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A multi-objective multi-drug model for cancer chemotherapy treatment planning: A cost-effective approach to designing clinical trials

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ABSTRACT

One of the important areas of concentration in medical sciences is the development of the treatment regimens in chronic diseases like cancer. This paper provides insights on how to design new clinical trials for gastric and gastroesophageal cancers which can discover the optimal and cost-effective chemotherapy treatment regimens. First, we extract data from the previously published clinical trials for the mentioned cancers to develop statistical models being capable of predicting trial outcomes. Then, using the statistical models, we present a multi-objective multi-drug model for cancer chemotherapy treatment planning. The proposed model yields a wide range of solutions establishing a reasonable tradeoff between patient's survival and treatment costs while satisfying some prevailing limitations on toxicities and the feasibility of treatment regimens. Results show that the proposed approach needs much less time and cost than the trial-and-error manipulation of cancer treatment. It also takes the advantage of saving and improving the quality of patients' lives by suggesting the new drug regimens which improve the survival time of patients and have reasonable treatment costs compared to the current practice trials.

1. Introduction and literature review

Cancer is a generic term for a large group of diseases specified by an uncontrolled growth of cells leading to invasion of surrounding tissues and metastasis. Cancer may seriously threaten the human health; according to the latest figures released, it is placed among the leading causes of morbidity and mortality in the worldwide, with approximately 14 million new cases and 8.2 million cancer-related deaths in 2012. The number of new cases is expected to rise by about 70% over the next two decades (World Health Organization, 2014).

There are different ways for tackling cancer such as surgery, chemotherapy, radiotherapy, hormone therapy and so on. Each of these treatment modalities has advantages and disadvantages. Although the choice of a cancer treatment method depends on the patient's condition, chemotherapy is still an effective one (Choices NHS, 2015). Chemotherapy consists on treating cancer with chemical substances, especially one or more anti-cancer drugs. The main purpose of an anti-cancer drug is to annihilate the cancerous cells; but in turn, the applied drugs would also affect the healthy cells and destroy them at the same time. Therefore, in the drug treatment, one must take under consideration a suitable balance between cancerous cells reduction and adverse side effects. In fact, the drugs dosage must be prescribed as much as the value which the patient suffers from the minimum toxicity effects and simultaneously, the number of cancerous cells is decreased as much as possible. Furthermore, since an inadequate amount of the drug may be ineffective to inhibit further growth of cancer cells, the regular administration of the drug in small quantities makes the cell drug resistant.

During the chemotherapy, some cancerous cells may resist to the treating agent via a random mutation. Due to the resistance, those cancerous cells cannot totally be annihilated; therefore, a high level of drug dosage is preferred. On the other hand, a high level of drug dosage will lead to an unallowable toxicity. Hence, two important difficulties in treating cancers with chemotherapy are drug resistance and toxicity. In order to make a reasonable tradeoff between the cancerous cells reduction, toxicity effects and drug resistance, it is necessary to develop the best chemotherapy treatment regimen which specifies the drug combinations and dosages for the given objectives (Dua et al., 2008; Shi et al., 2014; Batmani and Khaloozadeh, 2012, 2013).

Currently, chemotherapy treatments are developed and evaluated through the empirical clinical trials. A clinical trial, as a planned

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experiment, is designed to assess the efficacy of a treatment for the patients by comparing the outcomes in the test treatment group to the control treatment group, where patients in both groups are enrolled, treated, and followed over the same time period (Shein-Chung and Liu, 2014). Although the clinical trials are used to evaluate the reliability and effectiveness of treatment regimens, they are limited by certain factors such as high costs, long trial time consumption, and the difficulty of testing and evaluating the feasibility of various options since there is a large number of potential drug combinations.

To this end, mathematical modeling has provided a low-cost method for analyzing the effectiveness of different treatment regimens by quantifying the relationships among several important factors, such as overall survival, the population of cancerous cells, toxicity, and drug resistance. It can also provide the valuable insight for researchers to understand the effect of various factors on the performance of the optimal treatment regimens. Therefore, there is a growing interest among the researchers (clinicians, biologists, mathematicians, and control engineers) in the chemotherapy treatment optimization problem (Fallah Nejad and Ahmadi Yazdi, 2015; Sbeity and Younes, 2015). Mathematical modeling may help to mitigate the cost of choosing a better chemotherapy treatment regimen by reducing the trial-and-error manipulation to find the effective treatment regimens.

Since applying the optimal control to the various disease treatment by the 1970s, several studies were conducted (Sbeity and Younes, 2015). Chemotherapy treatment planning problem was first introduced by Swan and Vincent (1977) as an optimal control problem. They aimed at minimizing the total amount of drugs used for a specified tumor cell population. This study was critical for a basic understanding of the early mathematical modeling approaches in the field of chemotherapy treatment planning problem.

There are several studies conducted to formulate prediction models for the clinical outcomes. For example, Hurria et al. (2011) identified risk factors for the chemotherapy toxicity in older adults and developed a risk stratification model for it. Numerous studies, e.g., Snow et al. (2001), Kyrgiou et al. (2006) and Lisboa and Taktak (2006), developed models for predicting the clinical outcomes using prediction techniques such as artificial neural networks, regression and so on. However, such models were not able to plan new drug combinations.

De Pillis and Radunskaya (2003) constructed a general tumor growth model using the ordinary differential equations which showed the dynamics of tumor growth by means of the number of normal and immune cells. Itik et al. (2009) extended that model considering three types of cells: cancerous cells, normal cells, and immune cells. The anticancer drug annihilated all the three cell types with different annihilating ratios. They found an optimal chemotherapy treatment plan using a linear time varying approximation. However, they built their model using only one drug. Today, most successful chemotherapy treatments for the advanced cancers are conducted based on a combination of several different anticancer drugs in order to hinder the drug resistance and decrease the overall toxicity (Bertsimas et al., 2013). Some studies, e.g., Petrovski and McCall (2001) and Alam et al. (2013), explicitly derived the solutions for a multi-drug chemotherapy planning problem while some of the previously developed researches, e.g., Harrold and Parker (2009) and Itik et al. (2009), studied only one-drug cases. Regarding the importance of drug combination in chemotherapy, there is a growing interest in recent studies in the multi-drug chemotherapy treatment optimization problem.

Rao et al. (2014) developed stochastic models for the effective drug administration in cancer chemotherapy. This work focused on designing the multi-objective stochastic optimization problems to minimize the tumor size and the stay time of "cancer causing cells" during the treatment. However, the model does not contain enough details about the drug combination dosages for planning new drug combinations. Bertsimas et al. (2013) proposed an optimization approach for the analysis and design of clinical trials which was capable of discovering the best available drug combination to treat a particular form of cancer. Although they include enough details about the drug combination and dosages to enable the design of novel combination chemotherapy regimens, they neglected the treatment costs in their models.

An important dimension of the chemotherapy costs is the total cost of curing the patient. Considering the chemotherapy line, the treatment costs will vary. Generally, the first line chemotherapy has a lower cost compared to the higher lines. Moreover, the cost may exponentially increase from the lower to the higher lines of chemotherapy. Therefore, the clinicians apply the first line chemotherapy to the patients and if it fails, they use the second one and so on. However, the existing studies do not consider the treatment costs when optimizing the chemotherapy plan, which, in turn, causes a significant gap between the theoretical research and clinical application. Nevertheless, it seems to be wise to guarantee the quality of chemotherapy instead of focusing primarily on the treatment costs during chemotherapy. It is not only because of the importance of improving the survival time in patients, but also, it may lead to the significantly higher costs later since the costs increase dramatically from the first to the higher lines of chemotherapy if the first line fails. In fact, an effective chemotherapy would decrease the total chemotherapy costs by choosing the promising treatment which is unlikely to fail. In addition, there would be several numbers of promising treatment regimens which makes minimizing the current treatment costs an important objective (Clare et al., 2000; Shi et al., 2014).

The previous studies modeled the chemotherapy treatment optimization problem in different ways. However, it is obvious that their common purpose was to find the most effective treatment regimens which can improve the patient's well-being. Those studies thus ignored the related treatment costs. Although finding the high quality treatment regimens is the primary goal, if it is practically impossible to implement them due to the significant costs, they would not be valuable. Hence, it seems critical to consider the treatment costs in optimization models to make the cost-effective and feasible drug regimen choices.

In this paper, we propose new chemotherapy combinations for designing clinical trials which simultaneously improve the overall survival and take the toxicity and treatment costs into account. In this regard, we extend the model presented in Bertsimas et al. (2013) in such a way that it has the ability to determine the most promising chemotherapy plans which are practically feasible and cost-effective. Firstly, using the data from the previous clinical trials, two statistical models are developed to predict the outcome, i.e., survival and toxicity, of the clinical trials. Then, employing the results of the statistical models, a new multi-objective optimization model is formulated for cancer chemotherapy treatment which can provide a reasonable trade-off between the survival time and treatment costs during the whole period of treatment. The proposed model aims at maximizing the patient's overall survival and minimizing the current treatment costs simultaneously.

It is worth mentioning that based on the latest world cancer statistics (World Health Organization, 2013), gastric cancer is the third most common cause of cancer death in the worldwide; hence, this study specifically focus on this type of cancer (gastric and gastroesophageal). Although the proposed methodology is efficiently applicable to the other forms of cancer, it needs carefully re-consideration and validation when applied to different types of cancer.

The rest of the paper is organized as follows. Section 2 presents in summary the development of clinical trials database. In Section