

Division of Experimental Oncology, Cross Cancer Institute

Motivation:

While conventional cytotoxic chemotherapy has shown the ability to cure some cancers, it has fallen short of the high expectations of curing the most common cancers. Cancer remains a major cause of death, and conventional cytotoxic chemotherapy has proven unable to cure most cancers after they have metastasized. New knowledge about the molecular biology of cancer and new tools to specifically target aberrant proteins are opening up new possibilities. One of the most common methods of increasing cure rates using chemotherapeutic agents is to administer combination chemotherapy.

In contemporary usage, combination therapy most often refers to the simultaneous administration of two or more medicinal compounds or modalities to treat a single disease. This approach in cancer treatment can be traced back to 1965 when James Holland, Emil Freireich, and Emil Frei hypothesized that cancer chemotherapy should follow the strategy of antibiotic therapy for tuberculosis with combinations of drugs, each with a different mechanism of action. Cancer cells could conceivably mutate to become resistant to a single agent, but by using different drugs concurrently it would be more difficult for the tumor to develop resistance to the combination. Holland, Freireich, and Frei simultaneously administered an antifolate, a Vinca alkaloid, 6-MP and Prednisone - together referred to as the POMP regimen - and induced long-term remissions in children with acute lymphoblastic leukaemia (ALL). With incremental refinements of original regimens, using randomized clinical studies in the UK (UKALL protocols) and in a German clinical trials group (ALL-BFM protocols), ALL in children has become a largely curable disease. This approach was extended to the lymphomas and ultimately proved in the late 1960s that nitrogen mustard, vincristine, procarbazine and prednisone - known as the MOPP regimen - could cure patients with Hodgkin's and non-Hodgkin's lymphoma. Currently, nearly all successful cancer chemotherapy regimens use this paradigm of multiple drugs given simultaneously. The discovery that certain toxic chemicals administered in combination can cure certain cancers ranks as one of the greatest in modern medicine. These types of cancers, previously universally fatal, are now generally curable diseases.

Current clinical trials in oncology commonly focus on three key aspects: (a) extending the scope of known drugs to new types of cancer, (b) testing new compounds, (c) optimizing treatment by using combinations of known compounds. The latter aspect is of great interest and in the opinion of the proposer could benefit from a mathematical modelling approach aimed at achieving an optimized set of parameters for the dose, frequency and route of administration. Some aspects of this major medical issue can benefit from mathematical modelling as briefly outlined below.

Problem Description

Tumours cannot grow beyond a certain size through simple diffusion of oxygen and other essential nutrients into the tumor site. Angiogenesis, the formation of blood vessels from pre-existing vessels, is a crucial progression step, through which a tumour obtains its own blood supply and gains an enhanced ability to grow. Strategies that interfere with the development of tumor vasculature, known as anti-angiogenic therapy developed by the recently deceased Harvard scientist Dr. Judah Folkman, represent a relatively new approach to controlling tumour growth. Several pre-clinical studies have suggested that currently available angiogenesis inhibitors are unlikely to yield significant sustained improvements in tumour control on their own, but rather will need to be used in combination with conventional treatments such as anti-mitotic chemotherapeutics to achieve maximal benefit.

Optimal sequencing of anti-angiogenic treatment, chemotherapy and/or radiotherapy is essential to the success of the combined treatment strategies. Hence, a major challenge to mathematical modeling and computer simulations is to find appropriate dosages, frequencies and routes of administration of combination therapies in order to best control tumour growth. It would be crucial to analyze this problem by using clinical and cell-level data as a basis from which a mathematical model could be proposed and investigated. It should be able to quantify the growth of tumor cells and their vascular network, as well as the cytotoxic effects of the therapy. We should include the effects of two or more different treatments, conventional cytotoxic therapy (with various drug entities possible, even several at a time) and anti-angiogenic therapy. The challenge here is to link a molecular description of the action of each drug with a statistics-based clinical outcome. Models can also be developed for other types of combination therapy, for example a combination of surgery, radiation therapy and chemotherapy which is a standard of practice for gliomas, the most common primary brain tumors which are diffusive and highly invasive. In an effort to improve treatment strategies, we should analyze the results of a spatio-temporal mathematical model, based on proliferation and diffusion, that incorporates the effects of radiotherapeutic and chemotherapeutic treatments. In particular, we should study the effects of different schedules of radiation therapy, including fractionated and hyperfractionated external beam radiotherapy and compare the results with published clinical data. Below we briefly outline some modelling challenges in specific types of cancer.

Ovarian cancer has long been one of the most common forms of cancer in women. The main treatment for ovarian cancer comprises a combination of surgery and chemotherapy. In an effort to improve treatment strategies, a variety of mathematical models have been developed in the literature. A simple mathematical model has been developed that incorporates tumor growth as well as the effects of chemotherapeutic and surgical treatments in ovarian cancer. Several growth models have been proposed and combined with different cell-kill hypotheses. Surgery was assumed to eliminate a fixed fraction of tumour cells instantaneously. We should analyze and compare to clinical data how different models predict the optimal sequencing of chemotherapeutic and surgical treatments. The results of this study may also be useful for other kind of cancers.

Colorectal cancer (CRC) continues to be a major cause of all new cancer cases and cancer-related deaths in North America. Although advances in chemotherapy have increased overall survival for patients suffering from metastatic CRC, the survival rate continues to be poor. In order to develop new and more effective therapies for advanced CRC, it is important to understand the basic biologic processes that govern tumour growth. We need to focus on pathways involved in stimulating tumor growth and angiogenesis. Clinical efficacy of targeted anti-angiogenic therapy against growth factors important in angiogenesis and tumour proliferation gives renewed hope. Modelling the therapeutic effects of different angiogenesis inhibitors and how combination treatments with these agents might be beneficial is of critical importance and is hoped to lead to improved clinical outcomes.

For a subset of breast cancer patients that are HER2 positive, a novel therapeutic strategy has been used to block HER2 function using the small molecule tyrosine kinase inhibitor lapatinib. This monoclonal antibody acts by slowing the transition through G1 phase of the cancer cells targeted. However, recent experimental data indicate a previously unreported late cytotoxic effect, which has been incorporated into a mathematical model. Both effects depend on the dosage of the drug in a linear-saturating fashion. The model proposed recently separates quantitatively the cytostatic and cytotoxic effects of lapatinib and may have implications for preclinical studies with other anti-oncogene therapies. It would be of great interest to develop a combined model that described the behaviour of cancer cells exposed to lapatinib, anti-mitotic compounds (e.g. paclitaxel) and anti-angiogenesis drugs such as avastin

References:

M Kohandel et al , Dynamics of tumor growth and combination of anti- angiogenic and cytotoxic therapies 2007 Phys. Med. Biol. 52 3665-3677

Powathil,G Kohandel,M Sivaloganathan,S and Milosevic,M Phys Med Biol. 2007 Jun 7;52 (11):3291-306

Kohandel,M, Sivaloganathan,S, J Theor Biol. 2006 Mar 28; : 16580022

Peter Hinow, Shizhen Emily Wang, Carlos L Arteaga and Glenn F Webb, A mathematical model separates quantitatively the cytostatic and cytotoxic effects of a HER2 tyrosine kinase inhibitor, Theoretical Biology and Medical Modelling 2007, 4:14

Enderling, H., Chaplain, M.A.J., Anderson, A.R.A., Vaidya, J. (2007) A mathematical model of breast cancer development, local treatment and recurrence" J. theor. Biol. doi:10.1016/j.jtbi.2006.12.010

Stephanou, A., McDougall, S., Anderson, A., Chaplain, M.A.J. (2006) ``Mathematical modelling of the influence of blood rheological properties upon adaptive tumour-induced angiogenesis" Math. Comput. Modell. 44 , 96-123

