RESEARCH COMMUNICATION

Clinical Observation of Endostar® Combined with Chemotherapy in Advanced Colorectal Cancer Patients

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Abstract

Objective: Endostar® (Rh-endostatin injection) is a new recombinant human endostatin developed by Shandong Simcere-Medgenn Bio-Pharmaceutical Co., Ltd in China. This study was performed to evaluate the efficacy and safety of Endostar plus leucovorin calcium/ 5-fluorouracil/oxaliplatin (FOLFOX4) in treating patients with advanced colorectal cancer. Methods: Thirty-six patients with advanced colorectal cancer were retrospectively assigned to one of two treatment groups: FOLFOX4 (control) or FOLFOX4 plus Endostar (Endostar) according to patient accreditation. The observational end points were overall response rate, overall survival, progression-free survival and toxicity. Results: The response rate and progression-free survival of Endostar were significantly better than those of control group (P <0.05), but significance was not observed for median survival. In addition, gastrointestinal side effects and incidence of leucopenia were not lower than in the control group (P<0.05). Conclusions: The addition of Endostar to FOLFOX4 resulted in a higher objective response rate and longer time to disease progression. Hypertension and cardiac ischemia were the principal safety concerns, but were manageable. Endostar deserves to be further investigated by randomized controlled clinical trails.

Keywords: Endostar® - chemotherapy - advanced colorectal cancer - China

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Introduction

Colorectal cancer is one of the most common cancers worldwide (Huang et al., 2004). In China, with lifestyle being continuously westernized, the incidence of colorectal cancer has been on the rise, and also one of the most common cancers without sex difference. Although 40% to 50% colorectal cancer patients can be treated by surgery, many will die due to recurrence or metastasis. As for unresectable or metastatic colorectal cancer, chemotherapy is the main choice, to prolong survival and improve life quality. Fluorouracil, oxaliplatin, and irinotecan are the cornerstone of the treatment of metastatic colorectal cancer. However, chemotherapy is concerned regarding low responsiveness and existence of severe dose-limit toxicities.

Recently, research (Folkmen, 1971; Folkmen, 2001) has found that dependence of tumor growth, infiltration and metastasis on blood vessels makes angiogenesis a hallmark of cancer, which is of significance for tumor growth control, tumor treatment and tumor metastasis prevention. Endostar ® is a new recombinant human endostatin developed in China, and preclinical studies suggest that it is effective for treatment of many cancers. The aim of our study is to evaluate the clinical efficacy and toxicity of Endostar combined with FOLFOX4 in treating patients with advanced colorectal cancer.

Materials and Methods

Patients

Patients recruited into this study were required to be pathologically diagnosed as colorectal cancer, with karnofsky performance status ≥ 70 scores and expected survival overpassing 3 months. Other eligibility criteria were introduced elsewhere (Li et al., 2010; Yao et al., 2010) that included: adequate bone marrow (white blood cell count >4.0x109 and platelet count >100x109), liver function (bilirubin and transaminases <1.5 times the upper limit of normal and renal function (creatinine <1.5 upper limit of normal); and no evidence of metastatic disease; age between 18 and 75 years old ; signed an informed consent before chemotherapy. Patients were excluded from the study if they had active cardiac disease (LVEF <50%), significant arrhythmia, any serious medical or psychiatric condition, other malignancy, pregnant or lactating women were excluded from the study.

Treatment

The FOLFOX4 regimen were scheduled as follows: intravenous(iv) leucovorin calcium at a dose of 200 mg/m2, iv bolus fluorouracil(5-FU) at a dose of 400 mg/m^2 and continuous iv 5-FU at a dose of 600 mg/m^2 on day 1, day 2, oxaliplatin 85mg/m^2 repeated every 2 weeks. Daily dose of Endostar was 15mg, slowly intravenously

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Table 1. Results of Efficacy in Two Groups Treated by FOLFOX4 with or Without Endostar*

Measure	FOLFOX4 plus Endostar* N=18	FOLFOX4 N=18
Objective Response Rate n (%)		
Overall	7(38.9)	4(22.2)
Complete	0	0
Partial	7(38.9)	4(22.2)
Median Overall Survival (months)	12.1	11.4
Progression-free Survival (months)	6.4	3.8

FOLFOX4 - Leucovorin leucovorin/calcium Fluorouracil/ Oxaliplatin; *Endostar® (Rh-endostatin injection) is a new recombinant human endostatin developed by Shandong Simcere-Medgenn Bio-Pharmaceutical Co., Ltd in China

dropped from day 1 to day 14. Patients who received only FOLFOX4 termed control, received FOLFOX4 plus Endostar called Endostar group. Chemotherapy was biweekly administered until PD or unacceptable toxicities, withdrawal of consent, and physicians decision or treatment interruption for >2 weeks. Antiemetic treatment was granisetron 3mg by intravenous bolus infusion prior and during chemotherapy. Routine blood test including blood biochemistry and tumor markers were reviewed during and after chemotherapy weekly.

Efficacy Observation

Treatment efficacy was evaluated after two months treatment. Complete Remission (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were determined based on RECIST criteria (Therasse et al., 2000).

Toxicity Assessment

Patients were assessed and graded for toxicity according to WHO criteria (Miller et al., 1991).

Statistical analysis

The study data were analyzed by t and enumeration data by $\chi 2$ test. Statistic significance was determined if $p<0.05$.

Results

Patients

Thirty-six patients were enrolled into this study. Among them, 24 were male, and 12 female; median age was 58 years old; 14 diagnosed with rectal, and 22 with colon cancer; 16 had liver, 8 lung and 20 peritoneal metastasis. No significant difference was detected between two groups in terms of sex, age, ECOG scoring, pathological classifications, clinical staging, and metastatic status ($p>0.05$).

Efficacy

Thirty-six patients had completed at least 2 cycles of treatment. No CR was observed in both two groups. Response rate of Endostar group (CR+PR) was 38.9%, while that in control group was 22.2%. The difference between two groups was statistically significant ($p<0.05$) (Table 1).

Table 2. Toxicities in Two Groups Treated by FOLFOX4 with or Without Endostar*

Toxicity	FOLFOX4 plus Endostar* (%) N=18		FOLFOX4 (%) N=18	
Grade/	I- II	III -IV	I- II	III-IV
Hypertension	17.7	0	5.6	0
Bleeding	0	0	0	0
Leukopenia	38.9	16.7	44.4	11.1
Thrombocytopenia	22.2	5.6	22.2	0
Nausea,vomiting	66.7	5.6	61.1	5.6
Peripheral neuropathy	22.2	0	22.2	0
Thromboembolism	0	0	0	0
Cardiac ischemia	11.1	0	0	0

FOLFOX4- Leucovorin leucovorin /calcium Fluorouracil/ Oxaliplatin; *Endostar® (Rh-endostatin injection) is a new recombinant human endostatin developed by Sandong Simcere-Medgenn Bio-Pharmaceutical Co., Ltd in China

PFS and OS

All patients were followed up until December 2011. The PFSes of Endostar and control group were 6.4 months and 3.8 months separately, with statistical significance ($p<0.05$) (Table 1). While the OS of Endostar and control group were 12.1 and 11.4 months respectively ($p<0.05$) (Table 1).

Adverse reaction

The adverse effects possibly related to Endostar include hypertension and adverse cardiac event. Two patients had grade I hypertension, but recovered without any treatment; 1 patient with hypertension history suffered grade II hypertension after Endostar infusion, but the blood pressure remained stable after adjusting antihypertensive medications. Two patients had chest distress and discomfortableness, but the symptom relieved after adjusting the infusional speed. In our study, thrombus, bleeding and proteinuria were not found. Adverse effects related to chemotherapy included bone marrow suppression, gastrointestinal reactions , Peripheral neuropathy, liver function injury, and fatigue. In Endostar group, grade I-II leukopenia accouts for 38.9% for, grade III-IV leukopenia accouts for 16.7%, no infection was reported; 22.2% patients showed grade I-II and 5.6% grade III-IV thrombocytopenia; grade I-II nausea/vomiting was 66.7%, and grade III-IV 5.6%. In control group, leukopenia rate was 55.6%, 11.1% of them with grade III-IV; 22.2% patients with grade I-II thrombocytopenia and no grade III; grade I-II nausea/ vomiting was 61.1%, and 5.6% with grade III-IV (Table 2). No statistically significant difference was detected in hand-foot syndrome or peripheral neuropathy. Mild liver damage were observed in both two groups, but recovered without modification on dosage of chemotherapy. Additionally, no apparent renal damage was recorded.

Discussion

With the change of life style, especially changes in food consumption, the incidence of colorectal cancer has been in sharp rise, making it one of the cancers with the highest incidence worldwide. According to the statistical

data in 2005, colorectal cancer has become the third leading cancer in the world, accounting for 10% of the male new cases and 11% of the female new cases (Jemal et al., 2005). In several developed areas of China, the incidence of colorectal cancer is close to the level of developed countries (Center for Statistic Information Ministry of Health, China, 2002). In recent 10 years, the development of science has brought about progress in the diagnosis and treatment of colorectal cancer. Survival time of patients diagnosed with metastasis has been prolonged from half year to 2 years. However, the effectiveness of chemotherapy has been unsatisfactroy due to low respectiveness and high rate of dose-limit toxicities. In order to improve the treatment efficacy, researchers developed some new drugs targeted on molecular pathway of tumor pathogenesis and progression. Molecular targeted therapy is one of the most important progresses in this field, e.g. bevacizumab and cetuximab combined with standard chemotherapy are reported to significantly improve the survival of advanced colorectal cancer patients (Fernando and Hurwitz, 2004; Ki et al., 2005; Saltz et al., 2008).

In 1971, researchers (Folkman., 1971) suggest that the growth and metastasis of cancer depend on tumor new vessels, thus starting investigations on tumor angiogenesis and antiangiogenic treatment. Tumor vasculogenesis, namely the forming of newborn blood vessel, which is regarded as the key factor of tumor growth, provides not only nutrition and oxygen for tumors, but also the pathway for tumor cells entering circulation and tumor metastasis. It is reported that vascular endothelial growth factor (VEGF) is a strong and specificial factor in stimulating the proliferation of vascular endothelial cells, playing an up-regulation role in most tumors including colorectal cancer (Jain, 2005; Ooyama et al., 2008). Previous results showed that VEGF is closely related to tumor infiltration, increased microvessel density, tumor metastasis and recurrence, and prognosis. Bevacizumab is an recombinant human monoclonal IgG1 antibody aimed at VEGF (Fernando et al., 2004; Tebbutt et al., 2010). No.16966 research (Saltz LB et al., 2008) indicates that Bev combined with FOLFOX/Xelox can prolong PFS by 1.4 months compared to front-line therapy with only FOLFOX/Xelox, which has the trend to prolong OS, but has no effects on response rate. E3200 research (Giantonio et al., 2007) indicates that patients with front-line chemotherapy failure were randomly assigned to FOLFOX with or without bevacizumab, and showed that FOLFOX combined with bevacizumab is more effective than FOLFOX alone regarding response rate, PFS and OS. But, due to its high price in china, bevacizumab has a limitation in clinical uses.

Endostar is a recombinant human endostatin, and came into chinese clinical practice in 2005. The mechanism of Endostar is to inhibit the migration of vascular endothelial cells and tumor angiogenesis, further to prevent tumor nutrition supply, and finally to inhibit the tumor growth and metastasis. However, the indication of Endostar authorized by China government is only to treat non small cell lung cancer patients for initial treatment or retreatment in stage III/IV and combined with NP regimen(Yang et al., 2004; Wang et al., 2005). Besides the authorized indication, many doctors are researching on the efficacy and safety of Endostar in treating other tumors, including breast cancer, alimentary cancer (Wang et al., 2005; Yuan et al., 2007; Wen et al., 2009). Their research had proved that Endostar combined with chemotherapy for the treatment of cancer can improve efficacy and prolong PFS and OS.

In our study, we found that in advanced colorectal cancer patients, chemotherapy combined with Endostar is also associated with improved efficacy and prolonged median PFS. Because of the sample size in our study, the optimum dosage, administration route, administration time, and the course of the use of Endostar combined with FOLFOX could not be further investigated. However, it is concluded that Endostar combined with FOLFOX regimen for the treatment of advanced colorectal cancer is safe and able to improve response rate, and has not increased adverse reactions of chemotherapy, thus deserves further clinical studies.

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