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Original Article

Taxol for advanced gastric cancer and the expression of tumor markers

Huichun Xie, Feng Qiao, Jianbin Ma, Hongping Han

College of Life Science, Qinghai Normal University, Xining City, Qinghai Province, China

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Abstract: Objective: To investigate the efficacy of taxol in the management of advanced gastric cancer (GC) and its impact on the expression of tumor markers. Methods: Sixty patients with advanced GC admitted to our hospital from January 2014 to December 2016 were recruited in this study. The patients were randomly assigned to the experiment group (n=30) or the control group (n=30) according to a random number table. The patients in the experiment group underwent a combination chemotherapy of taxol and capecitabine, whereas those in the control group received chemotherapy of capecitabine alone. The patients in the two groups were compared in the remission rates, the 6-month and 1-year survival rates, the serum careinoembryonic antigen (CEA) level, CA199, vascular endothelial growth factor (VEGF) and endostatin, as well as the rates of adverse events. Results: The remission rate was remarkably higher in the experiment group than in the control group (73.3% vs 46.7%, P=0.035), so were the 6-month and 1-year survival rates (both P<0.05). After chemotherapy, the levels of serum CEA, CA199 and VEGF were considerably lower, but the endostatin level was higher in the experiment group (all P<0.05). Nevertheless, the rates of adverse events of patients differed mildly between the two groups (P>0.05). Conclusion: Taxol is effective and safe in the treatment of advanced GC, leading to reduced CEA, CA199 and VEGF levels, and elevated endostatin level. It can be applied as an effective alternative for management of patients with advanced GC.

Keywords: Taxol, advanced gastric cancer, tumor marker, adverse event

Introduction

Gastric cancer (GC), one of the most common malignancies involving in the digestive system, poses severe threats to the health of our human beings due to its high morbidity and mortality [1, 2]. Most of the patients are already in the advanced stage of GC when they are initially diagnosed as having the disease. The diagnostic rate of advanced GC reaches up to 75%; in such case, the patients have missed the best timing for radical gastrectomy, and chemotherapy has become the first-line treatment [3]. Chemotherapy agents vary greatly in their therapeutic effects for treatment of GC. Accordingly, choosing effective and safe drugs is of great practical implication to improve the efficacy of GC treatment and the quality of life in patients [4, 5].

Platinum, anthracycline and fluorouracil are commonly used as chemotherapeutic agents for the management of advanced GC; however, the agents are always associated with unsatisfactory efficacy and various adverse events [6]. Taxol is a kind of terpenoids extracted from taxaceae plants; it is a novel antitumor agent with mechanisms different from those of previous agents [7]. Taxol terminates mitosis of tumor cells and inhibits angiogenesis, hence promoting apoptosis of tumor cells; it also enhances the tumor inhibitory and killing capacities of the patient [8, 9]. Taxol has shown to be extensively used in chemotherapy for treating breast cancer, uterine cancer and lung cancer [10-12]. Nevertheless, few studies are concerned with the clinical application of taxol in the treatment of GC. Therefore, this study was designed to delve into the effects of taxol on patients with advanced GC by analyzing the clinical efficacy, the expression of tumor markers and adverse events in patients with advanced GC.

Materials and methods

Patients

The patients and their families were informed of this study and provided written informed con-

sent; the Hospital Ethics Committee reviewed and approved this study. A total of 60 patients with advanced GC admitted to our hospital between January 2014 and December 2016 were recruited in this study as participants.

Inclusion and exclusion criteria

All the enrolled patients were pathologically confirmed as having GC. Patients older than 18 years were eligible for this study if they underwent initial therapy for advanced GC; they were not candidates for tumor resection or radical gastrectomy; they had the TNM stage of IV, no previous chemo-radiation, no contraindications to chemotherapy; the life expectancy >3 months and the Karnofsky score >60. Patients were excluded if they were pregnant or lactating women or associated with cerebral or bone metastasis; if they had major organ dysfunction involving in the heart, brain, liver, kidney or other visceral organs. Moreover, the patients were allergic to toxol, capecitabine, cisplatin or other agents, or accompanied by other malignancies were also excluded. All the eligible patients were randomly assigned to the experiment group (n=30) or the control group (n=30) in accordance with a random number table.

Methods

All the enrolled patients received gastric-protective, hepato-protective and antiemetic symptomatic treatment. Each patient in the experiment group were treated with intravenous infusion of toxol (at 80 mg/m^2) plus normal saline (500 mL) on day 1 and day 8, and oral capecitabine tablets (at 1000 mg/m^2) twice a day from days 1 to 14. By contrast, each patient in the control group underwent chemotherapy with capecitabine alone, with the oral dose and the duration of medication matching to those in the experiment group. The patients in both groups received 4 three-week cycles of treatment [13].

Outcome measures

The remission rates of the patients were compared between the two groups. After the completion of chemotherapy, they took imaging examinations every 4 weeks for assessment of the efficacy of chemotherapy for advanced GC. Complete remission (CR) is defined as complete disappearance of tumor lesions for more than 4 weeks; partial (PR) remission is defined as a reduction of the tumor lesions by over 30% for at least 4 weeks, without new tumor lesions; stable disease (SD) is defined as a reduction of the tumor lesions by 30%, without new tumor lesions. Remission rate= (Cases of CR + Cases of PR)/Total cases *100%.

The survival rates of patients were compared. The patients paid follow-up visits by outpatient appointments or telephone calls once two months after chemotherapy, and their 6-months and 1-year survival rates were recorded.

The patients in the two groups were compared in the expression of careinoembryonic antigen (CEA), CA199, vascular endothelial growth factor (VEGF) and endostatin. Fasting venous blood (5 mL) was drawn from each patient on the day before chemotherapy and on the day after the end of chemotherapy, respectively. After anticoagulation, serum was centrifuged from the blood, followed by detecting the levels of VEGF and endostatin by the ELISA, and the CEA and CA199 levels by chemiluminescence immunoassay. The ELISA kits were purchased from the R&D Systems in the United States, and the kits for chemiluminescence immunoassay from Roche in Switzerland.

Additionally, the rates of adverse events were also compared between the two groups over the period of chemotherapy. Adverse events included diarrhea, nausea and vomiting, blood cell reduction (neutropenia, deoxyhemoglobin and thrombopenia), stomatitis, myelosuppression and hand foot-syndrome.

Statistical analysis

All the data analyses were conducted using the SPSS statistical software, version 21. Measurement data were described as mean ± SD, with the independent samples t-tests for intergroup comparisons and the paired t-tests for intragroup comparisons before and after chemotherapy. Count data were expressed as percentages, with the chi-square tests for intergroup comparisons. $P<0.05$ was deemed as significantly different.

Results

Basic characteristics of patients

The patients in the two groups were generally well-balanced in age, sex, the course of disease

Table 1. Basic characteristics of patients

Variable	Case (n)	Age (year)	M/F (n)	DC (mon)	Pathological type			
					HDA	ILDA	MA	SRCC
EG	30	61.5±3.2	14/16	7.2±1.1	1	25	2	2
CG	30	60.8±3.7	13/17	8.3±1.4	2	21	4	3
t/χ^2		0.784	0	1.070		1.493		
P		0.436	1	0.345		0.769		

Note: M/F denotes male/female, DC disease course, HDA highly-differentiated adenocarcinoma, ILDA intermediate-and-low differentiated adenocarcinoma, MA mucous adenocarcinoma, SRCC signet-ring cell carcinoma, EG experiment group, and CG control group.

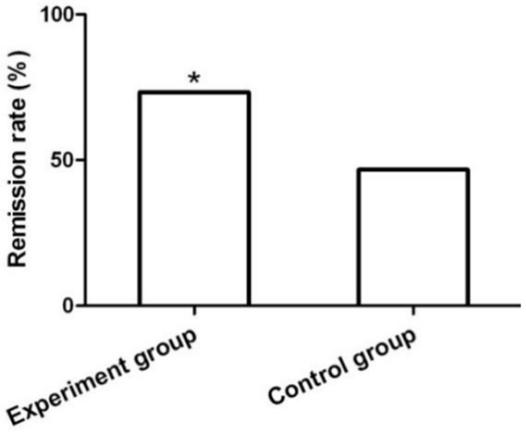

Figure 1. Comparison of the remission rates between the two groups. Compared with the control group, *P<0.05.

Table 2. Survival of patients

Variable	Case	Survival rate (%)	
		6 months	1 year
Experiment group	30	27 (90%)	24 (80%)
Control group	30	19 (63.3%)	16 (53.3%)
χ^2		4.565	4.800
P		0.033	0.028

and pathological types of tumors (all P>0.05), hence they were comparable (**Table 1**).

Clinical remission of patients

Complete remission occurred in 4 patients and partial remission in 18 patients of the experiment group, with a remission rate of 73.3%; 1 patient had complete remission and 13 patients had partial remission in the control group, with a remission rate of 46.7%. The remission rate was remarkably higher in the experiment group than in the control group (χ^2=4.444, P=0.035), as illustrated in **Figure 1**.

Survival of patients

The 6-month and 1-year survival rates of the patients in the experiment group were substantially higher than those of the patients in the control group (both P<0.05, **Table 2**).

CEA, CA199, VEGF and endostatin of patients

No significant disparities in the levels of CEA, CA199, VEGF and endostatin were observed between the two groups before chemotherapy (all P>0.05). The levels of CEA, CA199 and VEGF of the experiment group and the control group after chemotherapy decreased significantly, but the endostatin levels were elevated markedly as compared with those of the same groups before chemotherapy (all P<0.05). After chemotherapy, the levels of CEA, CA199 and VEGF of the experiment group were strikingly lower, but the endostatin level was remarkably higher than those of the control group (all P<0.05, **Table 3**).

Adverse events of patients

The patients in the two groups differed insignificantly in adverse events including diarrhea, nausea and vomiting, blood cell reduction (neutropenia, deoxyhemoglobin and thrombopenia), stomatitis, myelosuppression and hand-foot syndrome (all P>0.05, **Table 4**).

Discussion

In recent years, GC shows a trend of growing prevalence. Patients are mostly in an advanced stage of GC when they are diagnosed. Moreover, some patients might relapse and progress into advanced GC even after surgical treatment. However, there are no effective standard protocols for the treatment of advanced GC. Currently, chemotherapy is regarded as the main treatment method, with an aim to alleviate the growth of tumors. Active and effective chemotherapy not only improves the quality of life of the patients, but also prolongs their survival, rendering more benefits to them [14]. Recent studies have found that taxol use is associated with fewer cell division cycles, induction of tumor cell apoptosis and suppression of tumor cell proliferation; however, it has few adverse effects on the cell division of nor-

Table 3. CEA, CA199, VEGF and endostatin of patients

Variable	EG	CG	t	P
Case (n)	30	30		
CEA (U/mL)				
Pre-C	82.3±8.6	85.4±9.2	1.348	0.183
Post-C	14.8±2.9	27.9±3.4	13.532	<0.001
CA199 (U/mL)				
Pre-C	89.5±8.9	90.7±9.6	0.159	0.882
Post-c	19.5±3.8	31.2±4.5	11.219	<0.001
VEGF (pg/mL)				
Pre-C	448.3±30.1	453.6±32.4	0.208	0.846
Post-C	219.1±20.8	261.3±21.9	2.763	0.028
Endostatin (ng/mL)				
Pre-C	84.9±16.2	82.7±14.4	0.176	0.869
Post-C	121.8±16.0	106.4±16.7	2.303	0.031

Note: Pre-C denotes pre-chemotherapy, Post-C post-chemotherapy, EG experiment group, and CG control group.

Table 4. Adverse events of patients

Variable	Experiment group	Control group	χ^2	P
Case (n)	30	30		
Diarrhea	11 (36.7%)	8 (26.7%)	0.693	0.405
Nausea and vomiting	13 (43.4%)	12 (40%)	0.069	0.793
Neutropenia	10 (33.3%)	9 (30%)	0.077	0.781
DeoxyHemoglobin	16 (53.3%)	14 (46.7%)	0.267	0.606
Thrombopenia	19 (63.3%)	18 (60%)	0.071	0.791
Stomatitis	15 (50%)	13 (43.4%)	0.268	0.605
Myelosuppression	17 (56.7%)	12 (40%)	1.669	0.196
Hand-foot syndrome	15 (50%)	11 (36.7%)	1.086	0.297

mal tissue [15]. Therefore, it is of practical significance to investigate the efficacy of taxol in the treatment of advanced GC.

Capecitabine is a prodrug of 5-Fu. After oral medication and absorption, capecitabine is hydrolyzed to 5-Fu through liver metabolism and finally through transthoracic glucoside phosphorylase (TP), producing cytotoxicity. Capecitabine is not toxic to normal tissue because the thymidine phosphorylase level in the tumor tissue is higher than that of normal cells. According to a study, capecitabine has a high anti-GC activity, and the effective rate of capecitabine alone as the first-line treatment is 24% for advanced GC [16]. Taxol is a natural drug extracted from the trunks or the barks of yew trees and an anti-microtubule drug which suppresses microtubule depolymerization, promotes polymerization and maintains stable tubulin. Taxol up-regulates the activity of thymidine phosphorylase, the effective rate of taxol alone as the first-line treatment for GC ranges from 27% to 40% [17]. As a result, in the current study, we administered taxol plus capecitabine to the patients with advanced GC, with an aim to investigate the efficacy of taxol added to capecitabine in the treatment of advanced GC. The results of the present study demonstrated that the remission rate of the patients in the experiment group was 73.3%, which was strikingly higher than that of the patients in the control group. Moreover, the follow-up results after chemotherapy indicated that the 6-month and 1-year survival rates of the patients in the experiment group were remarkably higher than those in the control group. As far as adverse events are concerned, the rates of diarrhea, nausea and vomiting, blood cell reduction (neutropenia, deoxyhemoglobin and thrombopenia), stomatitis, myelosuppression and hand-foot syndrome in patients undergoing the combined chemotherapy of taxtol and capecitabine were different insignificantly from those of the patients receiving chemotherapy with capecitabine alone. This suggests that taxol has a favorable short-term efficacy in the treatment of advanced GC, and a combination chemotherapy of taxol and capecitabine results in an insignificant increase in adverse events as well as high safety.

Tumor markers are the substances fallen off or secreted from the tumor cells into the tissue or body fluid [18]. CEA, a structural antigen on the surface of tumor cells, has a low expression in the serum of healthy humans. CEA is currently utilized as an adjuvant agent in diagnosis and treatment of malignant tumors involving in the digestive tract. It is reported that the increasing or unreduced CEA levels in tumor patients imply poor prognosis or uncontrolled conditions; vice versa, it shows favorable curative effects [19].

CA-199 is also a common tumor marker related to malignancy. CA19 9 has shown to be superior to other tumor markers in evaluating the efficacy and prognosis of malignancies involving in the digestive system [20]. The results of the current study revealed that the serum CEA and CA199 levels were remarkably lower among the patients in the experiment group than among those in the control group, indicating that taxol chemotherapy is associated with an improvement or a delay in the progression of advanced GC in patients, which is consistent with the result reported by Yamaguchi et al. [21].

Angiogenesis is closely correlated with growth and metastasis of malignancies. VEGF, an endogenous pro-angiogenic factor, promotes the proliferation and migration of endothelial cells and enhances vascular permeability, contributing to invasion and metastasis of tumor cells. A previous study indicated that the VEGF level was high in serum of GC patients [22]. Contrary to VEGF, endostatin, an endogenous glycoprotein, inhibits the proliferation of vascular endothelial cells and alleviates neovascularization in tumor tissue [23]. In the current study, the serum VEGF level in the experiment group was substantially lower than that in the control group; conversely, the serum endostatin level was remarkably higher (both $P<0.05$), suggesting that the inhibition of taxol to tumor growth might be associated with the decreased neovascularization, which is similar to what reported by Cheng et al. and Dan et al. [24, 25].

In conclusion, chemotherapy with taxol is associated with more favorable efficacy and better safety in patients with advanced GC. Given the low prices, taxol is worthy of extensively clinical application. Due to the limits (such as a small sample size and single-center nature) of this study, additional multi-center, stratified studies with larger sample size are required for further validation for the efficacy and safety of taxol therapy.

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Disclosure of conflict of interest

None.

Address correspondence to: Hongping Han, The Key Laboratory of Medicinal Plant and Animal Resources of Qinghai-Tibet Plateau, College of Life Science, Qinghai Normal University, No.38, West Wusi Road, Chengxi District, Xining City 810008, Qinghai Province, China. Tel: +86-13639786217; E-mail: hongpinghan85@126.com

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