RESEARCH COMMUNICATION

Early Efficacy of Endostar Combined with Chemoradiotherapy for Advanced Cervical Cancers

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Abstract

The aim of this study was to investigate the early outcome of Endostar combined with chemoradiotherapy for advanced cervical cancer. Fifty-two cases (FIGO IIb to IVa) were divided randomly into two groups, receiving chemoradiotherapy alone (CRT group) and Endostar combined with chemoradiotherapy (CRT+E group). For the patients in the CRT+E group, Endostar was administered daily with the dosage of 7.5 mg/m^2, and cisplatin was administered weekly with the dosage of 20 mg/m^2 during the radiation. The regimens lasted for 4 weeks with no difference in chemoradiotherapy between the two groups. The early outcome complete remission rate was 73.1%, partial remission rate was 23.1% and the total response rate was 96.2% in CRT+E group, a significnat improvement on the 34.6%, 42.3% and 76.9%, respectively, in the CRT group. One year survive rates were 100% and 84.6% in the CRT+E group and CRT groups, the difference being significant. Endostar combined with chemoradiotherapy can improve the early outcome of the advanced cervical cancer, and adverse effects were not encountered.

Keywords: Cervical cancer - Endostar - chemoradiotherapy

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Introduction

Cervical cancer is the most common gynecologic cancer. Surgery or radiotherapy can achieve satisfactory effect for early stage cervical cancer, while in the late stage (II b-IV a period) the main treatment therapy is radiation. At present, many studies all over the world reported that radiotherapy combined with chemotherapy can improve the survival rate of patients with cervical cancer. Concurrent chemoradiation, using cisplatin-based chemotheraphy (either cisplatin alone or cisplatin/5-fluorouracil), is the treatment of choice for stages Ib-IV a disease based on the results of many randomized clinical trials. (Lu et al., 2003; Dubay et al., 2004; Eifel et al., 2004; Rose et al, 2007; Duenas-Gonzale et al., 2011). These trials have shown that the use of Concurrent chemoradiation results in a 30%-50% decrease in the risk of death compared to RT alone. Although the optimal Concurrent chemotheraphy regimen to use with RT requires further investigation, these trails clearly established a role for Concurrent cisplatin-based chemoradiation. However, cervical cancer is not always sensitive to Chemoradiotherapy. As one of the malignant tumor, the similar angiogenesis and lymphangiogenesis happen in cervical cancer, and the density of blood vessels and lymphatic vessels is related with the malignancy and biological characteristics of the tumor. Therefore, it sounds reasonable to suppress tumor development by way of suppressing angiogenesis and lymphangiogenesis. Jia et al. (2009) proved endostar can reduce the tumor growth and metastasis by inhibiting angiogenesis and lymphangiogenesis in nude mouse model of human cervical cancer. Recent research proved the endostatin could suppress the lymphangiogenesis and lymph node metastasis of tumor by direct or indirect method (Brideau et al., 2007). Endostar combined with chemotherapy is well-tolerated in patients with metastatic colorectal cancer, gastric cancer and advanced non-small cell lung cancer, and it is relatively effective as a first-line therapy (Ge et al, 2011; Han et al, 2011; Li et al, 2011; Zhou et al, 2011). To investigate the early outcome of the Endosta combined with chemoradiotherapy to the advanced cervical cancer. 52 patients with cervical cancer in II b-IV stage, who hospitalized in oncology unit from September 2009 to October 2010, were randomly divided into chemoradiotherapy group and Endostar combined with chemoradiotherapy group. The comparison of two groups is as follows.

Materials and Methods

Samples

All cases were pathologically confirmed in II b-IV stage, according to FIGO staging (Rose et al., 1999) and in their initial treatment. They all had KPS ≥ 70 points. Before treatment, their blood routine, liver and kidney function and ECG were normal. These 52 patients were randomly divided into two groups: chemoradiotherapy (CRT group) 26 cases, Endostar combined with chemoradiotherapy

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Table 1. The General Conditions of the Two Groups

Group	Cases	Age		Pathological type		Clinical stage			
		Range	Median	ScCC	Adenoca	IIb	IIIa	IIIb	IVa
CRT	26	32-63	52	19	7	8	13	4	1
CRT+E	26	31-62	51	18	8	9	13	3	1

SqCC, Squamous cell carcinoma; Adenoca, adenocarcinoma

Table 2. Early Efficacy in the Two Groups

Group	Cases	CR	PR	NC	PD	Response rate (%)
CRT	26	9 (34.62%)	11 (42.31%)	6 (23.08%)	0	76.92
CRT+E	26	19 (73.08%)	6 (23.08%)	1 (3.85%)	0	96.15

X^2 =4.13>3.84; P<0.05

(CRT + E group) 26 cases in the oncology hospital of jingzhou from September 2009 to October 2010 with the Ethical Approval. Patients' characteristics were shown in Table 1. There is no statistically significant in the difference between the two groups on general characteristics, past history and clinical performance.

Treatment

Chemoradiotherapy: They all accepted the 15Mv X-ray of 23-EX Varian linear accelerator and Ir192 high dose rate brachytherapy. The treatment to the pelvic was the first. The brachytherapy and the 4 beams radiotherapy to the pelvic were fulfilled simultaneously after the center of the pelvic got 40 Gy/20f/4weeks. The brachytherapy was fulfilled once a week, which gave the A point 6 Gy, the total doses 18-30 Gy. At the same time, the 4 beams to the pelvic gave the parauterus 10-16 Gy, 2 Gy every time. And the two methods didn't happen on the same day. The upper bound of the exobody radiotherapy was L4-L5, the low upper bound was lower margin of the obturator foramen, and the outer margin was 2 cm to the real pelvic. Cisplatin was administered weekly with the dosage of 20mg/m^2. The regimen lasted for 4 weeks.

For the patients in CRT+E group, Endostar was administered daily with the dosage of 7.5 mg/m^2, and cisplatin was administered weekly with the dosage of 20 mg/m^2 .The regimen lasted for 4 weeks. There was no difference of chemoradiotherapy between the two groups.

The observation target

The items need to be evaluated and monitored are clinical symptoms and signs, adverse reactions, blood tests every week, vaginal speculum examination once a week, electrocardiogram before and after treatment, liver and kidney function and related imaging tests before and after treatment, record tumor size (maximum diameter and the anteroposterior diameter), parametrial invasion; tumor shrinkage percentage = (volume before Chemoradiotherapy - Chemoradiotherapy volume) / volume before Chemoradiotherapy, after three months of treatment, efficacy and toxicity.

Statistics

All statistical analyses were conducted using the SPSS 13.0 statistical package for Windows. X^2 test was used to compare efficient and incidence of side effects in two groups. Statistical significance was available when the difference was P<0.05.

Table 3. Early Efficacy in the Two Groups with reference to Tumour Types

Group	Squamous cell carcinoma				Adenocarcinoma			
	CR	PR	NC	PD	CR	PR	NC	PD
CRT	9	9	1	0	0	2	5	0
CRT+E	17	1	0	0	2	5	1	0

Results

Effect of treatment

According to general standard for solid tumor treatment efficacy (Sun and Shi, 2007), the outcome of treatment divided into complete remission (CR), partial remission (PR), stable (NC) and deterioration (PD). Early cancer treatment efficacy data are shown in Tables 2 and Table 3.

In CRT group: CR 9 cases are squamous cell carcinoma, PR 9 cases are squamous cell carcinoma and 2 cases are adenocarcinomas, NC 5 cases are adenocarcinomas, 1 case is squamous cell carcinoma; In CRT + E group: CR 17 cases are squamous cell carcinoma, 2 cases of adenocarcinomas. PR 1 case is squamous cell carcinoma, 5 cases of adenocarcinoma; NC 1 case is adenocarcinomas, two groups compared, CRT + E group's squamous cell carcinoma CR was significantly higher than that of CRT group, the difference was statistically significant (X^2 = 9.81> 3.84, P <0.05); CRT + E group's Adenocarcinoma effective rate (CR + PR) was significantly higher than the CRT group, the difference was statistically significant (X^2 = 5.4> 3.84, P <0.05). CRT + E group's total effective rate (CR + PR) was significantly higher than the CRT group, the difference was statistically significant (X^2 = 4.13> 3.84, P <0.05).

CRT + E group's one year survive rate (100%) was significantly higher than the CRT group (84.62%), the difference was statistically significant (X^2 = 4.33> 3.84, P <0.05).

Acute toxicity

(1) Mainly reaction are fatigue, loss of appetite, stool frequency increased. Few cases have nausea, vomiting, stool sense of falling, urinary urgency, frequent urination. (2) Hematological toxicity: according to common grading criteria of anticancer drugs toxicity (Sun and Shi, 2007). CRT group has 9 patients with grade I myelosuppression, 3 patients with grade II myelosuppression, 1 patient with grade III myelosuppression, no grade IV myelosuppression.

Table 4. Comparison of Toxicity Effects in the Two Groups

	CRT group					CRT+E group				
Poison effect	0	I	II	III	IV	0	I	II	III	IV
WBC descend	13	9	3	1	0	17	7	2	0	0
Anemia	20	4	2	0	0	21	3	2	0	0
PLT descend	23	2	1	0	0	24	1	1	0	0
Vomiting	13	12	1	0	0	15	10	1	0	0
Diarrhea	14	10	2	0	0	18	7	1	0	0
UTI	24	2	0	0	0	25	1	0	0	0
kidney poison	25	1	0	0	0	26	0	0	0	0
Heart poison	26	0	0	0	0	24	2	0	0	0
Fever	25	1	0	0	0	24	1	1	0	0
Baldness	24	1	1	0	0	23	3	0	0	0

UTI, Urinary tract infection

CRT + E group has 7 cases with grade I myelosuppression, 2 cases with grade II myelosuppression, no grade III and grade IV myelosuppression, (X^2 = 1.26<3.84, P >0.05). Subcutaneous injections of recombinant human granulocyte colony stimulating factor were given for grade I, II, III myelosuppression. (3) 2 cases reported sinus tachycardia, proved by ECG.. Before and after treatment, patients within both two groups have their liver and renal function normal.

Adverse reactions are listed in Table 4, with no significant variation between the groups.

Discussion

Cervical cancer is one of the common gynecologic malignancies. It is a very important issue in gynecology. Its morbidity increases in these years. Radiation therapy is an effective choice for advanced cervical cancer treatment, but radiotherapy effect itself is not satisfactory, therefore, the U.S. National Cancer Institute (NCI) in February 1999 announced to the world, that the combination of radiotherapy and chemotherapy treatment at the same time in advanced cervical cancer have good effect and suggested for patients who received radiotherapy, chemotherapy should be given the same time (Peters et al, 2000). Recent studies confirmed that concurrent radiotherapy and chemotherapy in advanced cervical cancer is safe and feasible, have good effect (Rose et al., 2007; Dueñas-González et al., 2011). However, cervical cancer is not always sensitive to Chemoradiotherapy. As a result, local invasion could not been controlled and relapses, and lymph node metastasis and distant metastasis happen. Therefore, it's an important task for doctors to find new and effective drug.

Endostar, which adds 9 amino acids to the N-end of Endostatin peptide chain, improve the function and efficacy of the drug (Luo et al., 2006). Endostar suppresses the endothelial cell proliferation and migration, thus suppresses the angiogenesis of tumor. The nutrition supply is blocked and then the tumor cell proliferation and migration are suppressed. Besides, Endostar could suppress the formation of lymphatic ducts in tumor and lymph node metastasis. Results in vitro experiments showed the suppression of Endostar to the migration of HHEC and formation of Tube, and the suppression to the angiogenesis of Chorio Allantioc Membrane. Endostar could suppress human lung adenocarcinoma cell line SPC-A4. Results in vitro experiments showed the suppression of Endostar to mouse tumor models (S180 sarcoma, H22 liver cancer) and human xenograft tumor models (SPC-A4 lung adenocarcinoma, SGC7901 gastric cancer, Hela cervical cancer, SMMC-7721 liver cancer and Bel7402 liver cancer). In 2007, Endostar became the first-line drug in the treatment of NSCLC. The main adverse effects include heart reactions, and some rare effects include gastrological reactions, allergy of skin and its appendicular. No death related with drug was reported.

As one of the malignant tumor, the similar angiogenesis and lymphangiogenesis happen in cervical cancer, and the density of blood vessels and lymphatic vessels is related with the malignancy and biological characteristics of the tumor. Li Cheng (Fukumoto et al., 2005) found Endostar could suppress the angiogenesis and lymphangiogenesis of subcutaneous xenograft tumor of Hela athymic mouse. Besides, it can induce apoptosis of tumor cells. Endostar could decrease the expression of VEGF A, C, and D. Xin et al. (2011) found Endostar may normalize the tumor vasculature. And the time window is found at Days 4-6 post-treatment. During the time of vascular normalization, a combination therapy of endostar plus cisplatin has optimal efficacies. Li Y's study (Li et al., 2010) revealed that toxicity of Endostar combined with chemotherapy in the treatment of solid tumors was tolerable with moderate efficacy. Jia et al. (2011) proved Endostar enhanced the anti-cancer effect of chemoradiotherapy in a mouse xenograft model of cervical cancer. These findings thus provide a new strategy to treat cervical cancer.Endostar could alleviate the adverse effects of chemotherapy, and it may be one effective drug in the treatment of cervical cancer.

In this study two groups have chemoradiotherapy in the same manner. CRT + E group had the recent efficacy rate at 96.15%, CRT group was 76.92%. CRT + E group's total effective rate (CR + PR) was significantly higher than the CRT group, the difference was statistically significant (X^2 = 4.13> 3.84, P <0.05). CRT + E group's squamous cell carcinoma CR rate was significantly higher than that of CRT group, the difference was statistically significant (X^2 = 9.81> 3.84, P <0.05); CRT + E group's Adenocarcinoma effective rate (CR + PR) was significantly higher than the CRT group, the difference was statistically significant (X^2 = 5.4> 3.84, P <0.05). CRT + E group's one year survive rate (100%) was significantly higher than the CRT group (84.62%), the difference was statistically significant (X^2 = 4.33> 3.84, P <0.05).

Endostar combined with concurrent chemoradiotherapy for cervical squamous cell carcinoma and adenocarcinoma were increased efficacy, particularly more pronounced sensitizing effect of cancer, but in this study a small number of cases with adenocarcinoma may make the limitation. Study on large number of cases still needs to be done. Toxicity compared two groups: the recent reaction of fatigue, loss of appetite, CRT + E group emphasis without statistically significant, which did not affect the treatment. Hematological toxicity: CRT group has 9 patients with grade I myelosuppression, 3 patients

with grade II myelosuppression, 1 patient with grade III myelosuppression, no grade IV myelosuppression. CRT + E group has 7 cases with grade I myelosuppression, 2 cases with grade II myelosuppression, no grade III and grade IV myelosuppression, Compared two groups, the difference between incidence was not statistically significant (X^2 = 1.26<3.84, P >0.05). 2 cases reported sinus tachycardia, proved by ECG. This study shows that Endostar combined with concurrent chemoradiotherapy in advanced cervical cancer has a good short-term effect, and the adverse effects can be acceptable. Endostar could improve patients' life quality and prognosis. The sample size in this study is small with a short time follow up. The long-term effect needs further observation.

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