Clinical Observation of Recombinant Human Endostatin Combined with XELOX Regimen in the Treatment of Advanced Gastric Cancer

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Abstract: Objective: It is to observe the efficacy and safety of domestic recombinant human endostatin (endo) combined with XELOX regimen (oxaliplatin + capecitabine) in the treatment of advanced gastric cancer. Methods: 104 confirmed gastric cancer patients were randomly divided into two groups: a control group of 47 patients, using XELOX regimen: oxaliplatin 130 mg / m2, d1; capecitabine 1 000 mg / m2, d1 ～ 14,4 One week is a course of treatment; 57 cases in the treatment group have the same chemotherapy regimen, dosage method, and treatment course as the control group, and daily recombinant human endostatin 7.5 mg / m2, intravenous drip from d1 to 14 d. After 2 cycles of treatment, the efficacy evaluation and the evaluation of side effects were conducted. Results: The effective rate was 59.7% in the treatment group and 30.4% in the control group. The difference between the two groups was statistically significant ($\chi 2 = 4.6471$, $P < 0.05$). The time to disease progression (TTP) and median survival (MST) were 7.1 months and 11.8 months in the treatment group; 5.6 months and 9.6 months in the control group, and the difference was not statistically significant ($P > 0.05$); Compared with the control group, there was no significant increase ($P > 0.05$). Conclusion: Recombinant human endostatin combined with XELOX regimen is effective and safe in the treatment of advanced gastric cancer, and it is worthy of further study.

In China, the incidence of gastric cancer ranks second in malignant tumors, and the mortality rate ranks third [1]. Due to screening methods and patient consciousness, most patients with gastric cancer are diagnosed as having advanced or metastatic disease. For patients with advanced gastric cancer, systemic chemotherapy is the preferred treatment. At present, the Chinese CSCO guidelines recommend oxaliplatin combined with fluorouracil as the first-line chemotherapy. The current NCCN guidelines recommend platinum combined with fluorouracil as the first-line chemotherapy. For patients with good physical conditions, the DCF or ECF three-drug regimen is recommended. [2].

Foreign studies have added docetaxel on the basis of cisplatin combined with fluorouracil regimen to extend the median overall survival time (OS) of patients with advanced gastric cancer to 9.2 months [3]. For patients with HER-2 receptor-amplified tumors, the addition of trastuzumab on the basis of cisplatin combined with fluorouracil makes the median OS of advanced gastric cancer patients reach 13.8 months for the first time [4]. However, among patients with gastric cancer, HER-2 gene amplification is only 10. 3% ~ 14. 7% [5], which means that more than 80% of patients can not use trastuzumab. It is necessary to find a targeted drug that can be widely used and has good safety. Recombinant human endostatin (endo) is a multi-target vascular endothelial inhibitor. It inhibits neovascularization by inhibiting the migration of vascular endothelial cells and inducing their apoptosis. It has been shown and released in lung cancer and various tumors. Synergy of chemotherapy [6-9]. In this study, 103 cases of advanced gastric cancer were treated with recombinant human endostatin combined with XELOX regimen, and achieved good results. The reports are as follows.

1 Data and Methods

1.1 General Information

From June 2013 to June 2018, 103 patients with advanced gastric cancer who could not be surgically treated were admitted to the Oncology Department of Handan Central Hospital. All of them were diagnosed by histopathology or cytology. Among the 104 patients, there were 63 males and 41 females; aged 45-75 years, with a median age of 56 years. The patients were randomly divided into two groups: 47 cases in the control group and 57 cases in the treatment group. The median age of the two groups was 54 years and 57 years old; the ratio of men to women was 15: 9 and 18:11; the clinical pathological staging (UICC International Anti-Cancer Alliance Seventh Edition TNM staging criteria) stage Ⅲ and stage Ⅳ were 22 cases and 25 cases, respectively. And 30 cases, 27 cases. Histopathological classification: 23 cases of poorly differentiated adenocarcinoma in the control group, 10 cases of moderately differentiated adenocarcinoma, 7 cases of mucinous adenocarcinoma, 4 cases of tubular adenocarcinoma, 2 cases of signet ring cell carcinoma; 28 cases of poorly differentiated adenocarcinoma in the treatment group, medium Differentiation

There were 13 cases of adenocarcinoma, 8 cases of mucinous adenocarcinoma, 6 cases of tubular adenocarcinoma, and 1 case of signet ring cell carcinoma. 104 patients have not received anti-cancer treatment in the past 1 month, and KPS scores were ≥60 points. Blood routine, electrocardiogram, liver and kidney functions are within the normal range, and the expected survival time is greater than 4 months, and all have objective lesions that can judge the efficacy. The general data of the two groups of patients were not statistically different (P> 0.05) and were comparable.

1.2 The Treatment

The control group used the XELOX regimen: oxaliplatin 130 mg / m2 d1, continuous intravenous infusion for 3 h; capecitabine 1 000 mg / m2, taken twice daily d1-14 30 minutes after breakfast and dinner, 3 weeks for 1 Cycle; The dosage of chemotherapy in the treatment group is the same as that in the control group, and the recombinant human endostatin 7.5 mg / m2 is given daily from 1 to 14 days, and the intravenous infusion is slow within 2 hours. The therapeutic effect was evaluated after 2 cycles of treatment. Two groups of patients were given symptomatic and supportive treatment at the same time during chemotherapy, and timely treatment of chemotherapy-related toxic and side effects.

1.3 Evaluation Criteria

Objectively evaluate the efficacy according to the RECIST standard [10]: complete remission (CR), partial remission (PR), stability (SD), progression (PD), effective rate (RR) calculated by CR + PR, and CR + PR + SD Calculate the disease control rate (DCR), and disease progression time (TTP), median survival time (MST); drug toxicity is divided into 0 to 4 grades according to the NCICTC 3.0 standard [11].

1.4 The Statistical Analysis

SPSS 13.0 statistical software was used for data analysis. The data between the two groups were compared by $\chi 2$ test. The survival rate was calculated by Kaplan-Meier method.

2. Result:

2.1 The Curative Effect and Survival Time Curative Effect between the Two Groups Are Shown In Table 1.

Table 1 Comparison of efficacy and survival time of patients in control group and treatment group

Group	n	CR	PR	NC	PD	RR/%	DCR/%	TTP/ MST/

Control group	47	2	13	18	14	31.4	69.6
5.6	9.6						
Therapy group	57	8	27	18	4	59.7[a]	92.9[b]
7.1[c]	11.8[d]						

Note: Compared with the control group, a$\chi 2$ = 4.6471, b$\chi 2$ = 4.7138, P <0.05; c$\chi 2$ = 1.563, d$\chi 2$ = 1.162, P> 0.05

2.2 Safety and Adverse Reactions between the Two Groups

There were no treatment-related deaths between the two groups. The adverse reactions in the two groups were mainly bone marrow suppression, gastrointestinal reactions, liver function impairment and hand-foot syndrome. See Table 2 for details.

Table 2 Comparison of adverse reactions between the control group and the treatment group (n)

Side effects	Control group						Therapy group					
	0	I	II	III	IV	(%)	0	I	II	III	IV	(%)
White blood cell decline	26	10	4	4	4	(43.5)	32	28	6	2	2	(42.9)
Decreased hemoglobin	32	8	6	0	0	(30.4)	40	10	4	2	0	(28.6)
Platelet decline	31	14	12	4	0	(34.8)	36	16	4	0	0	(35.7)
Feel sick and vomit	16	20	6	4	0	(65.2)	20	24	8	4	0	(64.3)
Diarrhea	28	6	10	5	0	(39.1)	34	16	6	0	0	(39.3)
Peripheral neurotoxicity	32	8	4	5	0	(30.4)	40	10	6	0	0	(28.6)
Hand-foot syndrome	28	6	5	0	0	(17.4)	50	6	0	0	0	(10.7)
Abnormal liver function	34	4	6	5	0	(26.1)	42	8	4	2	0	(25.0)
Abnormal kidney function	42	4	0	0	0	(8.7)	52	4	0	0	0	(7.1)
Joint muscle pain	20	4	5	0	0	(13.0)	48	6	2	0	0	(14.3)
Oral mucositis	34	6	0	0	0	(26.1)	44	10	2	0	0	(21.4)

Note: There is no statistically significant difference in the side effects between the two groups, P> 0.05

3. Discussion

Locally advanced inability to surgically remove or metastatic gastric cancer has a poor prognosis, and palliative systemic chemotherapy is the treatment of choice. Phase III studies such as V325 and Real 2, median OS 9 to 11 months for combined chemotherapy]. However, these programs have serious adverse reactions. For example, the V325 study used the TCF program. 82% of patients had grade 3 to 4 hematological toxicity, and 50% of them

The patient could not tolerate the cessation of chemotherapy due to toxic and side effects, so its clinical application is limited. This study adjusted chemotherapy to XELOX regimen on the basis of

preserving the dose strength of the drug, and achieved good results. Professor Folkman first proposed that malignant tumors can induce neovascularization during growth, and anti-neovascular treatment can inhibit tumor growth. Especially vascular tumors [12]. Bevacizumab is the first anti-angiogenic drug to confirm this theory and be approved for marketing. It has been widely used clinically in the treatment of colorectal cancer, lung cancer and other tumors [13]. Gastric cancer is also a vascular-rich tumor with a rich tumor vascular network. In the AVAGAST study, the RR of cisplatin, capecitabine and bevacizumab was significantly higher than that of chemotherapy alone (46. 0% vs. 37.4%, P = 0. 0315), the median PFS also reached a significant extension (6.7 months vs. 5.3 months, P = 0. 0037) [14].

Recombinant human endostatin is a strong angiogenesis inhibitor developed in China. It can specifically act on tumor neovascularization and inhibit endothelial cell migration, and at the same time induce tumor cell apoptosis, thereby exerting an anti-angiogenic effect, and by regulating The expression of vascular endothelial growth factor on the cell surface regulates the activity of proteolytic enzymes, which indirectly leads to tumor cell retreat [15]. Endo combined with chemotherapeutic drugs for the treatment of non-small cell lung cancer has a clear effect. Several studies have shown that the effect of endo on advanced gastric cancer has also achieved good results [16-17].

In this study, the treatment group adopted Endolink XELOX regimen for the treatment of advanced gastric cancer with an effective rate of 59.7%, and the control group using XELOX regimen alone had an effective rate of 30.4%. The difference between the two groups was statistically significant ($\chi 2 = 4.6471$, $P < 0.05$); The difference in clinical benefit rate between the two groups was statistically significant ($\chi 2 = 4.7138$, $P < 0.05$); TTP and MST (7.1 months, 11.8 months) in the treatment group were more than those in the control group, both groups (5.6 months and 9.6 months) were prolonged; but the difference was not statistically significant (all $P > 0.05$). It is suggested that Endo combined with XELOX regimen can achieve good curative effect on gastric cancer, and it has synergistic antitumor effect with oxaliplatin and capecitabine chemotherapy. XELOX. The adverse reactions of the regimen mainly include bone marrow suppression, gastrointestinal reactions, liver function damage and surgical syndrome, nerve-related toxicity, mostly Ⅰ ～ Ⅱ degree, symptomatic treatment can be tolerated, no serious life-threatening adverse events were seen in all cases The event occurred. Phase II to III clinical studies have shown that the recombinant human endostatin has fewer toxic and side effects. It often shows that myocardial ischemia occurs within 2 to 9 days after treatment, most of them are first degree or second degree, and most are Reversible, not endangering the patient's life. Therefore, Endo combined with chemotherapy did not increase the incidence of chemotherapy-related toxicity.

The data in this group suggest that the incidence, frequency and severity of endotoxin combined with XELOX regimen are basically the same as those reported in the literature when using chemotherapy alone. There was no significant difference in the incidence of side effects in the treatment group compared with the control group ($P > 0.05$).

Therefore, the combined chemotherapy of Endo and XELOX has good efficacy, light toxicity and safety, which is worth conducting a large-scale randomized double-blind clinical study to further confirm the efficacy of Endo on advanced gastric cancer.

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