

Modeling and design of combined antiangiogenic and chemo-therapy

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ABSTRACT

Models of combined antiangiogenic therapy (indirect control) and chemotherapy (direct control) of cancer are proposed and analyzed. The models are based on the idea proposed by Hahnfeldt *et al.* and the analysis has two goals: first of all we check stability of the equilibrium point of the models to find conditions leading to tumour eradication then we propose an optimization problem and discuss necessary conditions of its solution.

Chemotherapy still belongs to the most often used methods of direct control of tumor populations. The most important obstacle against successful chemotherapy is drug resistance acquired by cancer cells while the normal tissues retain sensitive to the drugs. This negative feature of chemotherapy may be used as an advantage in the antiangiogenic therapy which is directed towards special part of normal tissues and only indirectly destroys tumor cells and it is why it has been called by Kerbel a therapy resistant to drug resistance. Therapy directed against tumor vasculature does not exploit tumor cell sensitivity, relying instead on tumor suppression consequent to inhibition of associated vasculature. Tumor angiogenesis belongs to the most inspiring areas of cancer research in oncology, and the idea of attack against it as a tool for tumor eradication originated from Folkman's works is one of the most hopeful areas of anticancer therapy. It has been also found to be efficient for slowly growing tumors which are difficult for classical chemotherapy. Yet another good news is that targeting tumor vasculature rather than tumor cell population would avoid the necessity of having to obtain intra-tumor drug delivery. The drawbacks are: difficulties in observations of the results, high dosage necessary for fast growing tumors, side effects related to menstruation, diabetes, wound healing. Still however the most important constrain in efficient antiangiogenic therapy is the accessibility of antiangiogenic agents. This is why the rational anticancer therapy should contain combination of antiangiogenic therapy with more standard techniques of anticancer treatment for example chemotherapy. On the other hand chemotherapy is usually regarded to be more efficient for fast growing tumors. Thus in some sense drawbacks of chemotherapy (induced drug resistance, smaller efficiency for slowly growing tumors) could be supported by advantages of antiangiogenic therapy and drawbacks of this therapy could be at least slightly moderated by the advantages of chemotherapy. Side effects of both therapies seem to be separable at least at some level.

The complexity of the process of vascularization as well as the way in which inhibitors, stimulators and antiangiogenic drugs act results in the complicated models applicable for simulation of the process but completely not useful in synthesis or even analysis of therapy protocols. The exception is a class of models proposed by Hahnfeldt *et al* who suggested that the tumor growth with incorporated vascularization mechanism can be described by Gompertz type or logistic type equation with variable carrying capacity which defines the dynamics of the vascular network. Roughly speaking the main idea of this class of models is to incorporate the spatial aspects of the diffusion of factors that stimulate and inhibit angiogenesis into a non-spatial two-compartmental model for cancer cells and vascular endothelial cells. This type of model or more precisely its modification will be used by us in our study. The most important feature of this modification is two-compartmental model of cancer growth which enables to involve the effect of drug resistance induced by chemotherapy. D'Onofrio and Gandolfi proved that using sufficiently high doses of antiangiogenic drugs we are able to annihilate completely the vascular network of the tumor and indirectly eradicate the tumor itself. We present similar analysis for the model of combined therapy. Nevertheless since the results have an asymptotic character it means that the process of eradication is theoretically infinite and the same the patient once treated by the antiangiogenic therapy should remain under such control to the end of his life. To overcome this difficulty we propose to optimize the therapy in finite horizon. We formulate necessary conditions of optimality based on Pontryagin Maximum Principle and explain the results in terms of therapy protocols.