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Optimization of drug regimen in chemotherapy based on semi-mechanistic model for myelosuppression

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ABSTRACT

Based on the latest statistics on trends in cancer incidence and mortality worldwide, cancer burden is growing at an alarming pace. Many anticancer drugs have been proved effective against cancer cells as well as toxic to human tissues, which prevents sufficient doses from being administered to obtain a complete cure. In this paper we build an optimal control model to optimize the scheduling problem along one cycle of chemotherapy treatment using a single anticancer drug etoposide (VP-16). In the model, three mathematic models are adopted to mimic physiological response of body under chemotherapy: (i) Pharmacokinetic model of anticancer drug; (ii) A two-compartment tumor growth dynamic model under the influence of cell-cycle-specific anticancer drugs; and (iii) A semi-mechanistic model for myelosuppression. In this new integrated model clinically relevant objectives are proposed to gain a trade-off between efficacy and toxicity. Simulation results of clinical protocols are consistent with real-life clinical data. Furthermore, we find a new optimal drug regimen which can improve the efficacy without the risk of severe toxicity.

1. Introduction

Cancer, also known as malignant tumor, is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. According to 'World Cancer Report 2014' released by the International Agency for Research on Cancer (IARC), in 2012 the worldwide burden of cancer rose to an estimated 14 million new cases per year, and the figure is expected to rise to 22 million annually within the next two decades. Over the same period, annual cancer deaths are predicted to rise from an estimated 8.2 million to 13 million. As pointed out by the Director of IARC, Dr. Christopher, "the rise of cancer worldwide is a major obstacle to human development and well-being. These new figures and projections send a strong signal that immediate action is needed to confront this human disaster, which touches every community worldwide, without exception".

Surgery, chemotherapy, radiotherapy, hormone therapy and immunotherapy are the primary treatment options for cancer. Since cancer cells can invade surrounding tissues and migrate to the other parts of the body, chemotherapy is commonly employed as a systemic treatment by clinicians. Combining with surgery, chemotherapy has been proven beneficial in many different types of cancer such as breast cancer, colorectal cancer, pancreatic cancer, osteogenic sarcoma, testicular cancer, ovarian cancer, and certain lung cancers. However, the effectiveness of chemotherapy is often limited by toxicity to other tissues in the body due to the interaction of the drug with normal cells. Clinicians need to put forward a drug regimen to balance the treatment efficacy with the toxic side effects.

Randomized clinical trials are the standard method for the evaluation of efficacy and toxicity of chemotherapy treatment plans. The current standard of practice of treatment is based on empirical evidence gathered from preclinical and clinical trials carried out during the drug development process. However, given the limited human and financial resources for clinical trials, optimal protocols cannot be determined empirically. To this end, mathematical modeling provides a low-cost method for evaluating different strategies more efficiently by describing the quantitative relations among several factors [1].

The optimal control model (OCM) constructed by Martin et al. [1,2] has been extensively used by the studies on chemotherapy treatment optimization problem. Martin et al. [1,2] use the Gompertz equation to describe tumor cell populations. Maximum tolerated dose (MTD) and area under concentration (AUC) are indicators of toxicity. A multiple characteristic time (MCT) constraint is

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used to ensure tumor population decrease at, or faster than, a given rate in a specified time interval. More recently, Liang et al. [3–5] modified the metabolism process of cumulative drug toxicity by introducing a new parameter representing the elimination rate of drug toxicity and applied several algorithms to the chemotherapy scheduling problem.

The Gompertz model is capable of capturing clinically observed tumor dynamics, but it cannot capture information regarding the progression of cells through the individual phases of the cell-cycle. Compartment models are developed to gain more insight into cell behavior [6]. Based on the previous research, Dua et al. [7] incorporate the cycle-specific chemotherapy effect mechanism into the optimal control model (OCM), in which they present two typical optimal control formulations that minimize the final tumor population subject to the constraints on toxicity and drug resistance. A more complex description of the system incorporates patient-specific parameters into their cell population growth model, where an approximately optimal treatment plan is found by applying simulated annealing algorithm [8].

Efforts have been made to shed light on interaction between tumor and immune system. Villasana et al. [9,10] formulated the action of a cycle-specific cytotoxic drug with the goal of maximizing cell kill fraction and minimizing normal cell killing and designed a heuristic algorithm to find optimal delivery schedules. Furthermore, they incorporated a cytostatic drug which arrest cells in a phase of their cycle. The problem of designing efficient combined chemotherapies is formulated as an optimal control problem and tackled using three heuristic algorithms for real-parameter optimization, namely, covariance matrix adaptation evolution strategy, differential evolution, and particle swarm pattern search method [11,12].

Research in the last five decades has led to the development of Medical Decision Support (MDS) applications using a variety of modeling techniques, for a diverse range of medical decision problems, such as diagnostic decision support [13] and management of hospital resources [14,15]. In this paper we focus on cancer chemotherapy and dose schedule optimization using mathematical methods.

Although extensive efforts have been invested in the theoretical investigation of chemotherapy control methods, we find several limitations to practical application. In most previous studies, the toxicity of a treatment is measured both by maximum tolerated dose and maximum drug exposure expressed as area under curve (AUC). It relies on the assumption that today's chemotherapy treatments achieve the maximum efficacy. However, we find this approach clinically unrealistic. In practical chemotherapy constantly suffers from the inability to control the efficacy-toxicity balance. More importantly, AUC as an indicator of toxicity is arguable, since it induced unreasonable timing for the first treatment in the optimization problem in Martin et al.'s work [1,2]. Liang et al. [3–5] attempted to fix this by introducing a new parameter. While Agur et al. [9] tried to model the interaction of drugs with normal cells. Nevertheless, those methods cannot be applied directly because parameters in their models are clinically unavailable. In order to reduce the gap between theoretical investigation and medical practice, we propose a more practical approach by integrating a physiology-based model, i.e., the semi-mechanistic model for myelosuppression proposed by Friberg et al. [16], into the chemotherapy dose scheduling problem. This semi-mechanistic model effectively captures the main physiological processes and predicts the whole time course of leukopenia. Based on this new model we are able to find optimal drug regimen, and identify new strategies to split the total drug dose so that toxicity will be reduced without compromising efficacy.

The rest of the paper is organized as follows: Section 2 gives a brief introduction on biomedical background and describes the pharmacokinetic model of VP-16, tumor growth dynamic model and chemotherapy-induced myelosuppression model in detail. Section 3 is the simulation results of different clinical protocols and Section 4 works on optimizing dose regimens in cancer chemotherapy. Conclusions and discussions are presented in Section 5.

2. Problem formulation

2.1. Biomedical background

In cancer treatment, measurement of tumor growth is necessary for preclinical and clinical assessment of efficacy. To model untreated tumor growth, exponential, Gompertz and logistic growth models are commonly used but cell-cycle models provide more insight into cell behavior. Cell cycle is a chain of phases that both normal and cancer cells undergo from their birth to death. In general, the cycle comprises of five stages which are G0, G1, S, G2 and M. G0 stands for resting phase, representing cell is quiescent. Cycling cell has four phases, including the gap period (G1), the synthetic period (S), the second gap period (G2), and mitosis (M). Usually, cancer drugs work by damaging the RNA or DNA to halt division. Anticancer drugs that are able to kill all cancer cells are called cell-cycle non-specific; while drugs that only kill cancer cells when they are dividing are called cell-cycle specific.

Since anticancer drugs attack both normal and cancer cells, their usage often lead to severe side effects. Side effects of anticancer chemotherapy include hematological toxicity, nausea, vomiting, diarrhea, fatigue, alopecia, and cardiac, neurological, and renal toxicity. The main toxicity of most anticancer drugs is hematological. Thus, the ability to anticipate hematological toxicity could be of great value for optimizing treatment and predicting complication for patients who undergo prolonged periods of myelosuppression [17].

Etoposide (VP-16) is a cell-cycle specific anticancer drug that has been widely used in chemotherapy treating childhood leukemia, testicular tumors, Hodgkin's disease, large cell lymphomas and small cell lung cancer (SCLC). The activity of VP-16 is dose- and schedule-dependent, and efficacy might be improved markedly with repeated drug administration. However, myelosuppression as the dose-limiting toxicity for VP-16 should be taken into account when planning the chemotherapy regimen. The chemotherapy treatment is given in cycles, attacking cancer cells at their most sensitive periods, and allowing normal body cells time to recover [18].

2.2. PK–PD model

Cancer progression in a patient undergoing chemotherapy is a very complex process. Engineers have considered the development of drug administration schedules for simulated cancer patients constrained by pharmacokinetic (PK) and pharmacodynamic (PD) models to meet the challenge [19] (see Fig. 1).

2.2.1. Pharmacokinetic model

Pharmacokinetic models can include the distribution of drugs by the circulatory system, the elimination of drug, and the amount of drug present at the site of action. Systems of linear ordinary differential equations (ODEs) are commonly used to describe the dynamic relationship between the kinetic behavior of the drug administered and corresponding concentration. Regarding VP-16, a two-compartment PK model (as in Fig. 2) has the best fit [20].

The mathematical models are as follow:

$$\dot{X}_c = K_{21} \times X_p - (K_{12} + K_{10}) \times X_c + X_0 \quad (1)$$

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