Population-based models of anti-tumor anti-angiogenesis therapy: theory and biomedical inferences.

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1. ANGIOGENESIS, TUMORS AND ANTI-ANGIOGENIC THERAPIES

Primary tumors and metastases require the formation of new blood vessels in order to grow beyond about 1 to 2 mm^3. This process is sustained by different mechanisms: tumors may coopt existing vessels, may induce the formation of new vessels from pre-existing ones or may exploit endothelial precursors originating from the bone marrow. Vessel formation is regulated by a number of pro- and anti-angiogenic molecules, released by tumor cells. There is compelling evidence from experimental work, that inhibiting angiogenesis may induce tumor regression or sometimes cure. Targeting tumor vasculature, composed of genetically stable endothelial cells, has been regarded as a means to overcome acquired drug resistance. Angiogenesis inhibitors are commonly classified as direct inhibitors, acting on the endothelial cells and inhibiting their proliferation and migration or inducing their apoptosis, indirect inhibitors, blocking the production of angiogenic factors by malignant cells. Most angiogenesis inhibitors are cytostatic, inhibiting the formation of new blood vessels, but some direct inhibitors may result cytotoxic, inducing rapid destruction of existing blood vessels. Various anti-angiogenic drugs are undergoing clinical evaluation, with conflicting outcomes despite some encouraging results.

2. MATHEMATICAL MODELING ANTI-ANGIOGENESIS THERAPIES

Modelling the interaction between tumor growth and the development of its vascular network, as well as the action of angiogenesis inhibitors, could help to plan effective anti-angiogenic therapies. Some mathematical models have been recently proposed (Hahnfeldt et al 1999, Agur et al 2004, d'Onofrio and Gandolfi 2004). Among the factors influencing the clinical effectiveness of angiogenesis inhibitors, the administration schedule appears to be particularly relevant. Anti-angiogenic therapy has always been proposed as uninterrupted, long term treatment, to obtain effective tumor growth control. Despite this concept has pervaded the clinical development of anti-angiogenic drugs, a deeper insight into the relationships between drug pharmacokinetics and anti-vascular activity could be useful to improve clinical results.

Hahnfeldt et al. (1999) proposed a simple mathematical model which describes the vascular phase of tumor growth assuming that it is strictly controlled by the dynamics of the vascular network, and that the vascular dynamics is the result of the opposite influence of pro-angiogenic and anti-angiogenic factors produced by the tumor itself. This model

provides a framework to portray the effects of anti-angiogenic therapies, and it was successful in fitting experimental data on the growth and response to different anti-angiogenic drugs of Lewis lung carcinomas implanted in mice. A mathematical analysis of that model was presented in (d'Onofrio and Gandolfi 2004), focusing on the tumor eradication, under regimens of continuous or periodic anti-angiogenic therapy.

3. THE INTERPLAY BETWEEN MATHEMATICAL MODELS AND MEDICAL INFERENCES

In this work we illustrate some biological and clinical inferences derived from the analysis of the model by Hahnfeldt et al. (1999) and of variants and generalizations of it. In particular, we shall focus on the following topics:

- Analytically, we shall derive conditions for the globally asymptotically stable eradication of the disease;
- Concerning the class of anti-angiogenic drugs that act by altering the proliferation related parameters of the vascular cells, we shall show that these drugs, even though can exert tumor control, are ineffective in leading to tumor eradication unless there is a sufficiently high rate of spontaneous loss of the tumor vasculature (d'Onofrio and gandolfi, 2006);
- Through numerical simulations, we shall compare the effect of a constant continuous infusion of a drug that induces vascular loss to the effect of a periodic, bolus-based, therapy. We shall investigate the role of drug elimination rate and dose fractionation, and show that different schedulings guaranteeing the same mean value of drug concentration may exhibit very different long-term responses according to their concentration versus time profile, with the profiles that approach the constant one being more effective (d'Onofrio et Al, 2006);
- We shall briefly study the problem of optimization of therapies (Swierniak et al., 2006)(Ledzewicz and H. Schättler, 2007);
- Finally, we shall show as some biological problems related to the anti-angiogenic therapy may lead to more complex phenomena that may be modeled by differential equations with distributed delays. In turn, we shall see as this way of modeling might give some contribution to the improvement of the therapy (d'Onofrio, 2006).

4. CONCLUSIONS

Summarizing, in this work we shall show how classical biological and medical features may naturally be translated in classical topics of the qualitative theory of differential equations such as global stability, delay differential equations, singular perturbation methods, cooperative systems, periodic solutions, persistence theory and optimal control..

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