RESEARCH ARTICLE

Clinical Observation on Recombinant Human Endostatin Combined with Chemotherapy for Advanced Gastrointestinal Cancer

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Abstract

Objective: To explore the clinical efficacy and toxic and side effects of recombinant human endostatin (rh-endostatin/endostar) combined with chemotherapy in the treatment of advanced gastric cancer. Materials and Methods: A total of 70 patients with advanced gastrointestinal adenocarcioma confirmed by histopathology and/or cytological examination were divided into group A (37 patients) and group B (33 patients). Patients in group A were given intravenous drip of 15 mg endostar added into 500 mL normal saline, once every other day until the cessation of chemotherapy or patients' maximal tolerance to chemotherapy. Patients in group B received chemotherapy alone. Two groups selected the same chemotherapy regimens. FOLFIRI scheme: 90-min intravenous drip of 180 mg/m^2 irinotecan, intravenous drip of 200 mg/m^2 calcium folinate (CF) and 400 mg/m^2 5-fluorouracil (5-Fu) on d1, and continuous intravenous pumping of 2 400 mg/m^2 5-Fu for 46 h. FOLFOX4 scheme: intravenous injection of 85 mg/m^2 oxaliplatin (L-OHP), 200 mg/m^2 calcium folinate (CF) and 400 mg/m^2 5-FU on d1 for 2 h, and then continuous intravenous pumping of 2 400 mg/m^2 5-Fu for 46 h. XELOX scheme: oral administration of 1 500 mg/m^2 xeloda (or tegafur 50~60 mg) in twice during d1~14 and intravenous drip of 135 mg/m^2 L-OHP on d1 for 2 h. The modified FOLFOX scheme: intravenous injection of 135 mg/m^2 L-OHP on d1 for 2 h, 200 mg/m^2 CF and 1.0 g tegafur during d1~5. Whereas, control Group B received chemotherapy regimens which were same as Group A, but no addition of endostar. Before chemotherapy, patients were given intravenous injection of 8 mg ondansetron, intramuscular injection of 10 mg metoclopramide and 20 mg diphenhydramine for prevention of vomiting, protection of liver and stomach as well as symptomatic supportive treatment. One cycle was 21 d, 4~6 cycles in total. The efficacy was evaluated every 2 cycles. Results: 32 patients in Group A could be evaluated, and the response rate (RR) and disease control rate (DCR) were 59.38% and 78.13%, respectively. 31 patients in Groups could be evaluated, and the RR and DCR were 32.26% and 54.84%, respectively. The differences between 2 groups were significant. The toxic effects include myelosuppression, gastrointestinal reaction, fatigue, cardiotoxicity and peripheral neurotoxicity. Conclusions: Preliminary observations show that endostar (once every other day) combined with chemotherapy is effective in the treatment of advanced gastrointestinal cancer, with low toxic effects, good tolerance, deserving further study.

Keywords: Recombinant human endostatin/endostar - gastrointestinal cancer - targeted therapy - chemotherapy

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Introduction

Gastrointestinal cancer is one of the most common malignant tumors seriously threatening human health and life. In recent years, the morbidity and mortality of colon cancer is increasing obviously in China, with the tendency of getting younger at the median age of 45, insidious onset, symptoms often appearing in late stage, stage IV taking up 20%~25% (Sun et al., 2007). The effect of chemotherapy on advanced gastrointestinal cancer is not satisfactory, but the appearance of the molecular targeted drugs makes great headway for the efficacy of gastrointestinal cancer, with the median survival time over 2 years (Chen et al., 2013; Wei et al., 2013; Liu et al., 2014; Xu et al., 2014). The occurrence, infiltration and metastasis of tumors is closely associated with angiogenesis. And targeting tumor angiogenesis for inhibiting angiogenesis and controlling the growth of tumors is of significance to the treatment of tumors and the prevention of tumor distant metastasis (Shao et al., 2014). Tumor angiogenesis

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pathway is the main molecular target for the treatment of gastrointestinal tract. Blood vessel endothelium, a new potent angiogenesis inhibiting factor found in recent years, specifically inhibit the proliferation and metastasis of tumor vasculature endothelial cells, and then inhibiting tumor angiogenesis. In present study, we intended to explore the efficacy, safety as well as survival of endostar combined with chemotherapy in the treatment of advanced gastric cancer. The results are as follows.

Materials and Methods

General data

A total of 70 initial treatment or re-treatment patients with metastatic gastrointestinal cancer conformed by pathology were divided into 2 groups. Patients could tolerate more than 2 cycles of chemotherapy and karnofsky scores were ≥60 points. In Group A (endostar group, 37 cases), there were 25 males and 12 females, aged from 35~75 years, with the median age of 54. There were 16 cases of gastric cancer, 7 cases of colon cancer, 8 cases of rectal carcinoma, 2 cases of pancreatic cancer, 1 case of esophagus cancer, 1 case of duodenal cancer, 2 cases of appendix carcinoma. Metastases in multiple sites include 3 cases of pulmonary metastasis, 15 cases of hepatic metastases, 8 cases of abdominal pelvic widespread metastasis, 1 case of cutaneous metastasis, 1 case of brain metastases and 2 cases of ovarian metastases. 15 cases were initially treated and 22 cases re-treated. In Group B (control group, 33 cases), there were 23 males and 10 females, aged 33~75 years, with the median age of 53. There were 18 cases of gastric cancer, 8 cases of colon cancer, and 7 cases of rectal cancer. Metastases in multiple sites include 5 cases of pulmonary metastasis, 15 cases of hepatic metastases, 10 cases of abdominal pelvic widespread metastasis, 1 case of osseous metastasis, 3 cases of ovarian metastases, 1 case of abdominal wall metastasis. 10 cases were initially treated and 23 cases re-treated. The blood routine examination and hepatic and renal function were normal and the observational indexes could be evaluated. EKG, abdominal ultrasound, abdominal and pelvic CT, hepatic and renal function, tumor markers were re-examined after chemotherapy and blood routine examination was re-examined twice weekly.

Therapeutic method

Group A (37 cases) were given endostar combined with chemotherapy. Endostar (15 mg/d) was added into 500 mL normal saline for intravenous injection for 3~4 h on the day before the first cycle of chemotherapy, once every other day until the chemotherapy was finished, or patients were not tolerated to chemotherapy, or didn't continue to receive chemotherapy for other reasons. Combined chemotherapy regimens were not used before and were without cross resistance compared with previous chemotherapy. FOLFIRI scheme (8 cases): 90-min intravenous drip of 180 mg/m^2 irinotecan, intravenous drip of 200 mg/m^2 calcium folinate (CF) and 400 mg/m^2 5-fluorouracil (5-Fu) on d1, and continuous intravenous pumping of 2 400 mg/m^2 5-Fu for 46 h, and 21 days as one cycle. FOLFOX4 scheme (10 cases): intravenous injection of 85 mg/m^2 oxaliplatin (L-OHP) on d1 for 2 h, 200 mg/m^2 CF and 400 mg/m^2 5-FU on d1 for 2 h, and then continuous intravenous pumping of 2 400 mg/m^2 5-Fu for 46 h, and 14 days as one cycle. XELOX scheme (3 cases): oral administration of 1 500 mg/m^2 xeloda (or tegafur 50-60 mg) in twice during d1~14 and intravenous drip of 135 mg/m^2 L-OHP on d1 for 2 h, and 21 days as one cycle. The modified FOLFOX scheme (13 cases): intravenous injection of 135 mg/m^2 L-OHP on d1 for 2 h, 200 mg/m^2 CF and 1.0 g tegafur during d1~5, and 21 days as on one cycle. Whereas, control Group B (33 cases) received chemotherapy regimens which were same as Group A, but no addition of endostar. Off all, 7 cases received FOLFIRI scheme, 11 cases received FOLFOX4 scheme, 5 cases received XELOX scheme, and 10 cases received modified FOLFOX scheme. Before chemotherapy, patients were given intravenous injection of 8 mg ondansetron and intramuscular injection of 10 mg metoclopramideand and 20 mg diphenhydramine for prevention of vomiting, protection of liver and stomach as well as symptomatic supportive treatment. The above schemes were conducted for 4~6 weeks, and the efficacy and toxic and side effects was evaluated every 2 cycles.

Efficacy evaluation

The objective efficacy was evaluated by RECIST 1.0 criteria every 2 cycles, including complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD). The response rate (RR)=CR+PR, and disease control rate=CR+PR+SD. Time to progression (TTP) refers to the time from the beginning of treatment to the onset of progressive disease confirmed by imaging examination. Overall survival (OS) is defined as the time from the beginning of treatment to death of patients. toxic reactions is evaluated by anti-cancer drug toxicity response evaluation criteria made by WHO, including 0~IV level.

Statistical data analysis

SPSS13.0 software package was used for data analysis. The enumeration data of 2 groups was compared by X^2 test. $P<0.05$ was considered statistically significant.

Results

Status of treatment completion of 2 groups

The cycles of chemotherapy for Group A were counted according to use of endostar and the cycles were excluded after the stop of endostar. In Group A, 3 patients with gastric cancer and 1 with appendix carcinoma were withdrawn after treatment less than 1 cycle because of family economic reasons, inability to be tolerant to chemotherapy, or rejection of chemotherapy due to change of family's mind. 1 inoperable patient with gastric cancer who was accompanied by pyloric obstruction was given the modified FOLFOX scheme for 1 cycle and his symptoms were improved obviously, but he was withdrawn because of economic reasons. Therefore, 32 patients finished more than 2 cycles of endostar combined with chemotherapeutics, 101 cycles in total. Of 33 patients in Group B, 2 patients were withdrawn because of inability

Table 1. Comparison of the Efficacy of 2 Groups [n (%)]

Groups	CR	PR	SD	PD	RR	DCR
Group A (n=32)	3 (9.38)	16 (50.00)	6 (18.75)	7 (21.88)	19 (59.38)	25 (78.13)
Group B (n=31)	0 (0.00)	10 (32.26)	7 (22.58)	14 (45.16)	10 (32.26)	17 (54.84)
x^2					4.661	3.842
P					0.031	0.050

Table 2. Subgroups Analysis of Efficacy of 2 Groups [n(%)]

	CR	PR	SD	PD
Group A (n=32)				
Initial treatment (n=12)	3(25.00)	6(50.00)	2(16.67)	1(8.33)
Re-treatment (n=20)	0(0.00)	10(50.00)	4(20.00)	6(30.00)
Classification of diseases				
Gastric cancer (n=12)	0(0.00)	7(58.33%)	2(16.67)	3(25.00%)
Colon cancer (n=7)	2(28.57)	4(57.14)	0(0.00)	1(14.29)
Rectal cancer (n=8)	1(12.50)	4(50.00)	2(25.00)	1(12.50)
Appendix carcinoma (n=1)	0(0.00)	0(0.00)	1(100.00)	0(0.00)
Pancreatic cancer (n=2)	0(0.00)	1(50.00)	1(50.00)	0(0.00)
Duodenal cancer (n=1)	0(0.00)	0(0.00)	0(0.00)	1(100.00)
Esophagus cancer (n=1)	0(0.00)	0(0.00)	0(0.00)	1(100.00)
Group B (n=31)				
Initial treatment (n=10)	0(0.00)	4(40.00)	2(20.00)	4(40.00)
Re-treatment (n=21)	0(0.00)	6(28.57)	5(23.81)	10(47.62)
Classification of diseases				
Gastric cancer (n=16)	0(0.00)	5(31.25)	3(18.75)	8(50.00)
Colon cancer (n=8)	0(0.00)	3(37.50)	2(25.00)	3(37.50)
Rectal cancer (n=7)	0(0.00)	2(28.57)	2(28.57)	3(42.86)
Appendix carcinoma (n=0)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
Pancreatic cancer (n=0)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
Esophagus cancer (n=0)	0(0.00)	0(0.00)	0(0.00)	0(0.00)

Table 3. Comparison of Toxic and Side Effects of 2 Groups [n(%)]

Toxic and side effects	Toxicity grading			
	Group A		Group B	
	I~II	III~IV	I~II	III~IV
Inappetence	14(43.75)	3(9.4)	15(48.39)	4(12.9)
Fatigue	12(37.50)	2(6.25)	5(16.13)	0(0.00)
Rash	2(6.25)	0(0.00)	0(0.00)	0(0.00)
Diarrhea,constipation	5(15.63)	1(3.13)	6(19.35)	0(0.00)
Nausea and vomiting	15(46.88)	3(9.40)	14(45.16)	4(12.90)
Peripheral neurotoxicity	7(21.88)	1(3.13)	8(25.81)	2(6.45)
Cardiotoxicity	2(6.25)	0(0.00)	1(3.23)	0(0.00)
Abnormal liver function	3(9.40)	0(0.00)	4(23.90)	0(0.00)
Myelosuppression	16(50.00)	3(9.40)	17(54.84)	5(15.63)
Hand-foot syndrome	5(15.63)	2(6.25)	4(12.90)	2(6.45)

to be tolerant to chemotherapy so symptomatic supportive treatment was given. The other 31 patients finished more than 2 cycles of chemotherapy, 208 cycles in total.

Objective response and survival situation

32 patients in Group A and 31 patients in Group B were available for objective evaluation of the efficacy and safety. The overall efficacy and subgroup efficacy analysis were shown in Table 1 and Table 2. The RR and DCR were 59.38% and 78.13% in Group A, higher than those (32.26% and 54.84%) in Group B, the differences were significant (*P*=0.031, 0.050).

Toxic and side effects

Toxic and side effects were evaluated by the grading of anti-cancer drug acute and subacute toxicity (WHO criteria), including 0~IV levels. The patients of 2 groups were with less adverse reactions during the process of endostar combined with chemotherapy (Table 3). Although fatigue patients in group A (12 cases) were higher than group B (5 cases), but there was no differences (x^2=3.65, *P* =0.056). The other toxic and side effects were similar between 2 groups.

Discussion

Angiogenesis, as a new target of modern tumor treatment strategy, plays an important in genesis and development of tumors (Li et al., 2010). In 1971, Folkman proposed the idea of tumor growth depending on the formation of new blood vessel, which laid the foundation for the theoretical basis of controlling tumor growth (Folkman, et al., 1971). From that on, Antitumor vascular researches has become a hot issue of targeting therapy of tumor. In 1997, O'Reilly et al from Harvard Medical School in America extracted endostatin from the supernatant of EOMA, having strongly inhibiting tumor angiogenesis (O'Reilly et al., 1997). Endostatin consists of 183 amino acid residues of endogenous collagen X, VIII carboxyl terminal, with relative molecular weight of 20KD. It can have endothelial cell proliferation stopped in phase G1 by directly acting on vascular endothelial cells, but didn't inhibit the proliferation of non-vascular endothelial cells (O'Reilly et al., 1997). So O'Reilly named it Endostatin. The growth of blood vessels is the premise of tumor metastasis, and the growth and development of solid tumor mainly depends on the formation of functional vessels. On one hand, tumors promote angiogenesis by releasing a large amount of angiogenic growth factors; on the other hand, the newborn blood vessels provide nutrition for tumor cells and pathwaya for metastasis of tumor from primary loci into bloodstream, thus promoting the growth and metastasis of tumors (Kirschm et al., 2004; Ge et al., 2011).

Bevacizumab, monoclonal antibody targeting monoclonal antibody, can enhance the curative effect of chemotherapy for advanced large intestine cancer. Avastin was approved by USA FDA and come into market in 2004. However, less patients didn't use Avastin for it is expensive beyond the scope of coverage of health insurance. Endostar is recombinant human endostatin independently developed by china. Endostar has the multiple pathways of inhibiting angiogenesis, such as VEGF, ID21, TIMP22, Masp in and EGFR. Of all, the role of vascular endothelial growth factor (VEGF) is consistent with the role of avastin to tumor angiogenesis. Endostar is a kind of broad-spectrum anti-angiogenesis drugs which induce apoptosis by mainly inhibiting the migration of vascular endothelial cells. In addition, endostar plays role of anti-angiogenesis by multiple target and indirectly

result in tumor dormancy and lessening by regulating the expression of VEGF on tumor cell surface and the activity of proteolytic enzyme (O'Reilly et al., 1997).

General patients can accept endostar because of its moderate cost. In present study, we applied endostar plus chemotherapy to treat patients with advanced gastrointestinal tract adenoca, 14 days of use and 7 days of rest according to conventional use of endostar. However, Common gastrointestinal tumor chemotherapy regimens last 14 days, 21 days as one cycle. To overcome vascular inhibit interrupt during interictal period of endostar, even illness relapse. We used endostar once every other day, which guarantees endostar covering the entire cycle of chemotherapy, with intention to lasting inhibition of tumor vessels, reduction of total amount of endostar, prolonging of time, cost reduction, cost reduction and reduced toxic and side effects. Research results showed that endostar combined with chemotherapy was effective in the treatment of advanced gastrointestinal cancer, with DCR being 78.13%, RR 59.4% which were higher than those (DCR 54.84% and RR 32.26%) in control group, and the differences were significant. Endostar is effective for both initial treated and retreated patients, especially completely effective for 1 patient with hepatic metastasis after colon cancer surgery who has 2 year disease-free survival. This is consistent with the results of endostar combined with chemotherapy in the treatment of advanced gastric cancer reported by Chen et al. (2009). No treatment-related death happened. And the occurrence rate of toxicity reaction of III~IV level was low, but most were relieved after symptomatic treatment. The main toxicity of all patients includes gastrointestinal reaction and myelosuppression which might be related to chemotherapy, no obvious cardiotoxicity. 1 cases were with stomachache and severe diarrhea without hematochezia, so endostar was stopped and dosage and dosage of irinotecan was adjusted. If patient rejected to continue to use after lasting 2 weeks, we considered diarrhea was caused by irinotecan. However, no evidence clearly proved it had no relationship with endostar. Additionally, patients were withdrawn mainly because of economic reasons. In present study, the short-term effect and toxic effects were observed, but due to small-size sample and short followup, the further study should be conducted for explore the long-term efficacy and survival.

In conclusion, endostar (once every other day) combined with chemotherapy, which is effective for treating advanced gastrointestinal cancers, with satisfactory efficacy, low toxic effects and good safety, is worth further clinical observation and wide application in clinic.

References

Chen G, Shen ZL, Wang L, et al (2013). Hsa-miR-181a-5p expression and effects on cell proliferation in gastric cancer. *Asian Pac J Cancer Prev*, **14**, 3871-5.

Chen YX, Qin SK, Liu XF, et al (2009). Clinical study of rh-endostatin combined with chemotherapy for advanced gastric cancer. *Chin Clin Oncol*, **14**, 327-31.

FolkmanJ, MerlerE, AbernathyC, etal. Isolated of a tumor factor responsible for anfiogesis. *J Exp Med*, 1971, **133**, 275-88.

Ge W, Cao DD, Wang HM, et al (2011). Endostar Combined with Chemotherapy versus Chemotherapy alone for Advanced NSCLCs: A Meta-analysis. *Asian Pac J Cancer Prev*, **12**, 2901-7.

Kirschm, Schackert G, Black PM (2004). Metastasis and angiogenesis. *Cancer Treat Res,* **117**, 285.

Liu J, Huang XE, Feng JF (2014). Further study on pemetrexed based chemotherapy in treating patients with advanced gastric cancer (AGC). *Asian Pac J Cancer Prev*, **15**, 6587-90.

O'Reilly MS, Boehm T, Shing Y (1997). Endostain: an endogenous inhibitor of angiofenesis and tumor growth. *Cell*, **88**, 277-85.

Sun Y, Shi YK (2007). Manual of Clinical Oncology. *People's Medical Publishing House*, 492-6, 817-9.

Shao Mingwen, Qiu Jinrong, Wu Hao, et al (2014). Mechanism of Shenyi Capsule Concomitant with Endostar and Chemotherapy on the Growth and Apoptosis of MCF-7 Breast Cancer Cells. *J Int Transl Med*, **2**, 299-302.

Wang JW, Sun Y, Liu YY, et al (2005). Results of randomized, multicenter, double blind phase III trial of rh-endostatin (YH16) in treatment of advanced non-small cell lung cancer patients. *Chin J Lung Cancer*, **8**, 283-90.

Li Y, Huang XE, Yan PW, et al (2010). Efficacy and Safety of Endostar Combined with Chemotherapy in Patients with Advanced Solid Tumors. *Asian Pac J Cancer Prev*, **11**, 1119-23.

Wei GL, Huang XE, Huo JG, et al (2013). Phase II study on pemetrexed-based chemotherapy in treating patients with metastatic gastric cancer not responding to prior palliative chemotherapy. *Asian Pac J Cancer Prev*, **14**, 2703-6.

Xu X, Wang L, Xu HQ, et al (2013). Clinical comparison between paclitaxel liposome (Lipusu®) and paclitaxel for treatment of patients with metastatic gastric cancer. *Asian Pac J Cancer Prev*, **4**, 2591-4.