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Original Article

Efficacy of oxaliplatin combined with Tiji'ao and recombinant human endostatin injection in treatment of late gastric cancer and the effects on serum tumor markers

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Abstract: Objective: To investigate the efficacy of oxaliplatin combined with Tiji'ao (Tegafur + gimeracil + oteracil) and recombinant human endostatin injection in treatment of late gastric cancer and the effects on serum tumor markers. Methods: In total, 120 patients with late gastric cancer hospitalized and treated in Central Hospital of Linyi City from June 2014 to December 2015 were selected and randomly divided into the observation group and the control group, with 60 patients in each group. The control group was given chemotherapy with Tiji'ao + oxaliplatin, while the observation group given recombinant human endostatin injection in addition to those of the control group. Three serum tumor markers (carcinoembryonic antigen and carbohydrate antigens (CA125 and CA199)) were detected before and during treatment, and the clinical efficacy, adverse reactions, and survival times were compared between the two groups. Results: The control group had a higher clinical response rate than the observation group (88.3% vs. 68.3%, P=0.03). The main adverse reactions of the two groups were bone marrow depression and gastrointestinal reactions, of which the incidences were insignificantly changed (P=0.19). Both groups had significantly decreased expression levels of serum tumor markers, and the observation group had significantly greater decreasing extents than the control group (P=0.01, P=0.01, P=0.02). The median survival times of the observation group and control group were (15.03±2.37) months and (14.41±2.74) months, respectively, and the difference was statistically insignificant (P=0.21). Conclusion: Oxaliplatin combined with Tiji'ao and recombinant human endostatin injection in treatment of late gastric cancer has excellent clinical efficacy, without increasing chemotherapy toxicity, and consequently is worthy of clinical application.

Keywords: Gastric cancer, recombinant human endostatin injection, chemotherapy

Introduction

Gastric cancer is one of the common malignant tumors of digestive system, with an increasing incidence year by year. But by the time of discovery, most cases are late and have missed the opportunity of surgery, and only can be treated with conservative treatments, among which, chemotherapy is the the most important. At present, the American National Comprehensive Cancer Network guide recommends chemotherapy with platinum combined with fluorouracil, but it is intolerable, with severe gastrointestinal reactions. Therefore, it is especially important to search for a safe and effective chemotherapy regimen [1]. Tiji'ao is a newly invented oral drug to treat gastric cancer, which has definite clinical efficacy and is easy to use. Oxaliplatin is a drug of platinum, with fewer adverse reactions than the other platinum chemotherapeutics [2, 3]. Recombinant human endostatin is a vascular endothelium inhibitor that can prevent vascular endothelial cell migration and promote cell apoptosis, and consequently can inhibit the angiogenesis, has synergistic effects on chemotherapeutics, and has been used for various tumors including lung cancer [4-7]. Regardless of the chemotherapy regimen used, the survival time of late gastric cancer is still hovering around 9-11 months and in very few cases, the survival time is longer than 1 year, and then reaches a huge bottleneck [8]. Hence, it is critical to actively look for new treatment modalities. In this study, we

Table 1. Comparison of general data between the two groups

	Observation group	Control group	t/χ^2	P
Case number	60	60		
Sex (male/female)	31/29	40/20	2.08	0.08
Age	49.73±12.32	51.06±20.06	4.06	0.16
Course of disease	4.15±0.15	4.41±1.42		0.29
Site				
Gastric body	16	14	1.64	0.13
Gastric fundus	13	13		
Pylorus	20	24		
Cardia	11	9		
TNM staging				
Stage III	37	35	2.52	0.09
Stage IV	23	25		
Pathological type				
Poorly differentiated adenocarcinoma	30	33	4.43	0.17
Moderately differentiated adenocarcinoma	20	20		
Signet-ring cell carcinoma	10	7		
Distant metastasis				
Abdominal cavity	20	21	2.51	0.21
Left supraclavicular part	22	20		
Liver	8	9		
Lung	10	10		

Table 2. Comparison of clinical efficacy between the two groups (n, %)

Group	Cases	Complete remission	Partial remission	Stable disease	Progressive disease	Response rate
Observation group	60	14	39	5	2	53 (88.3)
Control group	60	10	31	14	5	41 (68.3)
χ^2						8.15
P						0.03

investigated the efficacy of Tiji'ao combined with oxaliplatin and recombinant human endostatin in treatment of late gastric cancer, which was excellent. The details were reported below.

Materials and methods

General data

This was a prospective study. In total, 120 patients with advanced gastric carcinoma hospitalized and treated in Central Hospital of Linyi City from June 2014 to December 2015 were selected, including 71 males and 49 females, aged 42-68 years, average: (52.08±11.07) years and the course of disease was 7 years (with a mean duration of 4.27±0.59 years).

Inclusion criteria: (1) All the patients were diagnosed with stage II gastric cancer, which was confirmed by pathological examination; (2) All the patients were diagnosed with advanced gastric carcinoma (referring to lymphatic metastasis, penetration depth, and nearby organ invasion), which was confirmed by clinical staging, gastroscopy, B ultrasonography, and CT; (3) All the patients were treated with no other chemotherapeutics; (4) The liver and kidney functions, lung function, and ECG were all normal, and all the patients had no contraindications to chemotherapy [3]; (5) All the patients were cooperative in treatment, and had no history of drug allergy.

Exclusion criteria: (1) Patients complicated by tumors of other tissues or organs; (2) Patients who were uncooperative in the treatment, and those with incomplete follow-up data; (3) Patients complicated by severe nervous or mental disorders.

Table 3. Occurrence of adverse reactions in the two groups (n, %)

Adverse reaction	Observation group					Control group					t	P
	0	I	II	III	IV	0	I	II	III	IV		
Leucopenia	13 (21.7)	25 (41.7)	20 (33.3)	2 (3.3)	0	7 (11.7)	27 (45.0)	22 (36.6)	4 (6.7)	0	2.73	0.19
Thrombocytopenia	20 (33.3)	19 (31.7)	13 (21.7)	8 (13.3)	0	18 (30.0)	20 (33.3)	14 (23.3)	7 (11.7)	1 (1.7)	4.41	0.21
Neutropenia	16 (26.7)	18 (30.0)	18 (30.0)	7 (11.6)	1 (1.7)	10 (16.7)	20 (33.3)	20 (33.3)	9 (15.0)	1 (1.7)	3.84	0.08
Anemia	16 (26.7)	21 (35.0)	18 (30.0)	4 (6.6)	1 (1.7)	15 (25.0)	19 (31.7)	20 (33.3)	5 (8.3)	1 (1.7)	5.25	0.17
Appetite decrease	17 (28.3)	22 (36.7)	19 (31.7)	2 (3.3)	0	14 (23.4)	23 (38.3)	20 (33.3)	3 (5.0)	0	1.47	0.32
Diarrhea	19 (31.7)	18 (30.0)	19 (31.7)	4 (6.6)	0	17 (28.3)	17 (28.3)	21 (35.0)	4 (6.7)	1 (1.7)	1.28	0.06
Catarrh	15 (25.0)	26 (43.3)	16 (26.7)	3 (5.0)	0	16 (26.7)	22 (36.7)	18 (30.0)	4 (6.6)	0	2.04	0.23
Nausea and vomiting	19 (31.7)	19 (31.7)	18 (30.0)	4 (6.6)	0	17 (28.3)	18 (30.0)	20 (33.3)	5 (8.3)	0	8.27	0.13
Abnormal liver function	22 (36.7)	25 (41.6)	13 (21.7)	0 (0.0)	0	18 (30.0)	26 (43.3)	15 (25.0)	1 (1.7)	0	1.08	0.54

The lesions were at gastric body, fundus, pylorus, cardia, in 30, 26, 44 and 20 cases, respectively. The cancer degrees were staged as stage III (n=72) and stage IV (n=48) by TNM staging method. Pathological types: Poorly differentiated adenocarcinoma (n=63), moderately differentiated adenocarcinoma (n=40), and signet ring cell carcinoma (n=17). Distant metastasis: metastasis to celiac lymph nodes (n=41), to left supraclavicular lymph nodes (n=42), to liver (n=17), and to lung (n=20). The selected subjects were randomly divided into the observation group and the control group according to the admission date, with 60 patients in each group. The two groups had insignificantly differences in sites, TNM stages, pathological types, metastatic sites, etc. (P>0.05). See **Table 1**. All the selected subjects signed informed consent, and the study was approved by the Medical Ethics Committee of Central Hospital of Linyi City.

Treatment methods

The control group was given Tiji'ao Capsules (Qilu Pharmaceutical Co., Ltd.) 40 mg/m^2 p.o B.i.d (once after breakfast and the other after supper) for 2 continuous weeks; and oxaliplatin (Jiangsu Hengrui Medicine Co., Ltd.) 130 mg/m^2 i.v gtt within 2 h for at least 2 cycles (3 weeks a cycle). In addition to those of the control group, the observation group was given recombinant human endostatin injection (Shandong Simcere Maidejin Biological Pharmaceutical Co., Ltd.) 15 mg i.v gtt for 2 weeks, which was repeated after a 1-week interval, for at least 2 cycles (3 weeks a cycle). Before chemotherapy, the two groups were given routine hydration, diuresis, oral dexamethasone, antiemesis, fluid infusion, and other supportive and symptomatic treatments. In the chemotherapy period, raw, cold, and hard dietary stimulation were avoided, routine blood test and hepatic and renal functions were re-tested regularly, and drugs used for increasing in white cells were given when necessary.

Detection of tumor markers carcinoembryonic antigen (CEA) and S100

Before and after chemotherapy of both groups, 10 mL of peripheral venous blood was drawn and centrifuged at 1,500 r/min for 10 min, and the supernatant was taken and stored at -80C for test. The expression of tumor markers CEA and S1000 were detected by enzyme linked immunosorbent assay on a detection kit bought from Beijing Zhongshan Jinqiao Biotechnology Co., Ltd. strictly complying with the procedures described in the package insert.

Clinical efficacy judgment and follow-up

Short-term efficacy was judged according to WHO solid tumor efficacy criteria as follows [5]. Complete remission (CR): All the lesions disappeared and the minor axis of the any pathological lymph nodes (regardless of targeted lesion) should be <10 mm. Partial remission (PR): With the sum of critical radii as reference, the sum of all targeted lesion radii was decreased by at least 30%. Stable disease: With the minimum of the sum of the studied targeted lesion radii as reference, patients failed to meet the remission criteria and progressive criteria. Progressive disease: The number or size of the lesions was obviously increased compared with before. Overall response rate=(CR + PR)/total case number *100%. Long-term efficacy was analyzed based on median survival time. The follow-up time started from the end of chemotherapy to death, loss to follow up, or end of follow up, to January 2016.

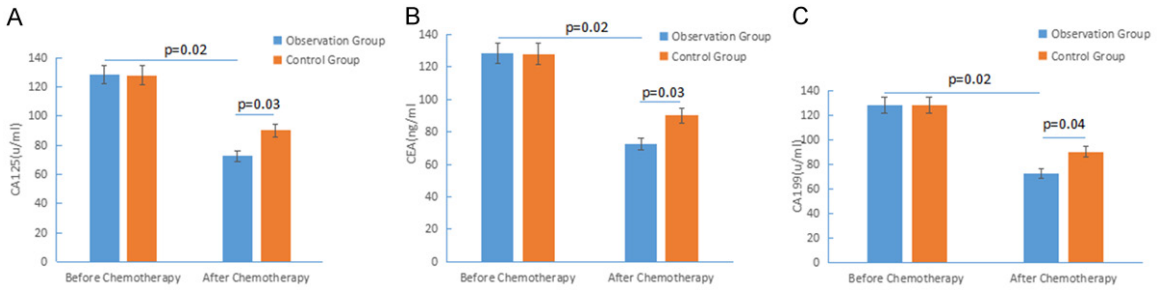

Figure 1. Comparisons of CEA, CA125 and CA199 before and after chemotherapy between the two groups. A: Comparison of CA125 before and after chemotherapy between the two groups; B: Comparison of CEA before and after chemotherapy between the two groups; C: Comparison of CA199 before and after chemotherapy between the two groups. CEA, carcinoembryonic antigen; CA125, carbohydrate antigen 125; CA199, carbohydrate antigen 199.

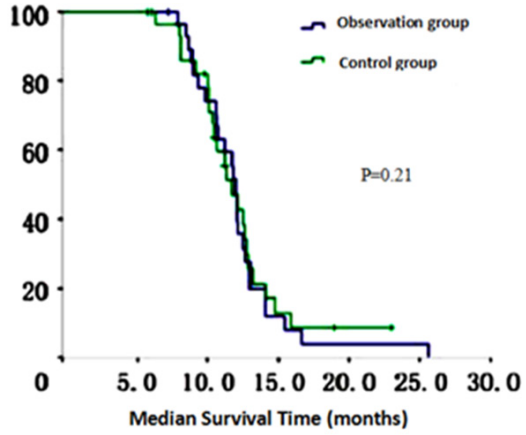

Figure 2. Comparison of survival curve between the two groups.

Adverse reactions

Adverse reactions were classified complying with the National Cancer Institute - Common Toxicity Criteria as grade 0-IV [9]. Grade 0: There were no or just mild symptoms, requiring no treatment; grade I: the symptoms were indicative of minimum, local, or non-invasive treatment, and age-related instrumental activities of daily living were limited; grade II: the symptoms were not life-threatening, but prolonged the length of stay and resulted in disability, and self-care activities of daily living were limited; grade III: the symptoms were life-threatening and required emergent treatment; and grade IV: death.

Statistical methods

The test data were treated by SPSS13.0 statistical software. Numeration data were expressed in %, and inter-group comparison was tested by χ^2 test; and measurement data are expressed as ($\bar{x}$ ± sd), and inter-group comparison was tested by t test. Survival time was analyzed based on Kaplan-Meier survival curve. The difference in survival between the two groups was analyzed by Log-rank test. When $P<0.05$, the difference was statistically significant.

Results

Comparison of clinical efficacy between the two groups

The observation group had a significantly higher overall response rate than the control group (53/60, 88.3% vs. 41/60, 68.3%; $\chi^2=8.15$, $P=0.03$). The details are shown in **Table 2**.

Comparison of adverse reactions between the two groups

Adverse reactions of the two groups were mainly digestive tract reactions and bone marrow depression, including leucopenia, nausea, vomiting, and decreased food appetite. The incidence of leucopenia of the observation group was 78.3% (47/60), among which, that of grade III-IV was only 3.3% (2/60); while the incidence of leucopenia of the control group was 88.3% (53/60), among which, that of grade III-IV was 6.7% (4/60); and the difference was statistically insignificant ($P=0.19$). Other differences in adverse reaction incidence were all statistically insignificant ($P=0.24$). The details are shown in **Table 3**.

Comparisons of tumor markers before and after chemotherapy between the two groups

After 4 cycles of chemotherapy, both the observation group and control group had significantly decreased CEA, CA125 and CA199 levels com-

pared with those before chemotherapy (t= 10.03, P=0.02; t=11.38, P=0.02; t=9.85, P= 0.02); and after chemotherapy, the two groups had significantly different tumor markers (CEA, CA125, CA199) with a statistical significance (t=7.06, P=0.03; t=7.31, P=0.03; t=6.95, P= 0.04). The details are shown in **Figure 1**.

Survival analysis

All the subjects of this study were followed up for more than 2 years. The follow-up was ended on January 1, 2016. Among the 120 patients, 113 completed the follow-up, and 3 of the observation group and 4 of the control group were lost, with a loss rate of 5.8%. The data on the lost population was treated as truncated. In total, 8 patients died of gastric cancer recurrence. The median survival times of the observation group and control group were (15.03 ±2.37) months and (14.41±2.74) months, respectively, and the difference was statistically insignificant (t=6.46, P=0.21). The details are shown in **Figure 2**.

Discussion

Gastric cancer is one of the common malignant tumors of digestive system, with an increasing incidence year by year following the aging of the population in our country. But by the time of discovery, most cases are complicated by penetration of surrounding tissues and organs, and have missed the best opportunity of surgery. As revealed by domestic and abroad clinical trials in recent years, systemic chemotherapy in patients with late gastric cancer can effectively relieve the clinical symptoms, improve the quality of life, prolong survival time, and inhibit tumor penetration [10, 11]. Systemic chemotherapy has become the first choice to treat late gastric cancer.

At present, there are many chemotherapeutics for late gastric cancer, such as fluorouracil, cisplatin, anthracyclines, and mitomycin, but the clinical efficacy of these chemotherapeutics is uncertain, with a low availability. In recent years, following the development of new chemotherapeutics and renovation of chemotherapy regimens, the chemotherapy efficacy is greatly elevated. Oxaliplatin is a third-generation platinum chemotherapeutic. It can combine with DNA to form a compound to hinder DNA transcription, with stronger effects, rapider action speed, and firmer compound formed than cisplatin. Therefore, it has greater antineoplastic effects and smaller toxic and side effects [12]. As confirmed by numerous clinical trials, oxaliplatin in chemotherapy of gastric cancer has excellent clinical efficacy and only a few adverse events [13].

Among chemotherapeutics for gastric cancer, 5-fluorouracil is one of the most frequently used chemotherapeutics, but its short half life, short action time, and many adverse reactions limit the clinical application to a great extent. Tiji'ao is an oral chemotherapeutic of the second-generation 5-fluorouracil, is a compound preparation made of tegafur, gimeracil, and oltirizine potassium in a certain proportion, and has become the first-line anti-tumor drug for digestive tumors in Japan. There are clinical drug trials suggesting Tiji'ao in treatment of advanced gastric carcinoma has a clinical response rate up to 45% and survival time of about 8 months, with only a few toxic and side effects [14]. It is confirmed by many clinical trial institutions that Tiji'ao in treatment of advanced gastric carcinoma has excellent safety, availability, and tolerance [15]. In this study, oxaliplatin combined with Tiji'ao were used for chemotherapy in patients with late gastric cancer, and the results suggested the response rate and median survival time were 56.6% and 14.4 months, respectively, which were basically accordant with the study results of other investigators [16]. Meanwhile, the co-administration of the two drugs could reduce the toxic and side effects, such as digestive adverse reaction and osteomyelitis.

Recombinant human endostatin is a strong angiogenesis inhibitor initially discovered by our country, and has longer half-life and higher activity and stability than natural endostatin. By interfering and blocking the vascular endothelial factor pathway, it can inhibit endothelial cell migration and the bioactivity of proteolytic enzyme, and consequently inhibit angiogenesis. It can limit the invasion and metastasis of tumor cells by inhibiting the angiogenesis of tumor tissues, it can block the nutritional supply to tumors, promote the apoptosis of tumors, and inhibit the metastasis of cells [17]. These effects can help chemotherapy regimens to treat advanced tumors, and then prolong the survival time and improve the prognosis. Some scholars used Recombinant human endostatin

combined with chemotherapeutics to treat non-small-cell lung carcinoma, with excellent clinical efficacy [16]. We observed the clinical efficacy of recombinant human endostatin combined with chemotherapeutics in treatment of late gastric cancer, and discovered that the response rate was up to 80.0% and the median survival time was 15.03 months, which were significantly higher than single chemotherapy group ($P<0.05$). Tumor markers are important indexes reflecting the presence and malignancy degree of tumors, and is an important reference index for chemotherapy efficacy. The results of our study suggested Recombinant human endostatin could effectively decrease the serum levels of each tumor marker (CEA, CA125 and CA199) in patients with late gastric cancer, and further confirmed the effects of recombinant human endostatin of inhibiting the growth and development of tumors.

When adding new drugs to the routine chemotherapy, the following two issues should be considered: the toxicity of the drug itself and aggravating the adverse reactions of chemotherapy or not. It is confirmed by generous drug clinical trials that the main adverse reactions of recombinant human endostatin were in the cardiovascular system, such as myocardial ischemia, but they are slight, most can be recovered to normal after symptomatic treatments, and result in no death [18-20]. Our study results discovered treatment with recombinant human endostatin combined with chemotherapeutics had basically accordant kind, frequency, and severity degree of adverse events with those of singe use, and suggested it had good safety. We know recombinant human endostatin is a vasodepressor, and may cause bleeding easily, while gastric cancer is a malignant tumor of a hollow organ; thus, whether using recombinant human endostatin will increase the chance of gastric bleeding or not needs large-sample clinical investigations.

To sum up, oxaliplatin combined with Tiji'ao and recombinant human endostatin injection in treatment of late gastric cancer has excellent clinical efficacy, can decrease tumor marker levels, without increasing the incidence of adverse events, and consequently is worthy of clinical application.

Disclosure of conflict of interest

None.

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References

[1] Shao H, Sun W, Li Y and Wang Q. A comparative study on the efficacy of oxaliplatin and FOLFOX4 in the treatment of advanced gastric cancer. Journal of Modern Oncology 2013; 21: 1273-1276.

[2] Fan CZ, Dai H, Huang DF, Yu D, Ke Y, Zhou WW, Fan SS, Yan D and Liu YM. Clinical observation of different fluorouracil preparations combined with oxaliplatin in the treatment of advanced gastric cancer. Chinese Journal of Cancer Prevention and Treatment 2013; 20: 539-543.

[3] Qiu GQ, Xu LZ, Lin ZC and Chen YQ. Clinical observation of Tiji'ao treating advanced stage gastric cancer in the elderly. Chinese Journal of Clinical Oncology and Rehabilitation 2011; 61-63.

[4] Peng F, Xu Z, Wang J, Chen Y, Li Q, Zuo Y, Chen J, Hu X, Zhou Q, Wang Y, Ma H, Bao Y and Chen M. Recombinant human endostatin normalizes tumor vasculature and enhances radiation response in xenografted human nasopharyngeal carcinoma models. PLoS One 2012; 7: e34646.

[5] Zhang LP, Liao XY, Xu YM, Yan LJ, Yan GF, Wang XX, Duan YZ and Sun JG. Efficacy and safety of endostar(R) combined with chemotherapy in patients with advanced soft tissue sarcomas. Asian Pac J Cancer Prev 2013; 14: 4255-4259.

[6] Cui C, Mao L, Chi Z, Si L, Sheng X, Kong Y, Li S, Lian B, Gu K, Tao M, Song X, Lin T, Ren X, Qin S and Guo J. A phase II, randomized, double-blind, placebo-controlled multicenter trial of Endostar in patients with metastatic melanoma. Mol Ther 2013; 21: 1456-1463.

[7] Sirohi B, Barreto SG, Singh A, Batra S, Mittra A, Rastogia S, Ramadwar M, Shetty N, Goel M, Shrikhande SV. Epirubicin, oxaliplatin, and capectabine is just as "MAGIC"al as epirubicin, cisplatin, and fluorouracil perioperative chemotherapy for resectable locally advanced gastro-oesophageal cancer. J Cancer Res Ther 2014; 10: 866-870.

[8] Van Wijngaarden J, de Rooij K, van Beek E, Bernsen H, Que I, van Hinsbergh VW and Lowik C. Identification of differentially expressed genes in a renal cell carcinoma tumor model after endostatin-treatment. Lab Invest 2004; 84: 1472-1483.

[9] Ohtsu A, Shah MA, Van Cutsem E, Rha SY, Sawaki A, Park SR, Lim HY, Yamada Y, Wu J,

Langer B, Starnawski M and Kang YK. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. J Clin Oncol 2011; 29: 3968-3976.

[10] Chen JH, Shen WX, Xia JX, Xu RL, Zhu MQ and Xu M. A comparative study of the treatment of advanced gastric cancer in the first-line treatment of oxaliplatin and DCF. Chinese Journal of Cancer Prevention and Treatment 2015; 22: 134-137.

[11] Fan WF, Wang J, Meng LJ, Liu FY, Pu XL and Yang M. A clinical study on the treatment of advanced gastric cancer in elderly patients with the combination of Tiji'ao and oxaliplatin compared with combination of Tiji'ao and cisplatin. Chinese Clinical Oncology 2013; 18: 50-53.

[12] Yang L, Song Y, Qin Q, Duan HJ, Dong Q, Zhong XM, Zhou AP, Huang J and Wang JW. Efficacy and safety of tiji'ao and oxaliplatin for advanced gastric cancer. Canc Res Prev Treat 2013; 40: 688-692.

[13] Yin BB, Li Y, Liang J, Liu HR, Liu XL and Xiao JJ. Clinical observation of 56 cases of advanced gastric cancer treated with Tiji'ao and oxaliplatin. Modern Journal of Integrated Traditional Chinese and Western Medicine 2013; 22: 1971-1972.

[14] Du CX, Chen SS, Liu XY and Zhang HG. Clinical observation of recombinant human vascular endostatin combined with docetaxel, platinum and fluorouracil in the treatment of advanced gastric cancer. J Clin Oncol 2014; 925-928.

[15] Jin JY, Guo Q, Wang ZR, Xie JJ, Jin D. Clinical efficacy of recombinant human endostatin injection combined with chemotherapy in the treatment of; patients with advanced gastric cancer and its influence on the quality of life. Chinese Journal of Primary Medicine and Pharmacy 2016; 23: 2881-2885.

[16] Li DN, Wang YB, Wang GJ, Ma YM and Jin Y. Effects of Endu and cisplatin on growth and angiogenesis of gastric cancer. Chinese Journal of Gerontology 2013; 33: 3101-3104.

[17] Pan ZH, Wang X, Su A, Lv X, Wu GY and Liu XD. Clinical observation of paclitaxel and capecitabine combined with ndu for the treatment of advanced gastric cancer peritoneal metastasis. Chinese Journal of Cancer Prevention and Treatment 2013; 20: 301-303.

[18] Zhang XL, Shi X, Wu SJ, XU JD and Zhou ZP. Effects of recombinant human vascular endostatin combined with cisplatin on the expression of VEGF and mmp-9 in S180 sarcoma. Journal of Clinical Oncology 2010; 15: 395-398.

[19] Jia CH, Wang WY, Ren Y, Zhang H, Lan L, Liu BW and Yu J. Effects of recombinant human vasopressin injection in the treatment of advanced gastric cancer and the effects of endothelial growth factor, S100A4 and cancer embryo antigen related cell adhesion molecules in serum. Chinese Journal of Gerontology 2014; 34: 208-209.

[20] Dkhissi F, Lu H, Soria C, Opolon P, Griscelli F, Liu H, Khattar P, Mishal Z, Perricaudet M and Li H. Endostatin exhibits a direct antitumor effect in addition to its antiangiogenic activity in colon cancer cells. Hum Gene Ther 2003; 14: 997-1008.