. Целью настоящей работы является нахождение аналитических соотношений для выживаемости клеток, подверженных комбинированному действию излучения и цисплатина *in vitro*. *Материалы и методы*. По оцифрованным экспериментальным данным по выживаемости клеток из ряда опубликованных в открытом доступе работ найдены соответствующие коэффициенты линейно-квадратичной (LQ) аппроксимации выживаемости при облучении без препарата α_R, β_R и при комбинированном воздействии излучения и цисплатина α_{RC}, β_{RC}. Далее произведён регрессионный анализ полученного набора коэффициентов и выживаемости клеток при воздействии одного цисплатина S_C. *Результаты и обсуждение*. Установлено, что α_{RC} статистически зависим от α_R, β_R и S_C. Данная зависимость может быть описана несколькими моделями, лучшей из которых по ряду показателей является $\alpha_{RC} = \alpha_R + a\beta_R \ln S_C$, где $a = -4,27 \pm 0,57$ — параметр, одинаковый для всех типов клеток и условий проведения эксперимента. Установлено, что β_{RC} статистически зависим от β_R. Признаков зависимости β_{RC} от α_R и S_C не обнаружено. Лучшей моделью для β_{RC} является $\beta_{RC} = \beta_R$. Указанные модели просты, но позволяют предсказать значение выживаемости клеток при комбинированном воздействии излучения и цисплатина S_{RC} по значениям α_R, β_R и S_C только приближенно. Полученным моделям сопоставлены кинетические уравнения и дана механистическая интерпретация, в основе которой лежит гипотеза об убывании скорости восстановления клеток от потенциально летальных повреждений r_+ при увеличении дозы облучения и концентрации цисплатина. *Выводы*. Установлен вид статистической зависимости LQ коэффициентов α_{RC} и β_{RC} от α_R, β_R и S_C. При высоких значениях токсичности цисплатина (низких значениях S_C) сочетание упомянутых выше моделей для α_{RC} и β_{RC} позволяет сделать полезный для практического применения прогноз выживаемости клеток S_{RC}. Результаты данной работы помогут для будущего построения более сложных моделей комбинированного действия излучения и цисплатина, а также могут иметь практическое применение в упомянутом выше случае.

Ключевые слова: цисплатин, LQ аппроксимация выживаемости клеток, фотонная лучевая терапия, регрессионный анализ, кинетические модели выживаемости клеток

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