Tropical Journal of Pharmaceutical Research December 2022; 21 (12): 2685-2691
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v21i12.25

Original Research Article

Efficacy of cisplatin and fluorouracil chemotherapy plus Jianpi Yiqi formula in the treatment of advanced gastric cancer

Xiting Qiao[1], Na Li[2]*
[1]Oncology Department, [2]Departmengt of Anorectal Surgery, Xianyang Central Hospital, Xianyang 712000, Shaanxi, China

For correspondence:* ***Email:* *Nalidr123@hotmail.com*

Sent for review: 4 August 2022 *Revised accepted: 19 November 2022*

Abstract

Purpose: *To investigate the efficacy of cisplatin and fluorouracil chemotherapy in combination with the Jianpi Yiqi formula in the treatment of advanced gastric cancer.*
Methods: *A total of 64 patients with advanced gastric cancer admitted and treated at Xianyang Central Hospital from April 2019 to October 2021 were recruited and assigned equally to chemotherapy group and combination group according to the time of admission. Chemotherapy group received cisplatin and fluorouracil, while the combination group received the Jianpi Yiqi formula based on the treatment given to the chemotherapy group. Some clinical indices were evaluated in the patients*
Results: *Intervention in the combination group was associated with a higher total effectiveness when compared with chemotherapy group ($p < 0.05$). Cisplatin and fluorouracil plus Jianpi Yiqi formula resulted in significantly higher European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item (EORTC QLQ-C30) score than cisplatin with fluorouracil ($p < 0.05$). Furthermore, cisplatin and fluorouracil plus Jianpi Yiqi formula led to considerably higher Karnofsky Performance Scale (KPS) scores versus cisplatin with fluorouracil ($p < 0.05$).*
Conclusion: *In the treatment of advanced gastric cancer, cisplatin-fluorouracil chemotherapy in conjunction with the Jianpi Yiqi formula produces remarkable efficacy. This strategy increases lesion dissolution rates, improves the quality of life and behavioral status of patients, and reduces adverse reactions, resulting in prolonged patients' progression survival (PFS) and overall survival (OS) levels.*

Keywords: *Cisplatin, Fluorouracil, Chemotherapy, Jianpi Yiqi formula, Advanced gastric cancer, Curative effect, Short-term prognosis*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, Web of Science, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Gastric cancer is the most common malignant tumor in China, and its incidence ranks first among all types of cancer [1]. Statistics reveal that approximately 170,000 people die of gastric cancer each year in China, posing a serious threat to the health, safety, and lives of Chinese citizens [2]. Most patients have progressed to the advanced stage at the time of diagnosis, resulting in dismal survival [3]. Due to the advanced stage, surgical option is not available, and chemotherapy is, therefore, the mainstay for advanced gastric cancer patients [4]. Although

chemotherapy may extend survival time for patients with advanced gastric cancer, chemotherapy is associated with a cascade of toxic and side reactions. Worse yet, many patients have to reduce the number of drugs or discontinue the treatment owing to their intolerance to chemotherapy [5].

The traditional Chinese medicine (TCM) theory believes that the occurrence of tumors is the result of long-term *yang* deficiency and evil excess. As previously reported, a number of cancers are treated with TCM by *strengthening essence* and *replenishing Qi*, promoting blood circulation, and removing stasis, enabling TCM a promising alternative for tumor diseases [6,7]. Wang et al [8] suggested that chemotherapy plus TCM intervention enhances the therapeutic outcomes, minimizes the toxic and side effects, and prolongs the patient's survival. In light of this, the present study aims to investigate the efficacy of cisplatin plus fluorouracil chemotherapy in combination with the *Jianpi Yiqi* formula in the treatment of advanced gastric cancer.

METHODS

Study design and participants

A total of 64 patients who were diagnosed and treated for advanced gastric cancer in Xianyang Central Hospital from April 2019 through October 2021 were eligible participants in this study.

Individuals were eligible if they satisfied the following conditions: have been diagnosed with advanced gastric cancer, have not received chemotherapy treatment in the past few months, had a survival time that is estimated to be no less than three months, and volunteered to participate. Patients with mental illnesses, complications associated with other serious diseases of the organs, and poor cooperation with the study were excluded from the study.

According to the admission time, patients were grouped 1:1 into a chemotherapy group and a combination group. The chemotherapy group included 21 females and 11 males, aged from 37 to 75 years, with a mean age of 54.59 ± 5.72 years.

The pathological types included undifferentiated carcinoma (3 cases), tubular adenocarcinoma (12 cases), mucinous adenocarcinoma (7 cases), papillary adenocarcinoma (4 cases), and poorly differentiated adenocarcinoma (6 cases); clinical stages: there were 15 cases in stage III and 17 cases in stage IV. The combination group consisted of 23 males and 9 females ranging in age from 36 to 77 years, with a mean age of (54.63 ± 5.79); pathological types: undifferentiated carcinoma (2 cases), tubular adenocarcinoma (12 cases), mucinous adenocarcinoma (6 cases), papillary adenocarcinoma (5 cases), and poorly differentiated adenocarcinoma (7 cases).

Patients and ethical considerations

There were 16 cases of stage III, and 16 cases of stage IV cancers. All patients and their families were informed of this study and signed an informed consent form. The study protocols were reviewed and approved by the Medical Ethics Committee of Xianyang Central Hospital (approval no. 2020190) and in strict accordance with the principles in the Declaration of Helsinki [9].

Treatments

Patients in the chemotherapy group were given cisplatin plus fluorouracil. The patients received docetaxel (Zhejiang Haizheng Pharmaceutical Co. Ltd, approval no. H20093092) on days 1, 8, and 15 at a dose of 38 mg/m^2 according to their body surface area (BSA); 200 mg/m^2 calcium folate (Guangdong Lingnan Pharmaceutical Co. LTD, approval number: H20040396) was administered from day 1 to 5 based on the patients' BSA; fluorouracil injections (Shanghai Xudong Haipu Pharmaceutical Co., Ltd, approval number: H31020593) were administered on day 1 to 5, at a dose of 500 mg/m^2 based on the patient's BSA. Cisplatin (Jiangsu Hausen Pharmaceutical Group Co. Ltd, approval number: H20040813) was given via injection every 1 to 3 days at a dose of 30 mg/m^2 based on the patient's BSA.

In the combination group, patients were additionally given *Jianpi Yiqi* formula based on the treatments in the chemotherapy group, and the chemotherapy regimen and dosage administered to patients in the combination group were equal to those in the chemotherapy group. The basic formula for *Jianpi Yiqi* consists of *Codonopsis pilosula, fried Atractylodes, Poria, Pinellia Fructus, Involvulaceae, Daisy Ochre, Ophiopogon japonicus, Amomum, honey-fried licorice root,* and other traditional Chinese medicines. In addition, it may also be tailored to the different symptoms. For patients with epigastric distention, *costustoot, aurantii immaturus fructus, exocarpium citrium leiocarpae,* etc, were added. For patients with *yin* fluid deficiency, *Gadenophora stricta*, dendrobe, *Lycium barbarum*, etc. were added. For patients with excessive heat due to *yin* deficiency,

Rhizome of Rehmannia, *Radix scophulariae*, *fructus cannabis, fructus trichosanthis*, etc. were added.

The patients in the combination group were treated with TCM one week prior to the commencement of treatment. The TCM medicine was decocted with water, and taken twice daily at 100 mL each time in the morning and evening until the completion of chemotherapy [9].

Evaluation of paraters/outcomes

Efficacy/clinical effectiveness

Complete response (CR): The lesions disappeared, and the tumor marker detection was normal, which lasted for no less than 4 weeks. *Partial response* (PR): There was more than a 30 % reduction in lesions, which lasted for at least 4 weeks. *Stable disease* (SD): The lesions were reduced but by less than 30 %. *Progressive disease* (PD): There was an increase in lesions or the appearance of new lesions.

QLQ-C30 Score

The quality of life was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item (EORTC QLQ-C30). The EORTC QLQ-C30 is a validated, cancer-specific instrument that contains 30 items resulting in five functional scales (physical, role, emotional, cognitive, and social functioning), one Global Health Status (GHS) scale, three symptom scales (fatigue, nausea, and vomiting, and pain) and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Higher scores represent greater GHS, better functioning, and worse symptoms, respectively.

Karnofsky Performance Scale (KPS) score

The behavior was assessed from three dimensions, namely, the ability to carry on normal activity and to work, the ability to care for self, and the condition. On a 100-point scale, higher scores indicate better behavior.

Adverse reactions

The potential adverse reactions include neurotoxic reactions, gastrointestinal reactions, liver and kidney toxicity, and bone marrow suppression.

Progression-free survival (PFS) and overall survival (OS)

The two groups of patients were followed up over a period of 24 months, and their PFS and OS were documented.

Statistical analysis

Measurement data are expressed as mean ± standard deviation (SD), and independent t-test samples were used for comparison. Categorical variables, including categorical baseline variables and incidence of adverse events, were analyzed using a Chi-square (χ^2) test. Statistical significance was defined as a two-tailed $p < 0.05$. Statistical analysis was performed by SPSS 20.0 (IBM SPSS Inc., Armonk, New York, USA) and SAS 9.2 software (SAS Institute Inc., Cary, USA).

RESULTS

Baseline characteristics

The baseline characteristics were generally balanced between the two groups ($p > 0.05$) (Table 1).

Clinical efficacy

Cisplatin and fluorouracil plus *Jianpi Yiqi* formula in the combination group was associated with a higher total effective rate as compared with cisplatin and fluorouracil in the chemotherapy group ($p < 0.05$; Table 2).

QLQ-C30 score comparison

After treatment, cisplatin and fluorouracil plus the *Jianpi Yiqi* formula resulted in a significantly higher QLQ-C30 score than cisplatin and fluorouracil alone ($p < 0.05$) (Figure 1).

KPS score

Cisplatin and fluorouracil plus *Jianpi Yiqi* formula led to a considerably higher Karnofsky Performance Scale (KPS) score versus cisplatin and fluorouracil alone ($p < 0.05$) (Figure 2).

Adverse reactions

There was no significant difference in the incidence of neurotoxicity between the two groups ($p > 0.05$), however, the incidence of gastrointestinal complications, liver and kidney damage, and bone marrow suppression were significantly lower in the combination group than

that in the chemotherapy group ($p < 0.05$) (Table 3).

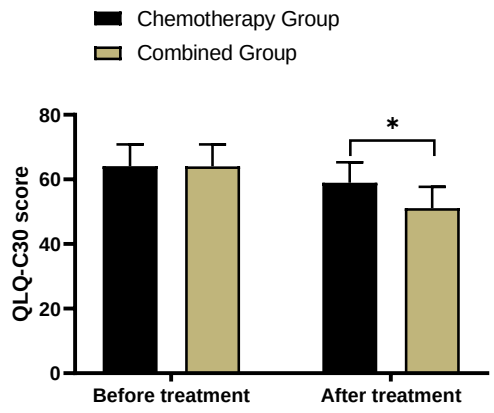

Figure 1: QLQ-C30 score comparison (mean ± SD). *$P < 0.05$

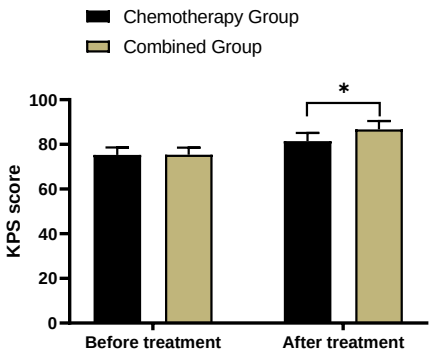

Figure 2: KPS score comparison (mean ± SD). *$P < 0.05$

PFS and OS

Significantly higher PFS and OS were observed in the combination group versus the chemotherapy group ($p < 0.05$) (Table 4).

Table 1: Comparison of baseline data (mean ± SD)

Item	Chemotherapy group (n=32)	Combination group (n=32)	t/χ^2	*P*-value
Gender			0.291	0.59
Male	21	23		
Female	11	9		
Age (years)	37-75	36-77		
Average age (years)	54.59 ± 5.82	54.63 ± 5.79	-0.028	0.978
Pathological type			-	>0.05
Undifferentiated carcinoma	3	2		
Tubular adenocarcinoma	12	12		
Mucinous adenocarcinoma	7	6		
Papillary adenocarcinoma	4	5		
Poorly differentiated adenocarcinoma	6	7		
Clinical stage			0.063	0.802
Phase III	15	16		
Stage IV	17	16		

Table 2: Comparison of clinical efficacy (n %)

Item	Chemotherapy group (n=32)	Combined group (n=32)	x^2	*P*-value
CR	3	2		
PR	13	9		
SD	13	14		
PD	3	7		
Total efficiency (%)	16 (50%)	11 (34%)	5.255	0.022

Table 3: Comparison of adverse reactions (n = 32, %)

Item	Chemotherapy group	Combination group	χ^2	*P*-value
Neurotoxicity	3 (9%)	2 (6%)	0.649	0.421
Gastrointestinal reactions	16 (50%)	8 (25%)	13.333	<0.001
Liver and kidney toxicity	14 (44%)	9 (28%)	5.556	0.018
Myelosuppression	12 (38%)	7 (22%)	6.095	0.014

Table 4: Comparison of progression survival (PFS) and overall survival (OS) levels (n = 32; mean ± SD)

Group	PFS (months)	OS (months)
Chemotherapy group	11.71 ± 1.63	16.56 ± 0.44
Combined group	13.15 ± 2.88	16.07 ± 0.51
t	-2.462	4.115
P-value	0.017	<0.001

DISCUSSION

In China, gastric cancer is the most common malignant tumor. since most patients with early gastric cancer present insidious symptoms that always disguise as problems of the digestive system, thus missing the optimal treatment period for surgical resection [10]. As a consequence, surgery is not available for advanced gastric cancer, and chemotherapy is, therefore, a common option. As previously reported, gastric cancer is relatively sensitive to chemotherapy, and metastasis and recurrence are the major contributors to the collapsed treatment of advanced gastric cancer [11]. Accordingly, chemotherapy for advanced gastric cancer patients involves primarily systemic therapy, yet with a dismal prognosis [12].

Cisplatin and fluorouracil are the two most commonly prescribed first-line chemotherapy drugs for patients with advanced gastric cancer. Fluorouracil plays a critical role in the S phase of the cell cycle, is a cycle-specific drug, and has a short half-life, and a wealth of evidence confirmed its benefits for patients with advanced gastric cancer [13]. Cisplatin is a platinum-metal complex that is one of the most commonly used drugs in clinical chemotherapy. It targets DNA and interferes with the copies of DNA in cancer cells, thereby inhibiting the growth of cancer cells and causing anti-cancer effects. Furthermore, it binds to multiple anti-tumor agents, yielding a synergy with no cross-resistance. Considering its merits, cisplatin is one of the most commonly used chemotherapy drugs currently available on the market [14]. Despite the significant effect on advanced gastric cancer, a number of clinical studies have argued that it may also damage normal cells [15].

In TCM, advanced gastric cancer is primarily the result of prolonged fatigue and internal injury as well as improper eating habits, both of which are characterized by an imbalance of *Yin* and *Yang* in the body, leading to *Qi* stagnation, blood stasis, and food stagnation [16]. According to the theory of TCM syndrome differentiation, gastric cancer is a result of an imbalance of visceral functions, causing phlegm to coagulate and blood to stasis [17]. The lack of healthy *Qi* within the body of the patient causes blood stasis and dampness, and further a carcinogenic reaction. *Jianpi Yiqi* formula is one of the medications derived from different research studies conducted in China. *Jianpi Yiqi* formula can effectively reduce the toxic and adverse effects of chemotherapy, as well as improve the effectiveness of clinical anti-tumor therapy as evidenced by prior studies [18].

As per the hypothesis of this study, the intervention in the combination group was associated with a higher total effective rate as compared with the chemotherapy group; Cisplatin and fluorouracil plus *Jianpi Yiqi* formula resulted in a significantly higher EORTC QLQ-C30 score than cisplatin and fluorouracil alone. In support of this hypothesis, cisplatin, and fluorouracil plus *Jianpi Yiqi* formula led to a considerably higher KPS score versus cisplatin and fluorouracil alone. Importantly, the safety profile of cisplatin and fluorouracil plus the *Jianpi Yiqi* formula is promising. Moreover, both the PFS and overall survival in the combination group were significantly higher than those in the chemotherapy group.

Armed with the aforementioned findings, it has been postulated that the combination of *Jianpi Yiqi* formula decoction and cisplatin and fluorouracil chemotherapy might be a reliable option in treating patients with advanced gastric cancer. The possible explanation may be attributed to the fact that *Glycyrrhiza uralensis Fisch, Poria cocos, Codonopsis pilosula*, and *Rhizoma Atractylodis* in the *Jianpi Yiqi* formula can moisten the spleen and invigorate *Qi*, and *pericarpium citri reticulatae* and *Pinellia ternatacan* regulate *Qi*, *Costustoot* relieves pain and dehumidifies [19]. Encouragingly, modern pharmacological studies have confirmed that the components in *jianpi Yiqi* exert anti-tumor function, resulting in tumor cell apoptosis and boosting immunity in patients, and minimizing the adverse reactions of chemotherapy [20,21].

CONCLUSION

In the treatment of advanced gastric cancer, cisplatin-fluorouracil chemotherapy in conjunction with the *Jianpi Yiqi* formula produces remarkable efficacy. This strategy increases lesion dissolution rates, improves the quality of life and behavioral status of patients, and reduces adverse reactions, which is beneficial to prolong patients' PFS and OS.

DECLARATIONS

Acknowledgements

None provided.

Funding

None provided.

Ethical approval

The study protocols were reviewed and approved by the Medical Ethics Committee of Xianyang Central Hospital (approval no. 2020190).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

Open Access

REFERENCES

1. *Choi AH, Kim J, Chao J. Perioperative chemotherapy for resectable gastric cancer: MAGIC and beyond. World J Gastroenterol 2015; 21(24): 7343-7348.*
2. *Tokunaga M, Sato Y, Nakagawa M, Aburatani T, Matsuyama T, Nakajima Y, Kinugasa Y. Perioperative chemotherapy for locally advanced gastric cancer in Japan: current and future perspectives. Surg Today 2020; 50(1): 30-37.*
3. *Kang BW, Kim JG, Kwon OK, Chung HY, Yu W. Non-platinum-based chemotherapy for treatment of advanced gastric cancer: 5-fluorouracil, taxanes, and irinotecan. World J Gastroenterol 2014; 20(18): 5396-402.*
4. *Marino E, Graziosi L, Donini A. Neoadjuvant Chemotherapy for Locally Advanced Gastric Cancer: Where we Stand; An Italian Single Center Perspective. In Vivo 2021; 35(6): 3459-3466.*
5. *Coccolini F, Cotte E, Glehen O, Lotti M, Poiasina E, Catena F, Yonemura Y, Ansaloni L. Intraperitoneal chemotherapy in advanced gastric cancer. Meta-analysis of randomized trials. Eur J Surg Oncol 2014; 40(1): 12-26.*
6. *Han Q, Li HH, Fan CP, Liu C, Liang YL. Analysis on composition principles of prescriptions for nausea by using traditional Chinese medicine inheritance support system. Zhongguo Zhong Yao Za Zhi 2016; 41(13): 2549-2554.*
7. *Qi XJ, Chen XR, Mo JH, Li PX, Cai MY, Lan WN, Chen HR, Chen ZZ, Chen GM, Lin LZ. Analysis of prescription regularity of traditional Chinese medicine for colorectal cancer based on data mining. Zhongguo Zhong Yao Za Zhi 2021;46(15): 4016-4022.*
8. *Gao JL, Chen G, He QY, Li J, Wang J. Analysis of Chinese patent medicine prescriptions for Qi stagnation and blood stasis syndrome. Zhongguo Zhong Yao Za Zhi 2017;42(1): 187-191.*
9. *World Medical Association General Assembly. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. J Int Bioethique 2004;15(1): 124-9.*
10. *Yi YQ, Fang R, Ge JW, Cheng SW, Wang GZ, Liu L. Analysis on medication rules for the treatment of dementia by ancient physicians based on data mining methods. Zhongguo Zhong Yao Za Zhi 2018; 43(16): 3376-3381.*
11. *Zou K, Yang S, Zheng L, Yang C, Xiong B. Efficacy and safety of target combined chemotherapy in advanced gastric cancer: a meta-analysis and system review. BMC Cancer 2016; 16(1): 737.*
12. *Luo H, Peng L, Wang N, Zhang J, Zheng X, Sun Y, Fan C, Ge H. Early brain metastasis of advanced gastric cancer with a pathological complete response to neoadjuvant chemotherapy followed by surgery: A case report and literature review. Cancer Biol Ther 2018; 19(10): 875-878.*
13. *Wang W, Peng Y, Feng X, Zhao Y, Seeruttun SR, Zhang J, Cheng Z, Li Y, Liu Z, Zhou Z. Development and validation of a computed tomography-based radiomics signature to predict response to neoadjuvant chemotherapy for locally advanced gastric cancer. JAMA Netw Open 2021; 4(8): e2121143.*
14. *Zhao B, Lv W, Lin J. Delaying adjuvant chemotherapy in advanced gastric cancer patients: Risk factors and its impact on survival outcome. Curr Probl Cancer 2020; 44(6): 100577.*
15. *Coccolini F, Fugazzola P, Ansaloni L, Sartelli M, Cicuttin E, Leandro G, De' Angelis GL, Gaiani F, Di Mario F, Tomasoni M, et al. Advanced gastric cancer: the value*

of systemic and intraperitoneal chemotherapy. Acta Biomed 2018; 89(8-S): 104-109.
16. Nakamura N, Kinami S, Fujita J, Kaida D, Tomita Y, Miyata T, Fujita H, Ueda N, Takamura H. Advanced gastric cancer with abdominal wall invasion treated with curative resection after chemotherapy: a case report. J Med Case Rep 2021; 15(1): 230.
17. Dou Z, Xia Y, Zhang J, Li Y, Zhang Y, Zhao L, Huang Z, Sun H, Wu L, Han D, et al. Syndrome differentiation and treatment regularity in traditional Chinese medicine for type 2 diabetes: a text mining analysis. Front Endocrinol (Lausanne) 2021; 12: 728032.
18. Qin LI, Huan LI, Song-Wei LI. Study on syndrome differentiation of ancient arthralgia syndrome and drug use rules based on latent structure model. Zhongguo Zhong Yao Za Zhi 2020; 45(19): 4784-4791.
19. Wu J, Zhang XX, Zou X, Wang M, Wang HX, Wang YH, Li CY, Zhao LG, Chen M, et al. The effect of Jianpi Yangzheng Xiaozheng Decoction and its components on gastric cancer. J Ethnopharmacol 2019; 235: 56-64.
20. Yang HS, Xie YM, Chen C, Zhuang Y, Zhang Y. Association rules analysis of Fufang Kushen injection in combination with modern medications in treating lung cancer: real-world study based on hospital information. Zhongguo Zhong Yao Za Zhi 2018; 43(8): 1708-1713.
21. Mokhtari MJ, Akbarzadeh A, Hashemi M, Javadi G, Mahdian R, Ghasemi S, Taghavi MS. Cisplatin induces up-regulation of KAI1, a Metastasis Suppressor Gene, in MCF-7 Breast Cancer Cell Line. Trop J Pharm Res 2012; 11(4): 523-529.