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INTRODUCING A MATHEMATICAL MODEL FOR BONE METASTASES CONTROL

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ABSTRACT

Bone metastases (secondary tumor) occurs when cancer cells spread from their original site to a bone. Some types of cancer such as breast cancer particularly spread to a bone. In this paper after investigating a specific drug to prevent progressing of bone metastases, a new mathematical model is introduced for affection of this drug. The aim is to express a control model for bone metastases preventing. The model is described as a nonlinear partial differential equations.

Indexing terms/Keywords

Mathematical control model; Bone metastases; Drug controlling

Academic Discipline And Sub-Disciplines

Mathematical modeling of Bone Metastases Control

SUBJECT CLASSIFICATION

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1. INTRODUCTION

When cancer spreads from the part of the body where it started to other part of the body it is called metastasis. Metastases can occur when cells break away from a cancerous tumor and travel through the bloodstream. If there is a single tumor, it is called a metastasis tumor and when there are 2 or more metastasis, it is called metastases. Bone is a common site for metastases and up to 70% of breast and prostate cancer patients develop secondary tumors in the bone environment [2].The bone metastases was investigated in this paper because of breast cancer.

Physiologically, bone is remodeled through the process where old or damaged tissue is resorbed by cells specialized in bone destruction, osteoclasts and new bone is produced by specialized bone-forming osteoblasts [5-8-13]. The RANK/RANKL/OPG pathway plays a crucial role in physiological bone remodeling. Receptor activator of nuclear factor kappa-B (RANK) is expressed by osteoclast precursors and mature osteoclasts. RANK ligand (RANKL) expressed by cells of the osteoblastic lineage stimulations osteoclast formation and directs osteoclasts towards sites of microdamage during remodeling. Mature osteoblasts also produce the soluble decoy receptor osteoprotegrin (OPG), which bind to RANKL and hence prevents it from interaction with RANK [8]. Cancer cells produce factors such as the parathyroid hormone-related protein (PTHrP), which induce the production of osteoclast-stimulating RANKL by osteoblasts.

Some researchers have been done on the influence of bone remodeling factors recently. These studies, introduced some models which have set out to describe bone remodeling and the interaction of various factors.

Svetlana V.Komorova and his colleague constructed a mathematical model of autocrine and paracrine interactions among osteoblasts and osteoclasts that allowed us to calculate cell population dynamics and changes in bone mass at a discrete site of bone remodeling [9]. A mathematical model was developed by Yanan Wang and his colleague at 2009. The model incorporated a new understanding on the interaction of PTHrP and other factors with the RANK-RANKL-OPG pathway into bone remodeling, which is able to simulate anabolic action of bone induced by PTH at cellular level [18]. Garzon-Alvarado simulated metastatic activation in bone marrow in a mathematical model that involve the activation of molecules from bone tissue cells [3]. Ryser and his colleague in 2012 described osteoprotegerin in bone metastasis in a mathematical model, they demonstrated that at lower expression rates, tumor-derived OPG, enhances the chemotactic RANKL gradient and osteolysis, whereas at higher expression rates OPG broadly inhibits RANKL and decreases osteolysis and tumor burden. They tested this hypothesis using a mathematical model of nonlinear partial differential equations describing the spatial dynamics of OPG, RANKL, PTHrP, osteoclasts, tumor and bone mass [15].

As literatures shows the effect of drug in bone metastases has not been studied in aspect of mathematics yet. In this research a new mathematical model is suggested for the dynamics between tumor cells, OPG, RANKL, PTHrP, osteoclast and chemotherapy drug, as a control problem. For this purpose, we intent to study systemic treatment when a special drug that prevent progressing bone metastases is used. These progress are eradicated in an optimal control problem. The bases of proposed model comes from [15], (this model describe bone metastases completely) with some changes in adding the effect of drug to the equations. It is necessary to remind that one of the important goals to present this model is the ability to find the way of using drug in an optimal way with different goals like minimizing the volume of tumor, reducing the amount of used drug and so on.

The effect of drug in bone metastases don't study in aspect of mathematics. In this paper the systematic treatment is studied and then a special drug that prevents progressing bone metastases is introduced.

The plan of the paper is as follows: after explaining Mechanism of metastases growth in mathematical model in section 2, we introduce a mathematical model in section 3 which Investigate drug for bone metastases, in section 4, Control Model for Bone Metastasis is expressed and finally conclusion is expressed in section 5.

2. MECHANISM OF METASTASES GROWTH IN MATHEMATICAL MODEL

A mathematical model uses the language of mathematics to produce a more refined and precise description of the system. In epidemiology, models allow us to translate between behaviors at various scales, or extrapolate from a known set of conditions to another.

The mathematical model that describes the process of bone metastases in [15], consists of 6 state variables: The local cell density of osteoclast is denoted by $u(\boldsymbol{x},t)$, where $\boldsymbol{x}=(\mathrm{x},\mathrm{y})$. The RANKL field is denoted by $\phi_R(\boldsymbol{x},t)$, the OPG field by $\phi_O(\boldsymbol{x},t)$, PTHrP field is denoted by $\phi_P(\boldsymbol{x},t)$, bone density (ρ_B) and tumor density (ρ_T).

Therefor the dynamic of the bone metastases model is:

$$\frac{\partial u}{\partial t}=\alpha u^g-\beta u-\xi\frac{\partial}{\partial x}\left(u_a\frac{\partial\phi_R}{\partial x}\right)+k_1\frac{\phi_R}{\lambda+\phi_R}u_a$$

$$\frac{\partial\phi_R}{\partial t}=\kappa_R\phi_p\rho_B+\sigma_R\frac{\partial^2\phi_R}{\partial x^2}-k_2\frac{\phi_R}{\lambda+\phi_R}u_a-k_3\phi_R\phi_O$$

$$\frac{\partial\phi_O}{\partial t}=\tau_O\rho_T+\sigma_O\frac{\partial^2\phi_O}{\partial x^2}-k_O\phi_o-k_3\phi_R\phi_O$$

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$$\frac{\partial \phi_P}{\partial t} = \tau_P \rho_T + \sigma_P \frac{\partial^2 \phi_P}{\partial x^2} - k_P \phi_P$$

$$\frac{\partial \rho_B}{\partial t} = -k_B u_a$$

$$\rho_T = 1 - \rho_B.$$

Table 1. Table captions should be placed above the table

Variable	Description
U	Density of osteoclasts
u_a	Density of active osteoclasts
ϕ_R	RANKL concentration
ϕ_O	OPG concentration
ϕ_P	PTHrP concentration
ρ_B	Bone density
ρ_T	Tumor density

Table 2. Table captions should be placed above the table

Parameter	Description
A	Production rate of osteoclasts
G	Autocrine stimulation of osteoclasts
B	Apoptosis rate of osteoclasts
Ξ	Chemotactic motility of osteoclasts
k_1	RANK RANKL stimulation rate
Λ	Half saturation of RANK RANKL binding
k_R	PTHrP mediated production rate of RANKL
σ_R	RANKL diffusivity
k_2	RANK RANKL binding rate
k_3	RANKL OPG binding rate
τ_O	Rate of OPG production by tumor
σ_O	OPG diffusivity
k_O	OPG degradation rate
τ_P	Rate of PTHrP production by tumor
σ_P	PTHrP diffusivity
k_p	PTHrP degradation rate
k_B	Resorption rate of bone by active osteoclasts

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The parameters of the model are described in [15]. They are estimated based on experimental findings, (*d* is abbreviate day):

$\alpha = 9.49mm^{-\frac{1}{2}}d^{-1}$ $\beta = 0.2d^{-1}$ $g = 0.5$ $\sigma_R = 0.5 * 10^{-2}mm^2d^{-1}$

$\sigma_O = 1.6 * 10^{-2}mm^2d^{-1}$ $\sigma_P = 3 * 10^{-2}mm^2d^{-1}$ $k_O = 10d^{-1}$ $\kappa_R = 1d^{-1}$,

$k_1 = 0.3d^{-1}$ $k_2 = 0.05pmol\,d^{-1}$ $\lambda = 13pmol\,mm^{-1}$ $\xi = 1.3 * 10^{-3}mm^3pmol^{-1}d^{-1}$

$k_B = 3d^{-1}$ $k_3 = 0.1mm\,d\,pmol^{-1}$ $k_P = 4d^{-1}$.

3. INVESTIGATION OF DRUG FOR BONE METASTASES

Local and systemic treatments are two main kinds of bone metastases treatment. One or both types of treatment may be used, depending on the extension and location of the cancer. Local treatments are directed at a single area. These kinds of treatments can be useful if the cancer has spread to only one bone (that is called a metastasis or a metastatic tumor), or if there is one or a few areas of cancer spread that are more advanced than others and need to be treated right away. Local treatments include external radiation therapy, surgery and related techniques.

Systemic treatments can affect the whole body. In many cases, especially if the cancer spreads to many bones, systemic treatments are used because they can reach cancer cells that have spread throughout the body. Systemic therapies include chemotherapy, hormone therapy, or other medicines which are taken by mouth or injected into the blood. When there are 2 or more metastatic tumors, it's called "metastases" and as metastases is investigated in this research, the systemic treatment is considered and a special drug that prevent progressing bone metastases is introduced.

There are different kinds of drugs that prevents metastasis progressing such as Bisphosphonates (zometa) and Tamoxifen. One of the famous and effective drugs that use for bone metastases is tamoxifen [6], which is a hormone drug. Hormones in the body drive the growth of some common cancers; for example, the female hormone estrogen promotes growth breast cancer. One of the main ways to treat cancers is to stop certain hormones from affecting the cancer cells. The main ways of doing this are lowering hormone levels and blocking the hormone's action at the cancer cell. One way which is used more often to lower hormone levels, is to give drugs to keep the hormones from being made. In this regard, tamoxifen is one of the best drugs that block the effects of estrogen on breast cancer. Indeed high-dose of tamoxifen is used as a treatment for bone metastases; which decrease bone reabsorption [17]. In this article we want to study the effect of this drug on dynamic system of metastasis growing. For this purpose it is require to have a glance to chemotherapy and special manner of output.

In order to understand how chemotherapy works, more knowledge is required about tumor cells. In fact, tumors are made up of cells which are reproducing at abnormally high rates. Normal cells know to stop reproducing when they come into contact with other cells; in the case of a tumor, this stop mechanism is missing and it causes cells to continue to divide over and over.

Cell replication occurs in a series of phases, called the cell cycle. The cell cycle phase are: G_0 (nothing is happening), G_1 (or gap 1, a growth phase), S (synthesis, the replication of DNA occurs), G_2 (gap 2, another growth phase) and M (mitosis, the actual division from 1 cell into 2 cells). Some chemotherapy agents are able to kill a tumor cell during any phase of the cycle; these are called cell-cycle nonspecific (CNS). Others are only able to kill tumor cells during a specific phase and are unable to work in the resting phase, called cell-cycle specific (CS)[16]. Tamoxifen is a kind of CNS drug [6]; it means that tamoxifen can kill a tumor cell during any phase of the cycle. Because of this ability, tamoxifen is in the top list of anti-tumor drugs.

It is assumed that cell killing rate over a short interval of time, is the exponential of drug concentration $y(t)$ at time. Hence an Exponential Kill (EK) model is proposed to predict the state of dose-response curve based on the cell cycle phase specificity of the used drug. EK model generates sigmoidal dose-response curves like those measured empirically [14]. In this regards, the fraction of cells killed by using a CNS drug of concentration $y(t)$, is shown in [4] as:

$$f(y) = M\left(1 - e^{-y(t)}\right), \qquad (2)$$

where M is the response coefficient that $0 \leq M \leq 0.5$ [7-11-12].

In bone metastasis model in [15], Ryser and his colleague showed that:

$$\rho_T = 3u_a; \qquad (3)$$

It is clear that that tamoxifen is an antiestrogen drug and directly inhibits tumor growth by blocking ER-mediated stimulation of cell growth [1].

Therefore if the efficiency of tamoxifen in preventing metastasis growing on tumor is, according to (2) the following relation can be presented:

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$$\frac{d\rho_T}{dt} = 3u_a - M(1 - e^{-y})\rho_T \qquad (4)$$

As an engineering point of view, since such kind of drug is an output agent for the body system, to prevent the illness in a prescribed manner; here drug acts as an input in control a system and one can get some help from control theory to present the problem.

4. CONTROL MODEL FOR BONE METASTASES

Presenting a control model is the aim of this article, because as we know drugs prevent illness progressing in general; in other words drug act as a controller for body. In this regards using control model to show this process is useful. The main purpose of this modeling is to control the process of progress bone metastasis by using Tamoxifen. In previous section the way of adding drug to the model was shown. In this section we intend to express a control model for bone metastases. When doctor prescribe drug to cancer patient, the main goal is to decrease tumor or prevention of progressing tumor. In this regards using control model to show this process is useful.

Propose the control model that based on the existed literature, clinical evidences and Tamoxifen properties for controlling bone metastases by this kind of drug is suggested as follows:

$$\frac{\partial u}{\partial t} = 9.49u^{0.5} - 0.2u - 1.3 \times 10^{-3}\frac{\partial}{\partial x}\left(u_a\frac{\partial \phi_R}{\partial x}\right) + 0.3\frac{\phi_R}{13 + \phi_R}u_a$$

$$\frac{\partial \phi_R}{\partial t} = \phi_p(1 - \rho_T) + \tau_R\rho_T + 0.5 \times 10^{-2}\frac{\partial^2 \phi_R}{\partial x^2} - 0.05\frac{\phi_R}{13 + \phi_R}u_a - 0.1\phi_R\phi_O$$

$$\frac{\partial \phi_O}{\partial t} = \tau_O\rho_T + S_0 + 1.6 \times 10^{-2}\frac{\partial^2 \phi_O}{\partial x^2} - 10\phi_o - 0.1\phi_R\phi_O \qquad (5)$$

$$\frac{\phi_P}{\partial t} = \tau_P\rho_T + 3 \times 10^{-2}\frac{\partial^2 \phi_P}{\partial x^2} - 4\phi_P$$

$$\frac{\partial \rho_T}{\partial t} = 3u_a - M(1 - e^{-v})\rho_T$$

According to bone metastases model that is described in [15] is periodic boundary conditions. The initial RANKL field consist constant concentration. The initial profile of active osteoclast is placed in the middle of the domain. The initial bone tissue is intact$\rho_B(t = 0) = 1$. There is no presented tumor and the OPG and PTHrP concentrations are zero.

5. CONCLUSION

Previous mathematical model have been extended in this study by adding drug to the model with the use of control theory. The main purpose of this modeling is to control the process of bone metastases progress by using tamoxifen. For this purpose, bone metastases and the mathematical models which are existed were studied. According to our review the effect of drug in bone metastases had not been studied yet in aspect of mathematics. One of the famous and effective drugs that is used for bone metastases is tamoxifen. After choosing drug, the way of adding it to the model was considered. Upon our review, tamoxifen is in the set of CNS drug and it effect to the model exponentially. In fact, since drug input to the body system, drug was considered as a control variable. As an introductory step, the bone metastasis model was studied deeply and it was introduced a development model for treatment with the use control theory. Metastases treatment can be discussed by using this model and solving the model.

REFERENCES

[1] Canon J., Brayant R., Roudier M., Branstetter G., Dougall W.C. 2012. RANKL inhibition combined with tamoxifentreatment increases anti – tumor efficacy and prevents tumor – induced bone destruction in an estrogen receptor – positive breat cancer bone metastasis model. Breast Cancer Res Treat 135: 771-780.

[2] Clohisy DR, Ramnaraine ML. 1998. Osteoclasts are required for bone tumors to grow and destroy bone. J Orthop Res. 16(6):660-666.

[3] Diego Alexaner Garzon-Alvarado. 2012. A mathematical model for describing the metastasis of cancer in bone tissue. Computer Methods in Biomechanics and Biomedical Engineering 15(4) 333-346.

[4] Gardner S.N. 2000. A mechanistic, Predictive model of dose – response curves for cell cycle phase – specific and – nonspecific drugs, Cancer Res, 60:1417 – 1425.

[5] Hernisken K., Neutzsky – Wulff A., Bonewald L., Karsdal M. 2009. Local communication on and within bone controls bone controls bone remodeling. Bone 44:1026-1033.

[6] Hurtado A,Holmes Ka.Geistlinger TR., Hutcheson P., Nicholson RI., Brown M., Jiang J., Howat WJ., Ali S,carroll JS. 2008. Regulation of ERBB2 by oestrogen receptor PAX2 determines reponse to tamoxifen, Nature 756 (7222): 663-6.

[7] Itik M, M.U. Salamci, S.P. Banks. 2010. SDRE optimal control of drug administration in cancer treatment, Turk J ElSc Eng & Com Sci, Vol.18, No.5.

[8] Kerns A., Khosla S., Kostenuik P. 2008. Receptor activator of nuclear factor kB ligand and osteo – protegrin regulation of bone remodeling in health and dicase. Endocr Rev 29: 155-192.

[9] Komarova SV, Sm L.G.de ith RJ, Jeffrey Dixon S, Sims SM, Wahh LM. 2003. Mathematical model predicts a critical role for osteoclast autocrine regulation in the control of bone remodeling, Bone 33, 206-215

[10] Lemaire V., Tobin F.L., Greller L.D., Cho C.R., Suva L. 2004. Modeling the interaction between osteoblast and osteoclast activities in bone remodeling, Journal of theoretical biology 293-309.

[11] Pillis L.G.de , A Radunskaya, 2003. A Mathematical tumor model withol immune resistance and drug therapy: an optimal control approach, Mathematical and computer modeling, 37, 1221-1244.

[12] Pillis L.G.de , W. Gu, A Radunskaya. 2005. Mixed immunotherapy and chemotherapy of tumors: modeling, aplications and biological interpretations.

[13] Parfitt A. 1994. Osteonal and hemi-oseonal remodeling: The spatial and temporal framework for signal traffic in adult human bone . J Cell Biochem 55: 273-286.

[14] Rupniak, H. T., Whelan, R. D. H., and Hill, B. T. 1983. Concentration and time-dependent inter-relationships for antitumour drug cytotoxicities against tumour cells in vitro. Int. J. Cancer, 32: 7-12.

[15] Ryser M., Yiding Qu, Komarova S. 2012. Osteoprotegerin in Bone Metastases: Mathematical Solution to the Puzzle. PLOS Comput Biol 8(10): e1002703

[16] Roe, Dale R., Isaascon D., kupferschmid M. 2011. A Mathe matical Model of breast cancer treatment with CMF and Doxorubicin , Bull Math Biol 73:586-608.

[17] Stathopoulos G.P., Trafalis D. 2013. High – dose tamoxifen in breast cancer bone metastasis, JBUON 18(2): 532

[18] Wang Y., Qin Q.H., Kalyanasundaram S. 2009. A theoretical model for simulating effect of parathyroid hormone on bone metabolism at cellular level, MCB, vol.6,no.2, pp.101-112.