A NONLINEAR MODEL IN THE DYNAMICS OF TUMOR-IMMUNE SYSTEM COMBINED WITH RADIOTHERAPY

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Using immunogenic tumors dynamics, A. Kuznetsov proposed a mathematical model for the interaction between effector cells and cells in a growing tumor. Adding radiotherapy to this mathematical model, we get a system that takes into account both destruction, repair and repopulation of tumor cells as well as the destruction and the inhibition of immune cells. In such context, using the computing environment Matlab, we have obtained the therapeutic diagrams, in which case the tumor is reduced to the subclinical stage.

Keywords: Kuznetsov model; system dynamics; immune cells; Matlab; radiotherapy.

1. Introduction

Introducing immune checkpoint inhibitors to clinical practice was a major breakthrough in the fight against cancer. For some patients, tumor responses to anti-PD-1/PD-L1 or anti-CTLA4 therapies are spectacular and have a long-lasting effect. It has been shown that disease regression can occur even after an initial phase of tumor growth during the therapy. However, despite major discoveries in the field, therapies based on checkpoint inhibitors are exhibiting quite low response rates. Therefore, scientists are trying to establish reliable patient-specific biomarkers that would allow solving this problem. The current focus is on using, among others, measures of pretreatment T cell infiltration, PD-L1 expression profiles, inflammatory status, and mutational burden of the tumor. Finding a reliable correlation will allow

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for designing patient-specific therapy scheduling or for incorporating appropriate adjuvant treatment [1, 2].

In such a context, tumor dynamics must be thoroughly analyzed. Therefore, dynamics models for tumor growth and interactions are more and more needed. In recent years, these dynamics models have been based on nonlinear phenomena, including notions and concepts such as non-differentiability, multifractality, stochasticity etc. [3-6].

Combining radiotherapy with an immune checkpoint blockade may offer considerable therapeutic impact if the immunosuppressive nature of the tumor microenvironment (TME) can be relieved. In this study, we employ a mathematical model that was first introduced by Kuznetsov and colleagues in 1994 [7], in order to investigate the effects of anti-PD-1/PD-L1 therapy depending on the pretreatment tumor characteristics, which could lead to the discovery of a potential synergism between immune checkpoint inhibitors and radiotherapy [8, 9]. This model allows for an elegant and straightforward incorporation of such a treatment.

Kuznetsov and co. introduced the following mathematical model describing tumor-immune system dynamics:

$$\begin{aligned} \dot{E}(t) &= s + p\frac{E(t)N(t)}{g+N(t)} - d_0E(t) - mE(t)N(t) \\ \dot{N}(t) &= aN(t)\left(1-bN(t)\right) - nE(t)N(t) \end{aligned} \tag{1}$$

where $E(t)$ and $N(t)$ are the numbers of immune effector cells and cancer cells, respectively; s is the normal rate of influx of effector cells in the region of tumor localization; a is the maximum population growth rate of tumor cells (this parameter incorporates both multiplication and death of tumor cells); b^{-1} is the maximum transport capacity of the biological environment for tumor cells; p, g, m, n and d_0 are parameters which values have been estimated based on experimental data obtained from in vivo studies on lymphoma in the spleen of chimeric mice. According to [7], for $a = 0.18$ day $^{-1}$, $b = 2.0 \times 10^{-9}$ cells $^{-1}$ and $s = 1.3 \times 10^4$ cells day $^{-1}$, the parameters p, g, m, n and d_0 become: $p = 0.1245$ day $^{-1}$; $g = 2.019 \times 10^7$ cells; $m = 3.422 \times 10^{-10}$ day $^{-1}$ cells $^{-1}$; $n = 1.101 \times 10^{-7}$ day $^{-1}$ cells $^{-1}$; $d_0 = 0.0412$ day $^{-1}$.

Considering that the anti-PD-1/PD-L1 treatment reduces the probability that the cytotoxic T cell will be “turned off” during the interaction with the cancer cell, we can assume that the treatment decreases the value of parameter m. In order for us to decrease the complexity of the following analysis, but without losing its generality,

we will not take into account any pharmacokinetics and pharmacodynamics of the drug, i.e. we simply assume that during the treatment parameter *m* has a lower value.

First, we should check the predicted model dynamics for the nominal parameter values proposed by Kuznetsov et al [7]. Let us simplify this task by performing a non-dimensionalization procedure first. After defining $x = E/E_0$, $y = N/N_0$, and $\tau = nN_0t$ with $E_0 = N_0 = 10^6$ we obtain the slightly simpler system

$$\begin{aligned} \dot{x} &= \sigma + \rho\frac{xy}{\eta + y} - \delta x - \mu xy \\ \dot{y} &= \alpha y(1-\beta y) - xy \end{aligned} \tag{2}$$

where

$$\sigma = \frac{s}{nE_0N_0},\quad \rho = \frac{p}{nN_0},\ \eta = \frac{g}{N_0}\ ,\ \mu = \frac{m}{n},\ \delta = \frac{d_0}{nN_0}\ ,\ \alpha = \frac{a}{nN_0} \text{ and } \beta = bN_0.$$

We can see that in the non-dimensional model μ is the parameter affected by treatment.

2. Adding radiotherapy (continuous radiation) to the tumor-immune system

In order to derive a model that includes continuous radiation, we use the "5 R's" of radiobiology [10, 11]. We first add a term to the existing tumor-immune system that reduces the amount of tumor cells if radiation is administered [10, 11]:

$$\begin{aligned} \dot{N}(t) &= aN(t)(1-bN(t)) - nE(t)N(t) - \mu_2 DN(t) \\ \mu_2 &> 0 \end{aligned} \tag{3}$$

The right hand side of equation (3) is the same as the tumor growth model (equation (1)) except for the term $\mu_2 DN$ being subtracted from the growth term. *D* is the amount of radiation administered (in Gy) and μ_2 indicate how much the drug damages the tumoral cell per Gy. We assume continuous radiation and therefore set $D = d$ for $t \in (t_0, t_{\max})$

d is a constant amount of radiation given during a finite interval of time from t_0 to $t_{\max}$; after this time, one makes the measurements. If $d = 0$, i.e. no radiation is administered, the model is reduced to the growth model of equation (1).

Repair: Since we know that DSBs caused by radiation can be repaired [12], we want to include this in our model by adding a term, which increases the number of cells. The equation reads:

$$\dot{N}(t) = aN(t)(1-bN(t)) - nE(t)N(t) - \mu_2 DN(t) + \rho_2\lambda_2 DN(t), \quad \rho_2 > 0 \tag{4}$$

In the previous relation ρ_2 represents the factor of cells that are able to repair themselves after radiation, while λ_2 is the repair rate, with $\lambda_2 = \ln 2/T_r$, T_r being the repair half-time.

Repopulation: In addition to repair, cells can also continue to proliferate, either between fractions of radiation or during continued low dose radiation. If we assume β_2 to be the amount of cells able to proliferate, then the model reads:

$$\dot{N}(t) = aN(t)(1-bN(t)) - nE(t)N(t) - \mu_2 DN(t) + \rho_2\lambda_2 DN(t) + \beta_2 DaN(t)(1-bN(t)), \quad \beta_2 > 0 \tag{5}$$

Also, we add a term to the existing model that reduces the amount of immune effector cells if radiation is administered [13], and thus obtain:

$$\dot{E}(t) = s + p\frac{E(t)N(t)}{g+N(t)} - d_0E(t) - mE(t)N(t) - \mu_1 DE(t), \quad \mu_1 > 0 \tag{6}$$

To be absolutely rigorous, we would have to employ the same "5 Rs" of radiobiology to act on the immune effector cells too, and introduce a repair and a repopulation term. Yet, this would have complicate too much the starting system (1) and we only wanted to test if adding radiation therapy to Kuznetsov's original model would change the behavior of the interaction between effector cells and cells in a growing tumor. On the significances of the parameters μ_1 and μ_2 we will return later.

Consequently, introducing the effect of continuous radiation therapy (5) and (6) by means of the terms μ_1, μ_2, ρ_2, λ_2, β_2, and $D = d$ the amount of continuous radiation administered (in Gy) and after some straightforward algebraic manipulation, we get the same form for the new immunotherapy-radiotherapy system, as in (1):

$$\begin{aligned} \dot{E}(t) &= s + p\frac{E(t)N(t)}{g+N(t)} - \Theta E(t) - mE(t)N(t) \\ \dot{N}(t) &= AN(t)\left(1-\frac{B}{A}N(t)\right) - nE(t)N(t) \end{aligned} \tag{7}$$

where we made the notations:

$$A = a + (a\beta_2 + \rho_2\lambda_2 - \mu_2)D;$$
$$B = ab(1 + \beta_2 D); \tag{8}$$
$$\Theta = d_0 + \mu_1 D.$$

We can check easily that if one takes $D = d = 0$ (i.e. no radiation is administered), the model (7) reduces to the growth model (1).

Finally, we get the same form for the new non-dimensional immunotherapy-radiotherapy system, as in (2):

$$\dot{x} = \sigma + \rho\frac{xy}{\eta + y} - \Delta x - \mu xy$$
$$\dot{y} = \alpha' y(1 - \beta' y) - xy \tag{9}$$

with the following notations:

$$\sigma = \frac{s}{nE_0N_0},\ \rho = \frac{p}{nN_0},\ \eta = \frac{g}{N_0},\ \mu = \frac{m}{n},\ \Delta = \frac{\Theta}{nN_0},\ \alpha' = \frac{A}{nN_0},\ \beta' = \frac{B}{A}N_0$$

We can see that in the new non-dimensional immunotherapy-radiotherapy we have μ, which is affected by the immune checkpoint blockade, and the parameters α', β' and Δ which are affected by the treatment with continuous radiation.

Using the unaffected parameters proposed by Kuznetsov in [7] and introducing the new parameters modified by the continuous radiation assumption, we obtain the following unified non-dimensional model's parameter values:

$$\rho_2 = 0.5;\ \lambda_2 = \frac{\ln 2}{4};\ \beta_2 = 0.3;\ \sigma = 0.118;\quad \eta = 20.19;\ \mu = 0.00311$$
$$\Delta = 0.374 + 9.083\cdot\mu_1\cdot d;\quad \alpha' = 1.635 + \frac{(0.141 - \mu_2)d}{0.1101};$$
$$\beta' = \frac{0.00036(1 + 0.3\cdot d)}{0.18 + (0.141 - \mu_2)\cdot d} \tag{10}$$

After running a script in MATLAB, we analyze the bifurcation diagrams which can describe stationary states and their stability for different values of μ_1 and μ_2 parameters and we can see that they still behave in the same manner Fig. 1.

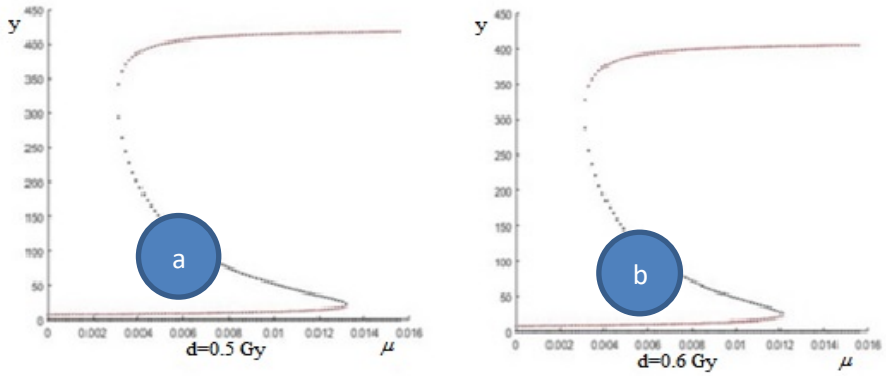

Fig. 1. Bifurcation diagram (in non-dimensional coordinates) for different values of d a) $\mu_1 = 0.0005$, $\mu_2 = 0.15$ and $d = 0.5$ Gy and; b) $\mu_1 = 0.005$, $\mu_2 = 0.15$ and $d = 0.6$ Gy

For a better understanding of the behavior predicted by equations (9), we qualitatively characterized different regions of behavior according to the action coefficients of radiotherapy on tumor cells and on immune cells. These results are shown in Fig. 2.

The values for μ_1 and μ_2 coefficients are derived from the literature and clinical trials, where μ_1 represents the radiotherapy action factor on effector immune cells and μ_2 is the effect of radiotherapy on tumoral cells.

We want to find the behavior of the system for different values of the parameter in the treatment with radiation. This can be done using a MATLAB script.

The variable x is the non-dimensional effector cell population and y the non-dimensional tumor cell population.

For the μ_1, μ_2 values estimated, we can notice that for a value of dose $d \geq 0.5$Gy, the state of the system becomes stable. This steady state is characterized by a relatively low TC (tumor cells) level and we refer to it as the "dormant tumor" steady state. Dormant states presumed that lethal tumor cells do not grow or they are growing at a slow rate during dormancy. This state appears after a radical treatment of a tumor.

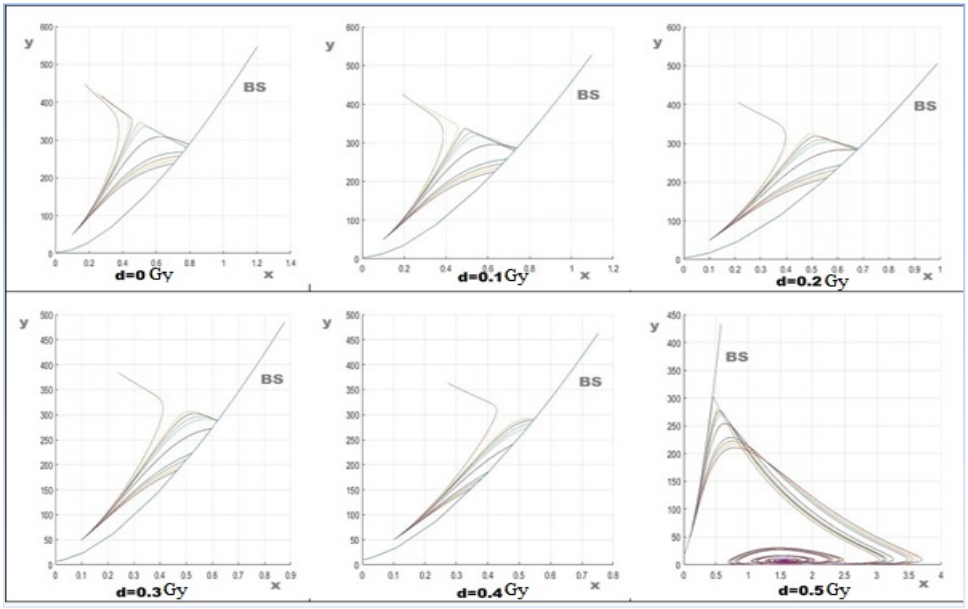

Fig. 2. Therapeutic diagram for $\mu_1 = 0.0005$; $\mu_2 = 0.15$ and d = (0 - 0.5 Gy) BS – boundary of separation

For the same initial conditions, the treatment curves running above the boundary of separation (BS) indicate that the tumor doesn't respond to radiation, and the treatment curves below BS, asymptotically approach the dormant tumor steady state. Thus the model is capable to explain both tumor dormancy and radio resistance.

The basin of attraction depends on the amount of immunotherapeutic medicine administered and the delivered dose of radiation.

Depending on the values of the coefficients μ_1 and μ_2, we can reduce the tumor to the subclinical stage, i.e. the healing process is irreversible, or we can reduce the size of the tumor only temporarily.

3. Conclusions

We propose the introduction of radiation therapy within a quantitative model for investigating tumor response to anti-PD-1/PD-L1 or anti-CTLA4 therapies, developed by Kuznetsov. We take into account the destruction, repair and repopulation functions of tumor cells and we also include some terms with destructive and/or inhibitory action on immune cells.

The new immunotherapy-radiotherapy system, obtained by us through simple algebraic manipulation, has the same shape as the original Kuznetsov model, modifying the parameters a, b and d_0 (see equation 8).

We use several already validated MATLAB programs and modify them for the purpose of our analysis. After running the programs we obtain the therapeutic diagrams (see Fig. 2.).

Using realistic values of parameters, we find a synergism between the immunostimulatory phenomena and the radiosensitivity of the tumor growth. We can then observe two types of behavior, the inactive state ("dormancy") and the radioresistant state. From the results of the concurrent action of immunotherapy and radiation, we can see that tumor reduction at the subclinical stage (irreversible healing process) is possible only for a well-defined parameter interval μ_1 and μ_2.

We can conclude that for the estimated parameters μ_1 and μ_2 at the values (0.0005; 0.005) and respectively 0.15, we achieve a positive therapeutic response, acting concurrently with immunotherapeutic drug and continuous radiation. In both cases, the value of the radiation dose, d, after which the system passes the separation barrier and becomes stable is in the range (0.5-0.6 Gy).

The concept of non-differentiability employed in our mathematical model, has been used, with specific adaptations, to describe various nonlinear biological phenomena [14-16].

The fact that our model is based on certain forms of the logistic equation allows us to affirm that generalizations of this equation, by employing non-differentiability, can be a starting point for developing various model classes which can describe specific types of tumor dynamics. Such mathematical procedures can be found, for example, in Refs. [17-34].

In any treatment combination involving multiple therapeutically modalities, sequence of the therapy and the time of initiation of each component could be essential to obtain the maximum benefit. Taking into account that different types of immunotherapy target different or different immune cells, the optimal therapeutic sequence should be chosen depending on both the type of immunotherapy and of tumor depending factors. For example, anti-CTLA4 therapy has shown increased efficacy in combination with hypofractional radiotherapy if administered prior to irradiation in an animal model. Another study in mice has shown synergy efficiency between hypofractionated radiotherapy and PDL1 blockade for tumors refractory to irradiation only in concomitant administration or after completion of the irradiation [35, 36].

In clinical practice an analysis of the KEYNOTE-001 trial (NCT01295827) has shown benefit in overall survival (OS) and progression free survival (PFS) for lung cancer patients receiving radiation therapy prior to PDE1 (Pembrolizumab) therapy. The more complex protocols included 3 treatment modalities (chemotherapy, immunotherapy and radiotherapy). In the PACIFIC study the role of the anti-programmed death ligand 1 antibody durvalumab as a consolidation for patients with stage III non-small cell lung carcinoma (NSCLC) with no progression after two or more cycles of platinum-based chemoradiotherapy was evaluated. The analysis of the results demonstrated the greatest benefit for starting durvalumab within 14 days after the completion of chemoradiation [37, 38].

In the case of the double anti-PDL1 and anti-CTLA4 blockade administered within 4 weeks of stereotactic radiosurgery on cerebral melanoma brain metastases, concomitant association led to a favorable response related to the treatments that had been separated for more than 4 weeks [39].

A number of clinical trials (NCT01449279, NCT01689974, NCT01557114, NCT01565837, NCT 01497808) evaluate the safety and tolerance profile of the combination immunotherapy radiotherapy in the treatment of metastatic malignant melanoma but also bring into question the systemic abscopal effect and the concept of the vaccine-like effect of radiotherapy , a historical treatment with locally-regional implications [40, 41].

The potential for synergic action between radiotherapy and immunotherapy demonstrated by the proposed model could be clinically applicable in the context of the development of stereotactic radiosurgery based on the administration of a high dose in a single fraction or in a reduced number of fractions. To apply the model in the context of standard radiotherapy based on fractionation concept, it is necessary to introduce the tumor radiobiological factors involved in response to irradiation.

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