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Optimizing the Future: A Game Theory to Tumor Therapeutic Strategies

Fang-Yuan Liu[1], Xin Liu[2], Dan-Ni Ding[1], Shao-Xuan Liu[1], Jing Xu[1], Yu-Xin Zhao[1], Yan-Hong Wang[3*] and Feng-Juan Han[3*]

Abstract

Background Cancer poses significant economic and societal burdens on countries in the coming decades. During chemotherapy, patients frequently encounter adverse reactions. Recent research has revealed that Chinese medicine plays a crucial role in mitigating the side effects of chemotherapy. Therefore, in this article, we propose that the cancer treatment process can be likened to an unequal game. To refine treatment strategies, we suggest employing the Steinberg model to incorporate Chinese medicine into the chemotherapy regimen for tumor treatment.

Results We found that when malignant tumors exhibit vigorous proliferation, doctors should administer Chinese medicine in conjunction with chemotherapy drugs, continuously optimizing the therapeutic effect of the Chinese medicine. Upon reaching a specific threshold in the treatment effect of the Chinese medicine, doctors may appropriately augment the dosage of chemotherapy drugs, building upon the initial regimen. Conversely, in cases where the proliferation ability of malignant tumors is weak, the dosage of chemotherapy and the adjuvant therapy with Chinese medicine should be kept in a relatively balanced state. Once the effect of the Chinese medicine attains a particular threshold, the dosage of chemotherapy can be concurrently increased to achieve a superior therapeutic result.

Conclusions From a game theory perspective, doctors can devise strategies to minimize drug toxicity and improve tumor treatment outcomes by coordinating the use of chemotherapy drugs with appropriate adjustments to Chinese medicine therapy methods.

Keywords Game theory, Chemotherapy drugs, Chinese medicine, Tumor therapeutic strategies, Steinberg game model

*Correspondence:
Yan-Hong Wang
wang.yanhong@163.com
Feng-Juan Han
hanfengjuan2004@163.com
[1] Heilongjiang University of Chinese Medicine, Harbin 150040, China
[2] Harbin Institute of Technology, Harbin 150001, China
[3] First Affiliated Hospital of Heilongjiang University of Chinese Medicine, Harbin 150040, China

Introduction

Cancer is the second leading cause of death worldwide [1]. According to the International Agency for Research on Cancer (IARC), there were close to 20 million new cancer cases in 2022 along with 9.7 million deaths from cancer. Estimates suggest that approximately one in five men or women develop cancer in a lifetime, whereas around one in nine men and one in 12 women die from it. With demographic-based predictions indicating, the number of new cancer cases will reach 35 million by 2050 [2]. Cancers bring enormous economic and social stress to countries in the coming decades. Novel approaches such as radiation, surgery, and chemotherapy, together with cutting-edge technologies such as gene therapy, stem cell therapy, targeted therapy, photodynamic therapy, nanoparticles, and precision medicine, can be used to identify and treat disease [3]. Furthermore, tumor and cell-free DNA profiling, immunological markers, proteomic and RNA analysis, and other techniques have recently been used to pinpoint these characteristics to optimize anticancer therapy in individual patients [4, 5]. However, during chemotherapy, patients often experience adverse reactions such as symptoms of the digestive system (nausea, vomiting, etc.), suppression of bone marrow, cancer-related fatigue, etc. Current research has found that Chinese medicine plays an important role in reducing chemotherapy side effects [6]. So, when and at what dose can we incorporate Chinese medicine, and how can we maximize its benefits and minimize its toxic side effects?

For cancer treatment, some scholars have suggested that it can be studied through the perspective of game theory. Cancer treatment can be regarded as a game of "leader vs. follower", where oncologists act as "leaders" and choose appropriate treatment plans, while tumor cells, as "followers", respond only and adapt to treatment [7]. In this case, if the treatment strategy is fixed, the tumor cells as "followers" will gradually adapt to it and "usurp the power", such as the emergence of drug resistance. The role of tumor cells will evolve from "followers" to "leaders", leading to failure of treatment [8]. Based on this, we propose that the cancer treatment process is an unequal game process, in which the active advantage of the leading player is utilized to change the intervention method for tumor treatment and improve the efficacy. In medical research, commonly used mathematical models include Lotka Volterra, Gompertz, Stackelberg, and so on. Lotka Volterra is a population competition model mainly used to explain the dynamic competition relationship between tumor cells and normal cells [9]. The Gompertz model is used mainly to describe biological phenomena, such as tumor cell proliferation characteristics [10]. The Stackelberg model is mainly used to describe the strategic relationship between leaders and followers, that is, the game relationship between doctors' treatment strategies and cancer cell resistance [11].

Clinically, high doses of chemotherapeutic drugs can effectively manage tumor load during treatment, despite the potential toxicity that may render them intolerable for patients. Hence, physicians strive to achieve a balance between tumor load reduction and drug toxicity to optimize drug administration and ensure superior therapeutic outcomes. However, there is currently no definitive treatment strategy outlining when to initiate or discontinue Chinese medicine based on specific therapeutic benefits. In this article, we explore the utilization of the Steinberg model to refine treatment strategies by integrating Chinese medicine into the chemotherapy regimen for tumor treatment. More precisely, we propose a Steinberg game model that encompasses both physicians and tumors, with the objective of identifying the optimal strategy for Chinese medicine intervention in cancer treatment. Our aspiration for future research is to provide substantial value in the formulation of clinical protocols.

Methods

In the Steinberg game model, there exists an order of adoption of the strategy by the participants. The doctor, as a "leader", is able to anticipate the response behavior of the tumor and make rational strategies on the basis of the expected tumor behavior; the tumor, as a "follower", is able to respond to the current environment and formulate rational strategies to maximize the target utility in that environment after the doctor has adopted a strategy.

We explore the best treatment strategy by comparing the benefits of doctors and tumor cells in the treatment process. For tumors, we considers three components that affect their growth and reproduction: 1) proliferation under ideal conditions, reflecting the growth of tumors under favorable environments such as abundant resources; 2) environmental constraints, reflecting the hindering effect of resource constraints in the host body and the tumor population's own factors on the value-added of the tumors; and 3) chemotherapy drugs inhibition, reflecting the inhibitory effect of therapeutic drugs on the tumor's proliferation. Accordingly, this paper proposes a gain function for tumors as follows:

$$\Pi_T = \alpha x - \frac{1}{2}\beta x^2 - dx$$

Among them, Π_T refers to the profit of tumor T, x represents the number of cells in the tumor population, $\alpha(\alpha > 0)$ represents the profit brought by tumor cell proliferation to the tumor population, $\beta(\beta > 0)$ represents the diminishing marginal utility of tumor population proliferation, that is, the inhibitory effect of environmental factors and tumor self factors on its proliferation, d represents the cost of therapeutic drugs for maintaining the survival of the tumor population. The benefit for the tumor, denoted as Π_T, arises from the increase in tumor count, represented as αx. However, this benefit exhibits diminishing marginal utility as the number of tumors grows, due to the quadratic term $-\frac{1}{2}\beta x^2$, reflecting the scarcity of resources such as nutrients and growth space within the body. Furthermore, during chemotherapy, a larger tumor count results in an increased absorption of chemotherapy doses, leading to a negative impact on the tumors, denoted as $-dx$.

For the benefit of physicians, we mainly consider these two influencing factors: the target utility consists of two components: 1) inhibition of the value added from the tumor, taking into account the benefit of reducing the number of tumor cells; and 2) limiting the dose of the drug, taking into account the benefit of reducing the toxicity of the drug. That is, the physician must weigh the number of tumor cells and the drug toxicity that comes along with the cost of tumor survival caused by the therapeutic drug. Consequently, this paper proposes the physician's benefit function as follows:

$$\Pi_D = -\theta x^2 - (1-\theta)d^2$$

Π_D refers to the benefit to physician D, and $\theta(0 < \theta < 1)$ refers to the weight of the benefit from reducing the number of cells in the tumour population. On one hand, the benefit for doctors stems from controlling the number of tumors, where a higher tumor count translates to lower benefit, represented as $-x^2$. On the other hand, it comes from the control of chemotherapy drugs. The larger the chemotherapy dose, the smaller the benefit $-d^2$. It is noteworthy that doctors' priorities between controlling the tumor count and mitigating the side effects of chemotherapy drugs vary based on the situation. When tumors pose a greater threat to life, doctors should prioritize controlling the tumor count, leading to a higher value of θ. Conversely, in cases where patients exhibit intolerance to the toxic and side effects of chemotherapy drugs, doctors should strictly control the chemotherapy dose, resulting in a higher value of $(1-\theta)$.

Based on this understanding, we incorporate it into the model according to the prevalent circumstances in clinical practice, aiming to maximize the doctors' income. Additionally, we delve into two research questions:

> **Question 1:** How can doctors maximize their income by optimizing the chemotherapy effect when solely considering the individual circumstances of patients, where θ is a fixed value?
>
> **Question 2:** Considering both the individual situation of patients and the adjuvant treatment with traditional Chinese medicine, where θ is a variable, how can doctors maximize their benefits by optimizing both the chemotherapy and the adjuvant treatment with Chinese medicine?
>
> **Hypothetical 1:** The physician's medication situation needs to satisfy: 1) the number of tumor cells in the patient's body cannot be less than zero after treatment; 2) the patient is still alive after treatment, the number of tumor cells cannot be greater than the maximum tumor load; and 3) the patient will ultimately die if no treatment is administered.

Maximization of tumor benefit function:

$$\frac{\partial \Pi_T}{\partial x} = \alpha - \beta x - d$$

Saving $\frac{\partial \Pi_T}{\partial x} = 0$, we obtain the following result:

$$x = \frac{\alpha - d}{\beta}$$

According to Hypothetical 1:

$$0 < \alpha - \beta q \leq d \leq \alpha$$

q refers to the maximum tumor load. Without loss of generality, the order $q = 1$. Thus, there is the following relationship:

$$0 < \alpha - \beta \leq d \leq \alpha$$

Question 1

From the above conditions, to obtain the optimal treatment, the physician must solve the following optimization problem with constraints:

$$\min_d F(d) = \theta\left(\frac{\alpha - d}{\beta}\right)^2 + (1-\theta)d^2$$

$$\text{s.t.} \quad d \leq \alpha$$

$$d \geq \alpha - \beta$$

The derivation of the objective function yields the following.

$$\frac{\partial F(d)}{\partial d} = -\frac{2\theta}{\beta^2}(\alpha - d) + 2(1-\theta)d$$

Saving $\frac{\partial F(d)}{\partial d} = 0$, we come to next equation: $d = \frac{\theta\alpha}{\theta + \beta^2(1-\theta)}$

$$d = \frac{\theta\alpha}{\theta + \beta^2(1-\theta)} < \alpha$$

When $\alpha \geq \frac{\theta}{\beta(1-\theta)} + \beta$, optimal solution is as follows: $d^* = \alpha - \beta$;

When $\alpha < \frac{\theta}{\beta(1-\theta)} + \beta$, optimal solution is as follows: $d^* = \frac{\theta\alpha}{\theta + \beta^2(1-\theta)}$

Therefore, if tumor cells have a high proliferative capacity, the physician should use a level of chemotherapeutic agent that is $\alpha - \beta$. Tumor cells are less able to proliferate, and the level of chemotherapeutic agent that the physician should use is $\frac{\theta\alpha}{\theta + \beta^2(1-\theta)}$.

Question 2

Hypothetical 2: Under ideal conditions, physicians can adjust weight by supplementing chemotherapy treatment with other treatment, θ∈[0,1].

Based on this, the doctor needs to solve the following optimization problem with constraints:

$$\min_{d,\theta} G(d,\theta) = \theta\left(\frac{\alpha - d}{\beta}\right)^2 + (1-\theta)d^2$$

$$\begin{aligned} \text{s.t.} \quad & d \le \alpha \\ & d \ge \alpha - \beta \\ & \theta \le 1 \\ & \theta \ge 0 \end{aligned}$$

First, constructing the Lagrangian function yields the following.

$$L(d,\theta,\lambda_1,\lambda_2,\lambda_3,\lambda_4) = \theta\left(\frac{\alpha - d}{\beta}\right)^2 + (1-\theta)d^2 + \lambda_1(d-\alpha) + \lambda_2(\alpha-\beta-d)$$

$$+\lambda_3(\theta - 1) + \lambda_4(0 - \theta)$$

Derivation of the objective function separately yields the KKT condition as follows:

$$\frac{\partial L}{\partial d} = -\frac{2\theta}{\beta^2}(\alpha - d) + 2(1-\theta)d + \lambda_1 - \lambda_2 = 0$$

$$\frac{\partial L}{\partial \theta} = \left(\frac{\alpha - d}{\beta}\right)^2 - d^2 + \lambda_3 - \lambda_4 = 0$$

$$\lambda_1(d-\alpha) = 0$$

$$\lambda_2(\alpha - \beta - d) = 0$$

$$\lambda_3(\theta - 1) = 0$$

$$\lambda_4(0 - \theta) = 0$$

$$d - \alpha \le 0$$

$$\alpha - \beta - d \le 0$$

$$\theta - 1 \le 0$$

$$\theta \ge 0$$

$$\lambda_1, \lambda_2, \lambda_3, \lambda_4 \ge 0$$

Solution:

When $\alpha = 1 + \beta$, solutions satisfying the KKT condition as $d = 1, \theta < \frac{\beta}{1+\beta}, G(d,\theta) = 1$;

When $\alpha < 1 + \beta$, solutions satisfying the KKT condition as $d = \alpha - \beta, \theta = 1, G(d,\theta) = 1$;$d = \frac{\alpha}{1+\beta}, \theta = \frac{\beta}{1+\beta}, G(d,\theta) = \frac{\alpha^2}{(1+\beta)^2}$.

Besides, considering whether or not θ^* takes values on the boundary affects the objective function solution, so the $\theta^* = 0$ and $\theta^* = 1$.

When $\theta^* = 0$:

$$\min_{d} d^2$$

$$\begin{aligned} \text{s.t} \quad & d \le \alpha \\ & d \ge \alpha - \beta \end{aligned}$$

Optimal solution is as follows: $d^* = \alpha - \beta$, $\theta^* = 0$, $G(d^*, \theta^*) = (\alpha - \beta)^2$.

When $\theta^* = 1$:

$$\min_{d} \left(\frac{\alpha - d}{\beta}\right)^2$$

$$\begin{aligned} \text{s.t} \quad & d \le \alpha \\ & d \ge \alpha - \beta \end{aligned}$$

Optimal solution is as follows: $d^* = \alpha$, $\theta^* = 1$, $G(d^*, \theta^*) = 0$.

In summary, the optimal solution is that $d^* = \alpha$, $\theta^* = 1$. Therefore, with Chinses medicine, physicians should completely eliminate drug toxicity and thus maximize the administration of chemotherapeutic drugs to patients. This conclusion is consistent with common sense, so the model constructed in this paper can better match reality.

In fact, this result is derived under completely ideal assumptions; in practice, conditions for adjuvant therapy are often limited, and physicians can usually only adjust the weights in $\theta \in [\underline{\theta}, \overline{\theta}](0 < \underline{\theta} < \overline{\theta} < 1)$. For this reason, according to the physician's benefit function:

$$\Pi_D(d,\theta) = -\theta x^2 - (1-\theta)d^2,$$

In this paper, a numerical simulation is utilized for further analysis. The numerical simulation results are shown in Fig. 1.

The results reveal that when the capacity for cell proliferation is high (as illustrated in Fig. 1 with α=2, α=2.3), as the peak attainable level of Chinese medicine rises, the amount of chemotherapy administered by doctors to the

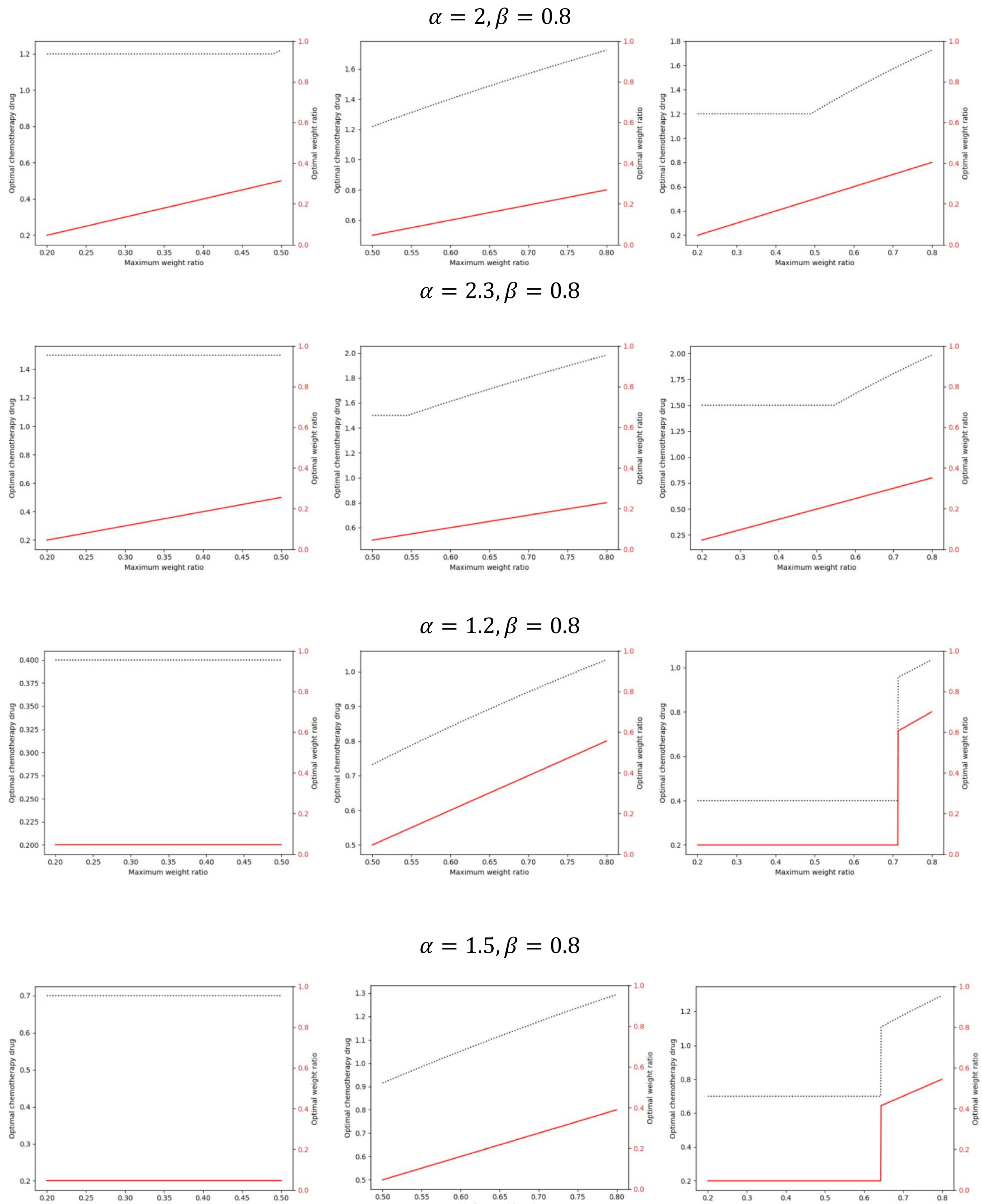

Fig. 1 The numerical simulation results of optimize chemotherapy treatments and adjuvant therapies to maximize benefits. Note: The abscissa represents the maximum value of θ; the ordinate is the dose of chemotherapy drugs

patient remains constant at a particular level. Nonetheless, once the peak attainable level of Chinese medicine crosses a specific threshold, the amount of chemotherapy prescribed by doctors to the patient should be escalated accordingly. On the other hand, when cell proliferation capacity is lower (as depicted in Fig. 1 with $\alpha = 1.2$, $\alpha = 1.5$), both the levels of Chinese medicine and chemotherapy remain steady at certain levels until the maximum achievable level of adjuvant therapy reaches a particular threshold. If the maximum achievable level of Chinese medicine surpasses this threshold, then the levels of both Chinese medicine and chemotherapy prescribed by the doctor to the patient should be increased in tandem.

The threshold for changing the level of Chinses medicine and chemotherapy is related to cell proliferation capacity α, proliferation constraints β, and the minimum $\underline{\theta}$ level of Chinses medicine, with the higher the cell proliferation capacity or the higher the minimum level of adjuvant therapy, the higher the threshold.

Discussion

Oncologists have made great strides in cancer research in the last few centuries, from understanding the function of key genes and proteins and highlighting the detailed molecular mechanisms that promote tumorigenesis to the emergence of therapies such as radiation, chemotherapy, and immunotherapy. However, in many ways, patient outcomes remain frustrating. For example, side effects such as nausea, vomiting, and bone marrow suppression, as well as the development of drug resistance. These issues remain major obstacles in cancer treatment. Problems including in vivo studies' inability to respond to particular mechanisms, in vitro studies' inability to identify intercellular mechanisms of action, and ethical restrictions on clinical investigations have historically plagued. To supplement the shortcomings that predominate in current cancer research, we need a deeper understanding of the ecological and evolutionary processes that shape cancer if we are to properly understand and treat it effectively.

In fact, many of the earliest mathematical models of cancer, such as the Lotka-Volterra, logist, von Bertalanffy, and Gompertz growth models, were inspired by ecological issues. A model is a side or level abstraction and simplification of the real world, which can be used to build a tumor treatment model for guiding practice. In this paper, with the help of the Steinberg game model, we argue that the physician, as a "leader", is able to anticipate the tumor's response behavior and preferentially make a rational strategy based on the expected tumor behavior, while the tumor cells, as "followers", are able to make a rational strategy to the current environment after the physician has adopted a strategy. Tumor cells, as "followers", can respond to the current environment and formulate rational strategies to maximize the utility of the target in the environment after the doctor has adopted a strategy. By considering the growth of the tumor itself and the physician's benefits, the benefits are optimized, and by solving the model and constructing the simulation. When malignant tumors exhibit vigorous proliferation, doctors should administer Chinese medicine in conjunction with chemotherapy drugs, continuously optimizing the therapeutic effect of the Chinese medicine. Upon reaching a specific threshold in the treatment effect of the Chinese medicine, doctors may appropriately augment the dosage of chemotherapy drugs, building upon the initial regimen. Conversely, in cases where the proliferation ability of malignant tumors is weak, the dosage of chemotherapy and the adjuvant therapy with Chinese medicine should be kept in a relatively balanced state. Once the effect of the Chinese medicine attains a particular threshold, the dosage of chemotherapy can be concurrently increased to achieve a superior therapeutic result.

Multiple studies have demonstrated the effectiveness of Chinese medicine in treating various tumors, including colon, breast, colorectal, melanoma, and bladder cancer [12]. A meta-analysis conducted by scholars further reveals that combining Chinese medicine with platinum-based chemotherapy exhibits superior efficacy in treating non-small cell lung cancer compared to platinum-based chemotherapy alone [13], enhancing patients' quality of life while alleviating related symptoms without increasing adverse drug reactions, particularly among breast cancer survivors [14]. It can be seen that this model can effectively balance the load and dose toxicity in the process of tumor treatment, get the optimal solution of the treatment strategy of traditional Chinese medicine and chemotherapy drugs when the doctor benefits the most, reduce the impact of chemotherapy drug dose toxicity on the doctor's benefit, and further improve the doctor's benefit.

Conclusion

This paper is important because it establishes the foundations for the clinical development of drugs and advances the accuracy and rationality of doses in clinical medicine. It also encourages the cross-fertilization of medicine and other disciplines from an experimental point of view, allowing for better results without wasting additional resources. However, this study primarily focuses on the theoretical aspect of the intervention. The model lacks comprehensiveness by only considering a single chemotherapy treatment and neglecting the complexities of multi-stage chemotherapy or chemotherapy resistance.

Therefore, further in-depth investigations into the intricate details of the intervention are warranted. As a practical discipline, the model necessitates verification and refinement through future clinical trials. Meanwhile, these results should be juxtaposed with real-world data, allowing for iterative hypothesis modifications if necessary. Optimizing cancer therapy involves integrating game-theoretic frameworks with clinical and experimental patient data to drive and inform clinical trials, ultimately facilitating clinical research and development. As the sun sets on this phase of research, it paves the way for a new dawn of exploration and refinement.

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Authors' contributions
Fang-Yuan Liu prepared the original draft. Xin Liu conducted formula calculations. Yan-Hong Wang and Feng-Juan Han reviewed and edited the manuscript. Dan-Ni Ding, Shao-Xuan Liu, Jing Xu and Yu-Xin Zhao were involved in finding references. Yan-Hong Wang and Feng-Juan Han were cocorresponding authors. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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