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Endostar combined with chemotherapy on the advanced digestive tract tumour.

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Abstract

Objective: To study the efficacy and side-effect of rh-endostatin injection (YH-16, Endostar), combined with the chemotherapy on the advanced digestive tract tumour.
Methods: 56 patients were divided into two groups, Endostar combined with chemotherapy was administrated to the treatment group (28 cases), and the control group (28 cases) only received chemotherapy.
Results: 56 patients completed two or six cycles. In the treatment group, there were 9 cases achieved PR, 15 cases SD, and 4 case PD; and in the control group, there were 7 cases achieved PR, 14 cases SD, and 7 cases PD. Between the two groups, the Objective Response Rate (PR) were 32.1% (9/28) and 25.0% (7/28), and Disease Control Rate (DCR) were 85.7% (24/28) and 75.0% (21/28) respectively. The Quality Of Life (QOL) between two groups improved on 23 cases (82.1%) and 14 cases (50.0%). The toxicities between two groups showed no significant difference.
Conclusion: The QOL of patients may be improved significantly by endostar combined with chemotherapy and the efficacy was increased, but side effects were not improved.

Keywords: Rh-endostatin/Endostar, Chemotherapy, Digestive tract tumour.

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Introduction

Gastrointestinal tumour is the most common cancer in the world, the morbidity and mortality of which accounts for 30% of all tumours. In China, the ratio even make up to more than 50% [1]. When seeing a doctor, it's always in an advanced stage for patients. In this way, it's better to take chemotherapy as major treatment for those tumours that cannot be excised easily. As the chemotherapy drugs arose, such as new generation platinum, Taxane, Gemcitabine and Irinotecan, the short-term effects increased slightly. However, plateau of chemotherapy effect are coming, so how to improve its efficiency?

In 1971, a concept that generation of cancer mainly depended on vascularization was put forward. Then, anti-angiogenesis has become an important research field in cancer treatment. In these years, as the angiogenesis inhibitor research deepens, anti-angiogenesis treatment opened up a new way for cancer. Bevacizumab, an angiogenesis inhibitor widely applied in clinic, was approved by FDA in 2004 in advanced colon and rectum cancer treatment. It has been proved that combined chemotherapy showed better efficacy for patients but with higher price.

However, Endostatin (ES) is the endogenous angiogenesis inhibitor with the most broad-spectrum. It selectively acted on micro vascular endothelial cell and played anti-proliferation, anti-migration, as well as apoptosis-promoting roles. A new type recombination human endostatin (Endostar) was produced by Xiansheng Maidejin Biological Pharmaceutical Co., Ltd using colon *bacillius* as vector. Phase I, II and III clinical trials were conducted at August 2001, March 2002, and April 2003, confirming its role in treating NSCLC. It has been proposed as first-line regimen of clinical practice guide in NSCLC treatment [2].

In September 2006, a pre-clinical research by Zhou and others found that Endostar combined with Fluorouracil showed synergistic effect on inhibiting colon cancer hepatic metastasis [3]. Thereafter, Endostar was widely applied in gastrointestinal tumours. In 2008, Shu reported that Endostar combined with chemotherapy could be applied in oesophagus, gastric and colon cancers with acceptable side effects [4].

Further comparative studies were needed to observe its curative effect. 5 randomized controlled trails were studied by Pan and others [5]. 220 patients with advanced colorectal cancer were treated with Endostar combined with chemotherapy or simple chemotherapy. Meta-analysis showed

that Endostar combined with chemotherapy proved to be better in CR, PR, and CBR.

Our hospital has employed angiogenesis inhibitor-recombination human vascular endothelium statin (Endostar) combined with chemotherapy in advanced stage malignant gastrointestinal tumours treatment. The treatment showed favourable effect.

Materials and Methods

Cases datum

From August 2006 to August 2014, 56 advanced gastrointestinal carcinoma patients including 32 males and 24 females, aged between 41 and 75, with median age 56 were included. The conditions were confirmed at stages III and IV by pathology or cytologic examination (except 3 pancreatic cancer patients whose CEA and CA199 increased significantly). ECOG score was no more than 2, and objective focus is measurable [6]. Blood routine, function of liver, kidney and heart are normal. Their expected survival time is more than 3 month.

Treatment group and control group were randomly divided, with 28 patients in each group. There are 15 males and 13 females in treatment group. 7 patients suffered from oesophagus cancer, and 10 patients with gastric cancer. 10 patients of the rest in treatment group suffered from colon cancer, and 1 with pancreatic cancer. The control group contained 17 males and 11 females, with 5 oesophagus cancer and 12 gastric cancers. Besides, 9 patients in the rest of control group were colon cancer, and 2 with pancreatic cancer. There were no significantly difference in age, height, weight, ECOG, clinical stages, pathological pattern and viscera transfer [7].

Treatment

Treatment group: Endostar combined with chemotherapeutics.

Endostar usage: 15 mg Endostar dissolved in 500 ml normal saline at one time, and then slowly dripped for 4 h. Administrated at Day 1 and 14, then repeated after 21 days interval.

Chemotherapy regimens: 12 cases of oxaliplatin, cis-platinum, calcium folinate and fluorouracil combined with chrono-chemotherapy were employed. Similarly, combination with taxol makes up for 4 cases, irinotecan for 1 case and gemcitabine for 1 case. The control group used similar project in treatment with 21 days treatment cycle. Blood routine, blood biochemistry and tumour markers were reviewed every week during or after treatment.

Efficacy and toxicity evaluation criterion

Based on RECIST criterion, the objective efficacy was divided into Complete Remission (CR), Partial Remission (PR), Stable (SD) and Progressive Disease (PD). Besides, Response Rate (RR) referred to CR plus PR, and Disease Control Rate (DCR) meaned CR+PR+SD. Additionally, the Quality Of Living (QOL) was also observed. According to Karnofsky score, when KPS increased to more than 10 after treatment, the life quality of patients improved better.

In contrast, when KPS varied no more than 10, the life quality remained stable, while the life quality declined when KPS decreased more than 10. The toxicity was evaluated according to anti-cancer drug toxic and adverse effect grading standard by WHO in 1981.

Statistical method

Data analysis was conducted using SPSS 12.0 software, and x2 test was employed.

Results

The patients were followed up to August 2014 and went through 2 or more treatment cycle. Specifically, there were 90 cycles in treatment group with 3.2 average cycles, while 102 cycles in control group with 3.6 average cycles. The evaluation of effect and safety was available.

Objective effect

There were 9 PR cases, 15 SD cases and 4 PD cases in treatment group. Besides, there were 7 PR cases, 14 SD cases and 7 SD cases in control group. The PR is 32.1% (9/28) and 25.0% (7/28), respectively. For DCR in the two groups, the value is 85.7% (24/28) and 75.0% (21/28), respectively. Though the curative effect was higher in treatment group, P>0.05 showed no significantly difference as shown in Table 1.

Table 1. *Effect of patients in two groups (n, (%)).*

Group	RR	DCR	x^2	P
Treatment	5 (27.8%)	17 (94.4%)	0.00	1.00
Control	5 (21.7%)	18 (78.2%)		

Living quality evaluation

In treatment group, 23 patients (82.1%) showed enhanced life quality, and 3 patients (10.7%) showed stable QOL. Only 2 patients had decreased life quality (7.1%) in treatment group. In contrast, the conditions in control group was 14 (50.0%), 6 (21.4%) and 8 (28.6%), respectively. Upon test, the x^2 value is 6.789, and P<0.05 showed significant difference as shown in Table 2.

Table 2. *Life quality of patients in two groups (n, (%)).*

Group	Enhanced	Stable	Decline	x^2 value	P value
Treatment	23(82.1%)	3(10.7%)	2(7.1%)	6.789	0.034
Control	14(50.0%)	6(21.4%)	8(28.6%)		

Toxicity evaluation

Main toxic effects were myelosuppression and gastrointestinal effects. Myelosuppression were manifested by WBC and platelet decline. The WBC drop rate was 39.2% in treatment group (11/28), among which the drop rate of Grade III and IV WBC was 7.1% (2/28). As for platelet, it decreased by 17.8% (5/28), among which the drop rate of Grade III and IV platelet was 7.1% (2/28). In control group, the WBC drop rate was 32.1% (9/28), and the drop rate of III and IV grade WBC was 10.7% (3/28). As for platelet, it decreased by 14.2% (4/28), among which the drop rate of Grade III and IV platelet was 7.1% (2/28). Gastrointestinal effects were mainly manifested by sick, vomit, diarrhoea and liver function impairment. The occurrence rate of nausea and vomit in treatment group was 28.6% (8/28) with 3.6% in Grade III. 3 patients (10.7%) suffered from diarrhoea with 3.6% (1/28) in Grade III. 2 patients suffered from mild hepatic lesion (7.1%). In control group, the occurrence rate of nausea and vomit was 32.1% (9/28) with 7.1% in Grade III. 4 patients (14.2%) suffered from diarrhoea with 7.1% (2/28) in Grade III. 2 patients suffered from mild hepatic lesion (7.1%). Additionally, 1 patient showed nodal tachycardia when using Endostar. However, it showed no statistical difference by test.

Table 3. *Grade III and IV side effect of two groups (n, (%)).*

	WBC decline	Platelet decline	Nausea and vomiting	Diarrhoea	Grade 0,I, IIeffect	x^2	P
Treatment	2 (7.1%)	3 (10.7%)	1 (3.6%)	1 (3.6%)	21	0.999	0.91
Control	3 (10.7%)	2 (7.1%)	2 (7.1%)	2 (7.1%)	21		

Discussion

In this work, 28 patients with advanced malignant digestive tract tumour were treated by Endostar combined with chemotherapy. Another control group with 28 patients was established, comparing efficacy, life quality and side effects. Results showed that 9 patients acquired PR in treatment group, including 2 with oesophagus cancers, 3 with gastric cancers, and 4 with colon cancers. Besides, 15 patients acquired SD in treatment group. The RR accounted for 9/28 (32.1%), while DCR made up to 24/28 (85.7%). In control group, the results were as follows: 7 with PR (including 1esophagus cancer, 3 gastric cancer and 3 colon cancer), 14 with SD, 5 with PD. The RR accounted for 7/28 (25.0%), while DCR made up to 21/28 (75.0%). The $P>0.05$ showed no statistical difference. During study, we found that many patients acquired SD after treatment (53.3%), the result of which showed equal life quality with PR patients. Traditional cytotoxic drugs were evaluated by tumour size; however, this assessment could not be applied to molecular target drugs [8]. For example, Sorafenib was effective for primary hepatic cancer, but patients didn't acquired CR or PR after treatment. Instead, the SD patients accounted for up to 71.0%. Moreover, PFS, TTP and Overall Survival (OS) extended significantly after treatment. It showed that stabilized conditions may be an evaluation index for assessing molecular target drugs [9]. Additionally, tumour tissue necrosis was observed when patients were treated with Imatinib or Sorafenib. It indicated that inner necrosis may also be an index for assessing treatment for molecular target drugs. Change of tumour metabolism was antecedent to its volume change. In this way, new assessment methods were needed to evaluate its role in patients, such as PET-CT or MFRI. Besides, Doppler ultrasound and vascular contrast examination were also employed to explore the blow flow and blood supply. Surprisingly, one pancreatic cancer patients acquired SD in treatment group. The patient was diagnosed as locally advanced pancreatic cancer in May 2007. Endostar combined with gemcitabine project was conducted in 6 treatment cycles. November 2011 saw the last chemotherapy, and the tumour marker returned to normal. After 47 months survival, the patient died as a result of progressive disease. It is well known that survival time for pancreatic cancer patients was only 6 months, and 90% patients died in 1 year. In control group, two pancreatic cancer patients survived 5 and 8 month, respectively. The result showed Endostar combined with Chemotherapy could improve lifetime. In addition, one patient with locally advanced colon cancer acquired PR. The patient was 58 year old, and was diagnosed as right-side colon ascendens glandular cancer. The adhesion to mesentery indicated that the lesion was hard to operate on. In August 2008, a chronochemotherapy that employed Endostar combined with oxaliplatin, calcium folinate and flurouracil was conducted. The focus narrowed significantly after 2 treatment cycles. Then excision was performed, and postoperative pathology indicated negative in incisal edge and surrounding lymph glands. The result also showed that Endostar combined with chemotherapy was available for assisting treatment in colon cancer, improving resection rate. It is widely accepted that life quality enhancement should be the ultimate goal for advanced tumours. In our study, 23 patients in treatment group showed improved life quality (82.1%), and 14 patients in control group (50.0%). The $P<0.05$ showed significant stastical difference. The result also showed that Endostar combined with chemotherapy could be applied to weak or old patients. On the aspect of toxicity, small molecular compounds directly injured DNA or hindered mitosis process [10]. Hence, the lack of selectivity on normal cells and cancer cells, as well as its toxicity restricted its widely application. On the other hand, chemotherapy injured the organs function and immune system, losing protective barrier for protecting ourselves from tumours. At last, chemotherapy intensified cytogene instability, causing cancer cell adaptation towards chemotherapy drugs. In a word, the toxicity and drug resistance made it difficult for patients to sustain. In contrast, molecular targeted therapy aimed at

unusual signal path. The high selectivity, low toxicity and high therapeutic index made it ideal way for long-term prescription. However, some special toxicity could also be observed, such as rash and diarrhoea caused by Gefitinib, anaphylaxis and cardio toxicity by trastuzumab McAb, as well as cutaneous reaction by Sorafenib. Therefore, prevention and treatment were needed in clinical use. In our treatment group, 3 patients showed G3/4 myelosuppression, 1 patient showed sick and vomits and 1 patient showed diarrhoea symptoms. While in control group, the number raised to 5, 2, and 2, respectively. Sick and vomiting were related with DPP, and leukopenia was often observed in taxol and Irinotecan administration. G3 thrombocytopenia observed in treatment was those who employed Gemcitabine as major project, and each group had 1 patient with this symptom. Consequently, Endostatin didn't increase toxicity of chemotherapy drugs. The side effect of patients in combined treatment group showed no significant difference with single chemotherapy group. As is reported, the occurrence of heart adverse effect of Endostatin ranged from 5.5% to 13.1%, manifested by myocardial ischemia and electrocardiogram change [11]. These symptoms were mostly observed in patients with pre-existent hypertension and coronary heart disease. In our study, a gastric cancer patient appeared flustered when employing Endostatin combined with oxaliplatin chronochemotherapy. Possible cause may lie in the effect of Endostatin on endothelial cells of coronary vessels. But the specific mechanism remained further study.

Regarding on the limitation of this research, few participants were included in this project. As a consequence, the extension of this research still needs more consideration.

In conclusion, recombination human endothelium statin (Endostar) combined with chemotherapy was effective for patients with advanced digestive tract cancer. The improvement of RR, DCR and QOL was observed in all patients. Synergistic effect and low side effect implied this combined therapy to be promising. However, electrocardiograph monitoring was still needed for patients with pre-existed heart diseases. Further popularization and research was expected to promote this combined therapy in clinic.

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