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The study of antitumor efficacy of bevacizumab antiangiogenic therapy using a mathematical model

Abstract: A continual multicomponent model of growth of a low-invasive tumor is developed subject to the angiogenesis and single bevacizumab therapy. The model takes into account the differences in permeabilities of the pre-existent vasculature and the vasculature formed as the result of angiogenesis. The dependence of the antitumor therapy efficacy on the bev dosage is studied. It is found out that in the case of successful treatment the tumor may pass from a compact convective growth to diffuse intergrowth followed by significant reduction in the growth rate and the number of active tumor cells. It is shown that the bev dosage sufficient for successful treatment is significantly less than it is commonly accepted in clinical practice. A scheme of bev prescription allowing a significant reduction of both the costs of therapy and its negative effects while maintaining antitumor efficacy is proposed.

Keywords: Tumor modelling, antiangiogenic therapy, VEGF, bevacizumab.

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A significant change in the ideology and strategy of treatment for cancer patients has been observed recently. Within the framework of new approaches, the increasing life expectancy in combination with the improvement of its quality has come to the fore [29]. Since the classic chemotherapy using cytotoxic acting drugs is characterized by a low antitumor selectivity and high toxicity against normal organs and tissues, the development of a new low-toxicity antitumor therapy becomes an urgent problem.

As early as 1966, Folkman with coauthors had showed that the pre-existent circulatory system ensures the growth of transplantable tumors in an insulated body up to a diameter of 3–4 mm [7]. Further growth requires neovascularization, i.e., formation of new blood vessels from the pre-existent vasculature. This process is also called the tumor angiogenesis. It was Folkman who proposed in 1971 the antiangiogenic therapy (AT) as a promising type of treatment aimed to block the neovascularization of tumors, which, in his opinion, would lead to an essential decrease and ideally to complete cease of its growth in the absence of any negative impact on normal tissue [8]. The central target of AT is not a tumor, but endothelial cells as a basic structural unit of vascular networks [4]. The main goal of AT is not the killing of an endothelial cell, but blocking its functions aimed at formation of new blood vessels, i.e., proliferation and/or migration and/or differentiation.

A large number of substances stimulating and inhibiting the tumor neovascularization are known now. However, the most universal mediator of angiogenesis is the Vascular Endothelial Growth Factor (VEGF) [1]. The action of the first specialized antiangiogenic anticancer drug, bevacizumab, is aimed just to block the activity of VEGF. Bevacizumab (bev) is a recombinant monoclonal hyperhaline antibody to VEGF, which is selectively and actually irreversibly bound with it [10]. A series of researches are carried out nowadays for other AT drugs, as similar to bev, so different in the action mechanism [19, 32].

At present, there are few works aimed to mathematical modelling of antiangiogenic therapy that has its own strengths and weaknesses. Different approaches to AT modelling are used, those are ranged from

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description of molecular interactions of VEGF isoforms with various chemicals and receptors in the blood with the use of ODE systems [6] and consideration of phenomenological dependencies of parameters of a nondistributed model [27] to complex multicomponent distributed models of tumor growth taking into account the density of endothelial cells and the concentration of antiangiogenic preparation in the tissue [30]. The latter type of models, as it seems to us, can perfectly take account of the relationship between the tumor growth, angiogenesis in the tissue, and antiangiogenic drug action. The main problem of such models is the correct consideration of relations between the density of endothelial cells or vasculature with the influx of key metabolites, i.e., oxygen and glucose into the tumor.

In this paper, using a multicomponent distributed model, we study the influence of the antiangiogenic single bevacizumab therapy on the growth rate and structure of a low-invasive tumor under different concentrations of preparation. The growth rate of such tumor is determined by convective flows appearing in proliferation of cells in a dense tissue. In this case the magnitude of these flows depends on the level of proliferation that is limited by nutrients substances and hence the blocking of angiogenesis can significantly reduce the growth rate of such tumors.

1 The model

The interrelations of variables in the model of tumor growth subject to the angiogenesis and bev action is presented in Fig. 1.

The tumor is considered in this model as a colony of cells surrounded by normal tissue with a pre-existent vascular network. Active tumor cells can be in two states: proliferating cells with the density $n_1(r, t)$ are divided with the constant rate B and do not diffuse, migrating cells with the density $n_2(r, t)$ diffuse with the coefficient D_n and are not divided. The intensities $P_1(S)$, $P_2(S)$ of transition from one state to the other depend on the glucose concentration $S(r, t)$, if this concentration is large, migrating cells actively pass to the proliferating state, if the concentration decreases, the cells stop to proliferate and migrate randomly. The cells not coming to domains with high level of nutrient substrate die with the rate d_n . This approach was already used in our paper [14] in the simulation of the growth of an invasive tumor, it is based on the principle of dichotomy of migration and proliferation of its cells [11].

The density of normal cells of the organism is $h_t(r, t)$. We consider a dense incompressible tissue so that $h(r, t) + n_t(r, t) = \text{const}$, where $n_t(r, t)$ is the total density of tumor cells including necrosis, $n_t(r, t) = n_1(r, t) + n_2(r, t) + m(r, t)$. This allows us not to consider the equation for normal cells separately. After reduction to dimensionless form, the total density of all cells is taken equal to one.

Taking into account the convection with the convection flow rate $I(r)$, the one-dimensional equations for tumor cells take the form

$$\begin{aligned} \frac{\partial n_1}{\partial t} &= Bn_1 - P_1(S)n_1 + P_2(S)n_2 - \frac{\partial(I(x)n_1)}{\partial x} \\ \frac{\partial n_2}{\partial t} &= D_n \frac{\partial^2 n_2}{\partial x^2} + P_1(S)n_1 - P_2(S)n_2 - d_n n_2 - \frac{\partial(I(x)n_2)}{\partial x} \\ \frac{\partial m}{\partial t} &= d_n n_2 - \frac{\partial(I(x)m)}{\partial x} \\ P_1(S) &= k_1 \exp(-k_2 S), \quad P_2(S) = k_3 (1 - \tanh[(S_{\text{crit}} - S)\varepsilon]). \end{aligned} \quad (1.1)$$

Here $I(r)$ is determined by the kinetics of cell populations in the tissue, in particular, by division and migration of tumor cells. Normal cells of the organism are not divided and do not possess their own mobility, but they die with the rate $H(n_1 + n_2)$ under the action of factors produced by active cells of the tumor, where H is the parameter characterizing the death rate. According to [13], the one-dimensional equation for the rate of convective flow has the form:

$$I(x) = D_n \frac{\partial n_2}{\partial x} + \int_0^x [Bn_1 - H(n_1 + n_2)(1 - n_t)] dr. \quad (1.2)$$

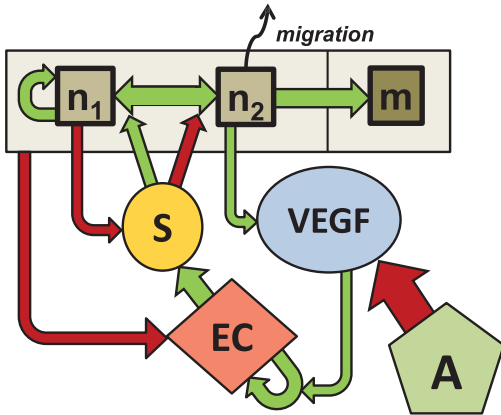


Figure 1. The block diagram of the model. n_1 , n_2 , and m are proliferating and migrating tumor cells and necrosis, respectively, S is the glucose, VEGF is the vascular endothelial growth factor, EC is the density of vasculature, A is the bevacizumab. Green arrows indicate stimulating links, red arrows correspond to inhibiting ones.

The model considers two types of vessels supplying the normal tissue and tumor, these are the pre-existent normal capillaries with the surface density $EC(r, t)$ and the capillaries formed as the result of tumor angiogenesis and having the surface density $FC(r, t)$. The inclusion of a separate variable in the model to describe these capillaries is necessary because their permeability for large nonliposoluble molecules such as molecules of VEGF proangiogenic factor and antiangiogenic bevacizumab preparation significantly increases compared to the pre-existent network of capillaries [17] due to the presence of a significant amount of large pores, so-called fenestrates, in their walls. In the absence of the tumor, $EC(r, t)$ is equal to one and new normal capillaries are not formed. In the absence of the tumor, $FC(r, t)$ is equal to zero. The rate of angiogenesis depends on the concentration $V(r, t)$ of VEGF, however, it is assumed that the capillary system can be compressed only to a certain limit EC_{max} . The tumor destroys the capillaries of both types with a constant rate l . The equations for the vasculature are written as follows:

$$\begin{aligned} \frac{\partial EC}{\partial t} &= -ln_t EC \\ \frac{\partial FC}{\partial t} &= \frac{RV}{V + V^*} (EC + FC) \left(1 - \frac{EC + FC}{EC_{max}}\right) - ln_t FC \end{aligned} \tag{1.3}$$

where R is the maximal growth rate of vessels.

The supply of molecules into the tissue through the capillary membrane due to diffusion can be described by the transformed Fick's law. i.e., $Q = PS(C_{cap} - C_{tis})$, where Q is the influx of substance, P is the permeability of the capillary membrane for it, S is the area of the capillary wall, $(C_{cap} - C_{tis})$ is the difference of concentrations of the substance in the capillary and cell. In order to estimate the permeability of pre-existent and newly formed capillaries for nonliposoluble molecules (glucose, VEGF, and bev), we used the formula $P = D'A_p h/S\varphi$ from [18]. In this case we assumed that all pores are the same and have a cylindrical form. Here A_p is the total area of pores, h is the length of a pore, $\varphi = (r - a)^2/r^2$ is a spatial zone available for a molecule in the pore, where a is the hydrodynamic radius of the molecule, r is the radius of a pore. D' is the coefficient of effective diffusion through the pore associated with the diffusion coefficient in the aqueous solution D by the Renkin's equation $D'/D = (1 - a/r)^2(1 - 2.1a/r + 2.09(ar)^3 - 0.95(a/r)^5)$ [25]. For definiteness sake, we assume that pores of pre-existent capillaries have the radius 5 nm and fenestrated capillaries differ from them so that each their hundredth pore is increased up to 35 nm, and the permeability is equal to the sum of permeabilities through the pores of two types. Using the values of permeability through somatic capillaries for glucose and some macromolecules found in the literature [3, 26] as reference, we obtain the values of the permeabilities we are interested in. It turns out that the permeability of fenestrated capillaries for glucose compared to pre-existent ones is increased about one and a half times, whereas, for VEGF it grows almost 40 times, and for bev this factor is almost 160. Certainly, this estimate contains a number of assumptions and approximations, but it suits well for the model because the order of magnitude is more important

for permeability parameters rather than specific values which, besides, may vary in real life both spatially and depending on the type of the tumor, patient’s age, and other factors. We assume that the surface area of pre-existent capillaries in the tissue is equal to $50 \text{ cm}^2/\text{cm}^3$ [28], which corresponds to $EC = 1$. We do not include this parameter in the equations explicitly, but take it into account when calculating permeabilities.

The distribution of glucose in the tissue is determined by the balance of its diffusion in the tissue, by income from the capillary network as pre-existent, so newly formed, and by the consumption of the tumor and normal cells. The supply of glucose is chosen so that in the absence of tumor the constant level of $S(r, t) = 1$ is maintained. The distribution of VEGF is affected by its diffusion in the tissue, production by tumor cells, utilization by endothelial cells, nonspecific degradation, irreversible binding with bev whose concentration in the tissue is $A(r, t)$, and the diffusion from the tissue into the capillary network where the concentration of VEGF is assumed to be negligibly small. The distribution of bev is determined by its diffusion in tissues, income from the capillaries, nonspecific degradation, and by binding to VEGF. The concentration of bev is normalized on its level in the blood, which is considered constant in modelling the antiangiogenic therapy.

After reduction to dimensionless form, the equations for concentrations of glucose, VEGF, and bev take the following form:

$$\begin{aligned} \frac{\partial S}{\partial t} &= D_S \frac{\partial^2 S}{\partial x^2} + Q_{S,EC}EC + Q_{S,FC}FC - \frac{q_t(n_1 + kn_2)S}{S + S^*} - \frac{q_h(1 - n_t)S}{S + S^*} \\ \frac{\partial V}{\partial t} &= D_V \frac{\partial^2 V}{\partial x^2} + p(fn_1 + n_2) - \omega V(EC + FC) - d_V V - (k_A A_0)AV - P_{V,EC}EC \cdot V - P_{V,FC}FC \cdot V \\ \frac{\partial A}{\partial t} &= D_A \frac{\partial^2 A}{\partial x^2} + P_{A,EC}EC(1 - A) + P_{A,FC}FC(1 - A) - d_{AA} - (k_A V_0)AV. \end{aligned} \tag{1.4}$$

Here D_S is the coefficient of diffusion of glucose into the tissue, $Q_{S,EC}$ and $Q_{S,FC}$ are the parameters determining the supply of glucose from pre-existent and newly formed networks, q_t , kq_t , and q_h are the rates of consumption of glucose by dividing and migrating tumor cells and the normal tissue, respectively, D_V is the coefficient of VEGF diffusion into the tissue, p and fp are the rates of production of VEGF by migrating and proliferating tumor cells, respectively, ω is the rate of its utilization by endothelial cells of vasculature in the process of angiogenesis, d_V is the rate of nonspecific degradation of VEGF, k_A is the constant of bev and VEGF binding, A_0 is the bev concentration in blood, $P_{V,EC}$, $P_{V,FC}$, $P_{A,EC}$, and $P_{A,FC}$ are the permeabilities of pre-existent and newly formed capillaries for VEGF and bev, respectively, multiplied by the normal area of capillary surface in a unit volume, D_A is the coefficient of bev diffusion in the tissue, d_A is the rate of its nonspecific degradation, V_0 is the normalization value for the concentration of VEGF.

System of equations (1.1)–(1.4) is solved in a one-dimensional plane domain of size $L = 4 \text{ cm}$. The left boundary contains the center of tumor which grows to the right in the direction of the normal tissue with a pre-existent vasculature. Since the differences in Laplace operators in the spherically symmetric, cylindrical, and plane cases are essential only for small radii where the tumor contains necrosis, then in our case the use of plane geometry does not lead to any essential distortion of the result. The boundary conditions have the form

$$\begin{cases} n_{1x}(0, t) = 0 \\ n_{2x}(0, t) = 0 \\ m_x(0, t) = 0 \\ EC_x(0, t) = 0 \\ FC_x(0, t) = 0 \\ S_x(0, t) = 0 \\ V_x(0, t) = 0 \\ A_x(0, t) = 0, \end{cases} \quad \begin{cases} n_1(L, t) = 0 \\ n_2(L, t) = 0 \\ m(L, t) = 0 \\ S(L, t) = 1 \\ EC(L, t) = 1 \\ FC(L, t) = 0 \\ V_x(L, t) = 0 \\ A_x(L, t) = 0. \end{cases} \tag{1.5}$$

The model contains many parameters whose values were generally taken from literature. In order to estimate the kinetic parameters of the model, the Lewis lung carcinoma (LLC) [24] was taken as the base type of tumor. The diffusion coefficient of the tumor cells s corresponds to a low-invasive tumors ($s = 10^{-10} \text{ cm}^2/\text{sec}$)

because our previous study [16] has showed that the antiangiogenic therapy is not effective for high-invasive tumors. The initial estimate of the maximal growth rate R of vascular network density was taken from [31]. The parameters determining the dynamics of VEGF in the tissue were taken from [21]. The rate of nonspecific degradation and bev diffusion coefficient were estimated from [10]. The constant k_A of binding to VEGF was taken from [22].

In order to make calculations more convenient, all the parameters were transformed to the dimensionless form. The following normalization values were taken: $t_0 = 1$ h for time, $L_0 = 10^{-2}$ cm for length, $n_{\max} = 10^8$ cells/ml for density of cells, $S_0 = 1$ mg/ml for glucose concentration, $V_0 = 10^{-13}$ mole/ml for VEGF concentration. As was already said, the normal surface density of pre-existent capillaries was taken equal to one, $EC_0 = 1$. The surface density of newly formed capillaries was normalized by the same value. The normalization value for the bev concentration A_0 was varied thus specifying different levels of the drug in the blood. After reduction to the dimensionless form, the following set of parameters was taken as basic.

Parameters taken from [24] :

$$\begin{aligned} B &= 0.047, & d_n &= 0.01, & D_S &= 108 \\ q_t &= 5.1, & k &= 0.025, & S^* &= 0.02 \\ p &= 20, & f &= 0, & k_1 &= 0.4 \\ k_2 &= 19.8, & k_3 &= 0.12, & S_{\text{crit}} &= 0.3 \\ \varepsilon &= 10, \end{aligned}$$

taken from [31] :

$$\omega = 1, \quad R = 0.0075$$

taken from [21] :

$$D_V = 21.6, \quad d_V = 0.1$$

taken from [22] :

$$k_A = 1.9 \cdot 10^{12}$$

estimated from [10] :

$$D_A = 7.2, \quad d_A = 0.0014.$$

The estimation of capillary permeability parameters for different molecules was described above. Other parameters of the model were taken from a physiologically justified range so that to reproduce the known tumor structure in the tissue, i.e.,

$$\begin{aligned} Q_{S,EC} &= 0.245, & Q_{S,FC} &= 0.337, & P_{V,EC} &= 0.03 \\ P_{V,FC} &= 1.1, & P_{A,EC} &= 0.002, & P_{A,FC} &= 0.325 \\ D_n &= 0.0036, & q_h &= 0.25, & V^* &= 0.1 \\ EC_{\max} &= 3, & l &= 1, & H &= 0.01. \end{aligned}$$

At the initial time moment $t = 0$ in the whole domain we assume that $S(x, 0) = 1$, $V(x, 0) = 0$, $EC(x, 0) = 1$, $FC(x, 0) = 0$, $A(x, 0) = 0$, $n_2(x, 0) = m(x, 0) = 0$, a small population of dividing tumor cells is located only near the left boundary of the domain, i.e., $n_1(x, 0) = 0.5 - 0.02x^2$ for $x \leq 5$ and $n_1(x, 0) = 0$ for $x > 5$. The initial bev concentration in the blood is $A_0 = 0$ and only if the radius of the tumor reaches 2 cm, A_0 gets a constant nonzero value, which simulates the antiangiogenic therapy.

System of equations (1.1)–(1.4) was numerically solved by the method of splitting with respect to physical processes. Convective equations were solved by the Lax–Wendroff method, kinetic equations were solved by the fourth-order Runge–Kutta method, Crank–Nickolson scheme was used for diffusion equations.

2 Results

The main aim of our work was to study the influence of bev concentration in the blood on the growth rate and the structure of tumors. Figure 2 presents the profiles of the densities of tumor cells and surface area of capillaries, as well as the concentrations of environment variables at the moment of ‘beginning of therapy’.

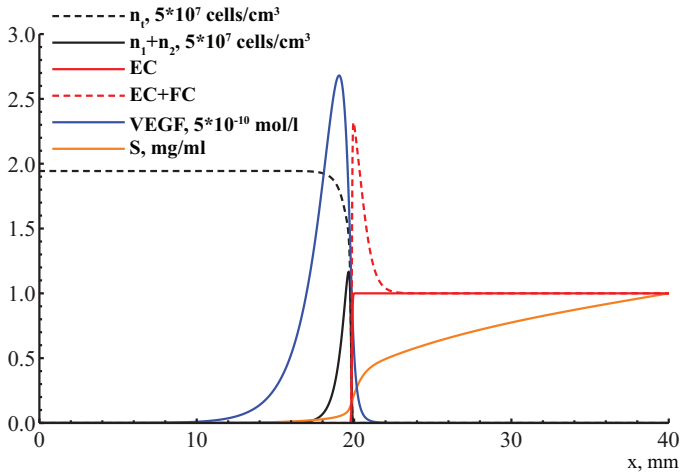


Figure 2. Density profiles of all tumor cells n_t , active tumor cells $n_1 + n_2$, pre-existent capillaries EC , total capillary network $EC + FC$, vascular endothelial growth factor VEGF, and glucose concentration S at the moment of ‘beginning of therapy’.

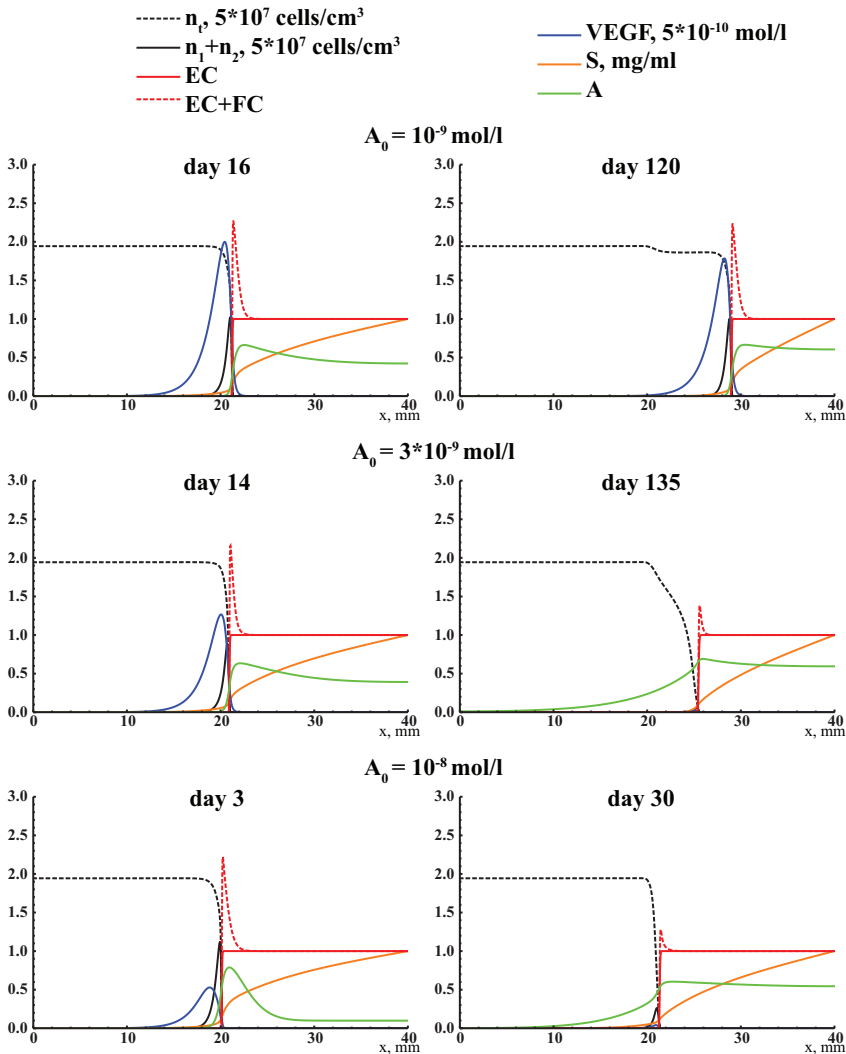


Figure 3. Density profiles of all tumor cells n_t , active tumor cells $n_1 + n_2$, pre-existent capillaries EC , total capillary network $EC + FC$, vascular endothelial growth factor VEGF, concentrations of glucose S and preparation A on different days for the preparation level in blood $A_0 = 10^{-9}, 3 \cdot 10^{-9}, 10^{-8}$.

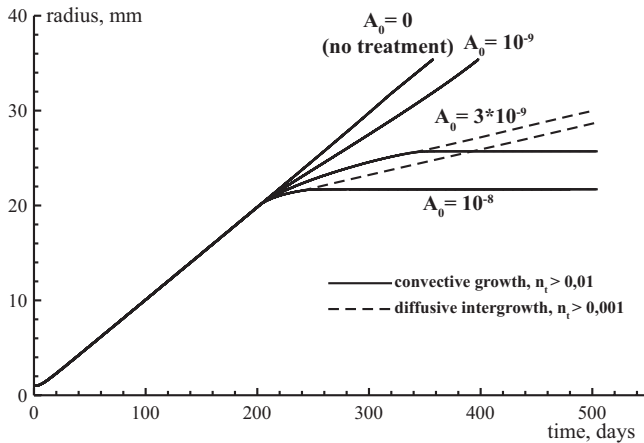


Figure 4. Dependence of the radius of the tumor on time for different levels A_0 of the preparation in the blood.

Figure 2 shows that the results of simulations correctly reproduce the structure of the tumor, i.e., a layer of active cells at the border and necrotic area in the center of the tumor. In this case, the maximal concentration of VEGF is inside the tumor close to its boundary and outside it and right up to the tumor the density the capillary network is increased due to newly formed capillaries, while there are practically no capillaries inside the tumor.

Figure 3 demonstrates the profiles of the variables of the model depending on the level of bev introduced in the blood, Figure 4 shows the dependence of the radius of the tumor on time for the corresponding cases and also for the case of tumor growth without therapy. The radius of the tumor was conditionally measured as the maximal coordinate where the total density of tumor cells is $n_t \geq 0.01$. It is clearly visible that an essential decrease of the tumor growth rate and a qualitative change in its structure occur with the increase of A_0 within the chosen range of values. If the concentration of bev in the blood equals $A_0 = 10^{-9}$ mole/l, a lot of unbound VEGF remains in the tissue and hence the tumor angiogenesis continues. However, the density of newly formed capillaries decreases, which leads to a slight (5–10%) decrease in the density of proliferating tumor cells and to thinning (by 10–15% of) of the layer of such cells. All this causes a decrease of the rate of tumor growth by approximately 20%, which is almost completely determined by the convection based basically on the total level of division of the tumor cells. In this case we could say that the anti-angiogenic therapy has no significant antitumor activity.

If the concentration of bev in the blood is increased three times ($A_0 = 3 \cdot 10^{-9}$ mole/l), then the unbound VEGF disappears completely from the tissue to 135th day of therapy, which means the termination of tumor angiogenesis. The tumor passes from convective growth to diffuse intergrowth followed by a critical reduction of its rate by more than three times, which is clearly seen in Fig. 4. The convective growth is characterized by a clear interface between the tumor and normal tissue, and in the diffusive intergrowth determined by their own motility of cells the density of the tumor is reduced significantly so that the boundary between the normal tissue and the tumor becomes visually indistinguishable. The antiangiogenic therapy cannot stop the process of diffusive intergrowth as this was shown previously in [15]. However, this passage occurs only after 4 months and during this period the tumor has time to grow significantly, its volume increases more than twice. All this means that the dosage of bev provides insufficient antitumor activity. Increasing the concentration of bev in the blood up to $A_0 = 10^{-8}$ mole/l, we get that the unbound VEGF does not practically remain in the tissue to the 30th day and tumor growth passes from convective to diffuse mode, which provides the highest possible antitumor effect. Further increase of bev dosage accelerates the clearance rate of VEGF from the tissue, for example, for the total bev concentration in the blood equal to $A_0 = 10^{-7}$ mole/l the angiogenesis stops already on the 2nd day of therapy since the total amount of VEGF in the tissue is reduced by approximately 150 times relative to its value at the beginning of therapy. However, this does not lead to an instant transition to the diffuse mode because the convective tumor growth from 2.0 to 2.2 cm is provided by the circulation network existing at the beginning of the therapy.

Thus, according to our model, the bev concentration on the blood equal to $A_0 = 10^{-8}$ mole/l is sufficient to obtain the maximal antitumor effect of antiangiogenic therapy. However, in clinical practice doctors prescribe to cancer patients bev doses of 5–15 mg/kg of patient's weight every two or three weeks [5]. Due to a low decomposition rate of bevacizumab and its small apparent volume of distribution, the dosage not lower than 10 mg/kg assigned not less than once every two weeks provides the concentration of drug in the blood at the level of 10^{-6} mole/l.

3 Discussion

In this paper we considered a model of growth of a low-invasive tumor subject to angiogenesis and single bevacizumab therapy. An advantage of this model is that it takes into account the differences in the permeabilities of pre-existent capillaries and the capillaries formed as the result of tumor angiogenesis. These differences indicated in several experimental works [12, 20] are essential for modelling the distribution of high-molecular substances such as VEGF and bev in the tumor and surrounding tissues.

It was shown that the antiangiogenic single bev therapy can significantly (several times) slow down the rate of growth of a low-invasive tumor, but cannot stop it completely. In addition, it was found that in the case of successful antitumor action of the anti-angiogenic therapy the low-invasive tumor may pass from the convective mode of growth to the diffusive one and the compact growth is replaced by infiltration of tumor cells in the normal tissue, and a clear interface between a dense tumor and the normal tissue is blurred. In the case considered here this appears because the convection dominates the diffusion only due to additional influx of food as the result of tumor angiogenesis, which increases the pool of proliferating cells and hence the speed of convection. In the case of successful block of the angiogenesis with bev, the number of dividing cells is decreased and the convection decreases putting in the forefront the diffusive spread of the tumor into the tissue. Obviously, the phenotype of the tumor does not change, but the clinical picture is changed dramatically, which complicates the situation from a medical point of view. The universality of this result depending on kinetic parameters of the tumor will be closely studied in the future.

The model shows that bev concentrations sufficient to block the angiogenesis successfully (10^{-8} mole/l) are actually less by two orders than those accepted in medical practice (10^{-6} mole/l). Naturally, those differences may be caused by the necessity to overcome the variability of physiological parameters of patient's organism (the density of vasculature, its permeability, rate of bev withdrawal from the blood) and difference in types of tumors in order to obtain a secure angiogenic effect. However, in our opinion, such differences cannot increase the bev dosage necessary to obtain the maximal antitumor effect more than by one order. Even a primary introduction of ultrahigh doses of bevacizumab (10^{-6} mole/l) should provide a rapid (within 1–2 days) binding of all active VEGF in tissues and hence the total block of tumor angiogenesis. And one can maintain the achieved effect by using much lower bev dosage. Such way of drug insertion does not decrease the antitumor efficacy and also decreases negative effects that, in particular, in the case of bowel perforation may be of fatal character [2, 9]. In addition, such schedule of introduction allows one to reduce significantly the cost of bev therapy since a course of such treatment costs currently approximately 50 thousand dollars, which is greater than the standard chemotherapy in terms of a single patient [23].

Thus, we consider it appropriate to undertake comparative clinical researches of the standard protocol of bev treatment (constant standard dosage) and the protocol with a standard high first dose of bev and subsequent supporting doses reduced 3–5 times.

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