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Short-term curative effect and safety of bevacizumab combined with chemotherapy for treating recurrent and metastatic cervical cancer

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Summary

Objective: To observe bevacizumab plus chemotherapy curative effect and safety for recurrent and metastatic cervical cancer. *Materials and Methods:* Retrospective analysis of 30 recurrent and metastatic cervical cancer cases. The experimental group received bevacizumab plus paclitaxel-, docetaxel-, and platinum-based chemotherapy. The control group received only chemotherapy. Curative effects were recorded after at least two treatment cycles; adverse reactions were recorded with every cycle. *Results:* Experimental group patients were treated for an average 2.6 cycles. Compared to the control group, the experimental group effective rate (26.7%) was similar, disease control rate (73.7%) was significantly higher, and median survival time was three months longer. Bevacizumab-associated adverse reactions were bleeding, hypertension, and thrombosis/embolism; most were level 1 and 2 reactions. Adverse reactions in the two groups were not statistically different. *Conclusions:* The bevacizumab plus chemotherapy disease control rate for recurrent and metastatic cervical cancer is comparatively high, prolonging median survival; bevacizumab-associated adverse reactions are mild and tolerable.

Key words: Cervical neoplasms; Bevacizumab, Drug therapy, Targeted therapy, Drug toxicity.

Introduction

Cervical cancer is the third most common cancer in women around the world [1]. Treating recurrent and metastatic cervical cancer is relatively difficult; the main treatment methods are radiotherapy and chemotherapy, but the curative effect is unsatisfactory. Current research on bevacizumab for treating patients with recurrent and metastatic cervical cancer has found that the regimen has a good curative effect [2]. During January 2013 and February 2014, the authors combined bevacizumab with chemotherapy to treat metastatic cervical cancer at their department of gynaecology, and analysed the curative effect and safety of this regimen in metastatic cervical cancer.

Materials and Methods

General information

The authors retrospectively analyzed 30 cases of cervical cancer admitted to the Henan Tumor Hospital Department of Gynaecology from January 2013 to February 2014. There were 15 patients in the experimental group (age range: 32–58 years; median age: 46 years). The experimental group comprised of 13 cases of cervical squamous carcinoma and two cases of adenocarcinoma. Six patients had undergone surgery, radiotherapy, and chemotherapy; nine had undergone radiotherapy and chemotherapy. Eleven patients had pelvic recurrence, eight had retroperitoneal and/or mediastinal lymph node metastasis, seven had lung metastasis, and five had hepatic metastasis (Table 1). The 15 patients in the observational (control) group were aged 34–60 years, and median age was 48 years. There were 12 cases of cervical squamous carcinoma and three cases of adenocarcinoma. Seven patients had undergone surgery, radiotherapy, and chemotherapy; eight had undergone radiotherapy and chemotherapy. Twelve cases had pelvic recurrence, seven had retroperitoneal and/or mediastinal lymph node metastasis, five had pulmonary metastasis, and six had liver metastasis (Table 1). The Karnofsky scores were ≥ 70 points, and patients did not have a history of serious diseases of the heart, liver, kidney, brain, or haemopoietic system. The pre-treatment electrocardiograms were normal, and there were no serious complications such as intestinal obstruction, active bleeding, or circulatory collapse.

Treatment regimens

Patients in the experimental group received 7.5 mg/kg bevacizumab once every three weeks. Among them, three received additional 135~175 mg/m^2 paclitaxel and 60~80 mg/m^2 cisplatin; 12 received additional 75 mg/m^2 docetaxel and 80 mg/m^2 nedaplatin. The average duration of bevacizumab was three cycles (range: 2–5). In the control group, five patients received combined paclitaxel and cisplatin and ten received the same doses of paclitaxel and cisplatin as the experimental group.

Results

Treatment results

In the experimental group, bevacizumab was stopped for three cases with disease progression, and bevacizumab and

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Table 1. — *Clinical information of patients (cases).*

Characteristics of cases	Experimental group	Control group
Age (years)		
< 50	6 (40%)	5 (33.3%)
≥ 50	9 (60%)	10 (66.7%)
Pathological type		
Squamous carcinoma	13 (86.7%)	12 (80%)
Adenocarcinoma	2 (13.3%)	3 (20%)
Treatment history		
Surgery, radiotherapy, and chemotherapy	6 (40%)	7 (46.7%)
Radiotherapy and chemotherapy	9 (60%)	8 (53.3%)
Hypertension history	3 (20%)	4 (26.7%)
Metastatic sites		
Pelvis	11 (73.3%)	12 (80%)
Retroperitoneal and mediastinal lymph nodes	8 (53.3%)	7 (46.7%)
Lung	7 (46.7%)	5 (33.3%)
Liver	5 (33.3%)	6 (40%)

Table 2. — *Comparison of short-term curative effect in the two groups [n (%)].*

	Cases	Effective rate	Disease control rate
Experimental group	15	4 (26.7)	11 (73.3)
Control group	15	2 (13.3)	5 (33.3)
x^2 value		0.833	4.821
p value		0.361	0.028

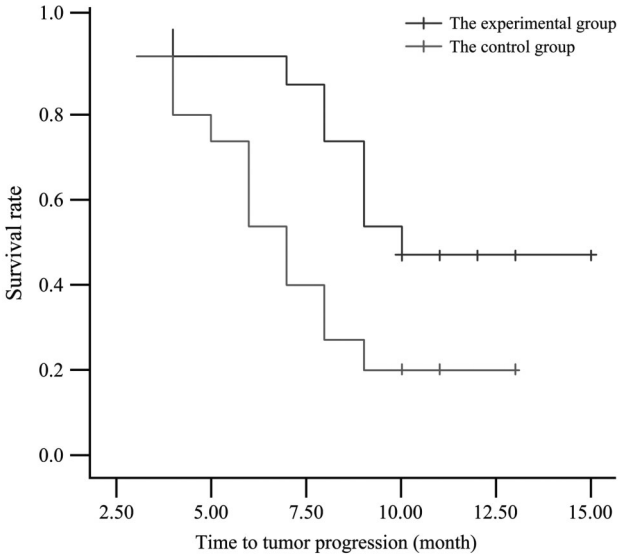

Figure 1. — Disease progression curves of the experimental and control groups.

chemotherapy were stopped for five patients due to weak constitution. Bevacizumab was stopped in one patient because of adverse reactions, and was stopped in two patients for economic reasons. In these 15 patients, the average duration of bevacizumab plus chemotherapy was 2.6 cycles. In the control group, two patients received only four cycles of chemotherapy due to adverse reactions; the remaining 13 patients completed six cycles of chemotherapy.

Short-term curative effect

The patients did not experience complete remission. Four patients in the experimental group had partial remission, seven had stable disease, and four had disease progression. The effective rate was 26.7% (4/15) and the disease control rate was 73.3% (11/15). Two patients in the control group had partial remission, three had stable disease, and ten had disease progression. The effective rate was 13.3% (2/15) and the disease control rate was 33.3% (5/15). The effective rates of the two groups were similar and not statistically different; the disease control rate of the experimental group was significantly higher than that of the control group ($p < 0.05$) (Table 2).

Time to tumour progression (TTP)

During the follow-up period, disease progression was observed in eight cases in the experimental group and in 12 cases in the control group. The median survival time of the experimental and control groups was ten months and seven months, respectively ($p = 0.023$) (Figure 1).

Adverse reactions

The predominant adverse reactions in the 30 patients were nausea, vomiting, fatigue, and myelosuppression; no patient experienced level 4 adverse reactions. The main adverse reactions associated with bevacizumab were hypertension, proteinuria, and bleeding; the incidence rates of the experimental and control groups was not significantly different ($p > 0.05$) (Table 3).

Table 3. — *Comparisons of adverse reactions in the two groups [n (%)].*

	Cases	Hypertension			Proteinuria		Bleeding		Thrombus	
		Level 1	Level 2	Level 3	Level 1	Level 2	Level 1	Level 2	Level 1	Level 2
Experimental group	15	2 (13)	1 (7)	1 (7)	1 (7)	1 (7)	3 (20)	2 (13)	1 (7)	0
Control group	15	2 (13)	0	0	0	0	1	0	0	0
x^2 value		0.833			2.143		3.333		1.034	
p value		0.361			0.143		0.068		0.309	

Discussion

Currently, the main treatment methods for recurrent and metastatic cervical cancer include radiotherapy and chemotherapy. If a patient develops recurrent and metastatic cervical cancer at the original radiotherapy site shortly after primary radiotherapy, secondary radiotherapy would be unacceptable. If a patient develops an unrespectable tumour due to wide neoplasm invasiveness, chemotherapy would be the only therapeutic regimen. The chemotherapy regimen of paclitaxel combined with cisplatin formulated by the United States Gynaecologic Oncology Group (GOG) is the currently recognised standard chemotherapy for metastatic or relapsed cervical cancer [3]. However, the choice of chemotherapic drugs is limited and the effective rate of chemotherapy is low [4].

With the development of targeting drugs in recent years, antineoplastic treatment with bevacizumab has garnered much attention, bringing with it new hope for palliative treatment. Bevacizumab is a recombinant humanised monoclonal antibody that can selectively bind to vascular endothelial growth factor (VEGF) and then block its biological activity, inhibiting the binding of VEGF with its receptors in endothelial cells, such as Flt-1 and kinase insert domain receptor (KDR), decreasing tumour angiogenesis, thus inhibiting tumour growth [5]. Bevacizumab has broad anti-tumour activity against a variety of human tumours, including colon cancer, non-small cell lung cancer, ovarian cancer, and breast cancer, and performed well in clinical trials [6-9].

Bevacizumab has been gradually introduced in the treatment of cervical cancer. Wright *et al*. reported up to 67% disease control for combined bevacizumab and 5-fluorouracil (5-FU), and the median overall survival was 4.3 months [10]. According to the interim analysis results of the GOG 240 study, Stage IVB patients and patients with recurrent or metastatic cervical cancer who received bevacizumab had increased median overall survival of about four months, where the median overall survival duration was 17 months, and there was 48% response rate and 29% reduced mortality [11]. Another multi-centre experiment reported that bevacizumab led to better tumour progression-free survival, where 24% of patients survived for more than six months, the median overall survival period was 7.29 months, and the drug response rate was 10.9% [12].

The present authors retrospectively studied 30 patients with recurrent and metastatic cervical cancer. In the experimental group, the effective rate of bevacizumab combined with chemotherapy was 26.7%, which was not statistically different from the control group. It is likely because patients in the experimental group already had rapidly developed disease; there was even recurrent tumour progression in three patients. However, the disease control rate of bevacizumab combined with chemotherapy was 73.3%, which was significantly higher than that of the control group (33.3%). In the experimental group, the median overall survival of the experimental group was three months, longer than that of the control group. Evidently, bevacizumab performs better for improving symptoms and delaying disease progression.

Adverse reactions to bevacizumab mainly include gastrointestinal perforation and haemorrhage, hypertension, fistula, pulmonary haemorrhage, thromboembolism, and proteinuria [13-14]. The GOG 240 study showed that patients who received bevacizumab were more susceptible to level 3 and 4 adverse effects, including haemorrhage (5%), thromboembolism (9%), and gastrointestinal fistula (9%) [11]. In this study, the main bevacizumab-related adverse reactions in patients in the experimental group were hypertension, proteinuria, and haemorrhage. There were few level 3 and 4 adverse reactions, i.e. there was one case of hypertension (7%), three cases of mild hypertension (20%), two cases of mild proteinuria (14%), five cases of mild haemorrhage (two vaginal and three rectal), and one case of thromboembolism (7%). The incidences of the adverse reactions were similar to that in the control group. The high rate of haemorrhages may have been due to the combined factor of haemorrhage after radiotherapy, while other mild adverse reactions may have been due to the younger age of the experimental group. In addition, selecting patients with suspicious factors (e.g. haemorrhagic tendency) to avoid using bevacizumab can decrease the incidence of related adverse reactions. The small sample size is another important factor in the incidence rate of adverse reactions.

In conclusion, combined bevacizumab and chemotherapy is a feasible regimen for treating intractable cervical cancer. This regimen has a superior disease control rate and advantages in that it improves symptoms and delays disease progression. Patients receiving this treatment regimen had good drug tolerance, low incidence of the more serious adverse reactions, and generally milder adverse reactions. The sample size of this study is small, but acts as a reference for the treatment of metastatic or relapsed cervical cancer. The authors recommend that the regimen be used for larger case cohorts in prospective studies.

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