Available online at www.sciencedirect.com

ScienceDirect

Chronic Diseases and Translational Medicine 1 (2015) 158−162

www.keaipublishing.com/en/journals/cdtm/

www.cdatm.org

Original article

Clinical observation and therapeutic evaluation of intravenous pump of recombinant human endostatin combined with TP regimen in treating patients with advanced ovarian cancer

Chi Zhang, Wen-Ying Deng, Ning Li, Su-Xia Luo*

Department of Internal Medicine-Oncology, Henan Cancer Hospital, The Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou 450000, China

Received 6 April 2015

Available online 9 October 2015

Abstract

Objectives: To observe the curative effects and adverse reactions of recombinant human (rh)-endostatin injection combined with a TP regimen for treating patients with advanced ovarian cancer.

Methods: Fifty-four patients with pathologically confirmed ovarian cancer were randomly divided into a combined treatment (intravenous pump of rh-endostatin + TP regimen) group and a control (single chemotherapy) group, twenty-seven patients in each group. All patients were given a conventional CT examination. The level of vascular endothelial growth factor (VEGF), the size of tumor before treatment, after 2 cycles and after 4 cycles of treatment were determined for the comparison of curative effects and adverse reactions.

Results: The effective rate was 37.0% (10/27) and disease control rate was 63.0% (17/27) in the combined treatment group after 2 cycles of treatment. The effective rate was 25.9% (7/27) and disease control rate was 63.0% (17/27) in the control group. The comparison between these two groups showed no significant differences ($P > 0.05$). The effective rate was 63.0% (17/27) and disease control rate was 92.6% (25/27) in the combined treatment group after 4 cycles of treatment. The effective rate was 29.6% (8/27) and disease control rate was 63.0% (17/27) in the control group. The effective rate and disease control rate between these two groups after 4 cycles of treatment showed significant differences ($P < 0.05$). The incidences of cardiovascular toxicity, myelosuppression, sore muscles and joints, alopecia and gastrointestinal reaction was not significantly different between two groups ($P > 0.05$).

Conclusion: The pump delivery of rh-endostatin can down-regulate the expression of VEGF in ovarian cancer and has the better curative effect and slighter adverse reactions.

* Corresponding author. Tel.: +86 371 65587697.

E-mail address: zhangc0923@163.com (S.-X. Luo).

Peer review under responsibility of Chinese Medical Association.

Production and Hosting by Elsevier on behalf of KeAi

http://dx.doi.org/10.1016/j.cdtm.2015.08.003

Keywords: Ovarian cancer; Recombinant human endostatin; Intravenous pump; Vascular endothelial growth factor; Angiogenesis

Introduction

Ovarian cancer is one of the most common malignant tumors; its incidence ranks third among the malignant tumors of the female genital system and the death rate is at the top of the gynecologic cancers and increases year by year.[1,2] Tumors can grow fast, invade surrounding tissues and metastasize to distant sites through entering the blood circulation only after the formation of new vessels.[3] Endostatin is an endogenous angiogenesis inhibiting factor, based on which recombinant human (rh)-endostatin, a new artificially synthesized targeted drug for anti-angiogenesis are modeled, and it has synergistic effects when combined with chemotherapeutics.[4,5] We observed and analyzed the efficacy of continuous pump delivery of rh-endostain with chemotherapy and chemotherapy alone to investigate a new clinical approach and the results are as follows.

Materials and methods

Case selection

Inclusion criteria: Patients with ovarian cancer confirmed by pathology and/or cytology; patients who had objective measurable primary lesions; stage IV before treatment according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO) in 2006; generally Eastern Cooperative Oncology Group (ECOG) scores are 0−2; the examination indexes confirm chemotherapeutic indications; no dysfunction of primary organs; drug discontinuance for more than 4 weeks in case of a history of use of other chemotherapeutics; an expected survival time $\geq$3 months; patients who were willing to accept this treatment plan and showed good compliance. Exclusion criteria: patients who had no measurable tumor lesions; pregnant and lactating women; patients with metastatic tumor to the central nervous system who did not get effective control; patients who did not complete the treatment course of chemotherapy; patients who did not have a CT examination.

General data

A total of 54 patients from October 2012 to January 2014 were enrolled for a forward-looking, randomized, and controlled clinical trial and randomly divided into a combined treatment group and a control group according to the ratio of 1:1. All 54 cases were evaluated. Age, performance status, clinical stage, and the pathological pattern between the two groups were comparable ($P > 0.05$) (Table 1).

Treatment methods

The combined treatment group received an intravenous pump to deliver the rh-endostatin along with the TP regimen: intravenous drip of paclitaxel and cisplatin on the first day of each cycle, 75 mg/m^2 and 135 mg/m^2, respectively, repeated every 21 days. The control group was given the TP regimen only. The above plan required completing at least four cycles.

VEGF detection method

Venous blood (10 ml) was drawn before treatment and after treatment. An enzyme-linked immunosorbent assay (ELISA) was employed to detect the levels of VEGF. The above procedures were completed by a supervising technician according to instruction under strict quality control.

Table 1
General data of patients with ovarian cancer between the two groups (*n*).

Clinical data	Combined treatment group	Control group	*P*-value
Pathological pattern			>0.05
Serous adenocarcinoma	25	26	
Mucinous adenocacinoma	2	1	
Clinical stages			>0.05
IIIc	3	5	
IV	24	22	
ECOG score			>0.05
0−1	21	24	
2	6	3	

ECOG: Eastern Cooperative Oncology Group.

Observational indexes

The short-term efficacy of the two groups was observed. Conventional CT examinations for the size of tumors were performed. The level of VEGF and the size of tumors were determined for comparison before treatment, after 2 cycles, and after 4 cycles of treatment.

Evaluation criterion

The size of the tumor lesion was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) and divided into complete remission (CR), partial remission (PR), stability of disease (SD), and progression of disease (PD). The remission rate (RR) = CR + PR, and total stability rate (TSR) = CR + PR + SD. A CT examination was performed one week before chemotherapy and one week after the completion of the second and fourth cycles. Security indexes were evaluated by WHO antitumor drug acute and subacute toxicity and grading standard.

Statistical data analysis

The SPSS17.0 software (Chicago IL, USA) was used for data analysis. A χ^2 test was used for comparison of the two groups and a paired t test for the differences between before and after treatment. $P < 0.05$ was considered to be statistically significant.

Results

Short-term efficacy and safety

Short-term efficacy: There was no CR in patients of either group after 2 cycles of treatment. Of 27 patients in the combined treatment group, 10 patients had a PR, 7 SD, and 10 PD; the RR was 37.0% (10/27) and the TSR was 63.0% (17/27). There were 7 PR, 10 SD, and 10 PD in the control group; the RR was 25.9% (7/27) and the TSR was 63.0% (17/27). Of 27 patients in the combined treatment group after 4 cycles of treatment there were 3 patients who had CR, 14 PR, 8 SD, and 2 PD; the RR was 63.0% (17/27), TSR was 92.6% (25/27). There were 0 CR, 8 PR, 9 SD, and 10 PD in the control group; the RR was 29.6% (8/27) and the TSR was 63.0% (17/27). Both the RR and TSR of combined treatment group were higher than in the control group after 4 cycles of treatment and the differences were significant ($P < 0.05$) (Table 2).

Safety evaluation: The adverse reactions of 54 patients can be evaluated and were mainly manifested as alopecia, sore muscles and joints, and gastrointestinal reactions, but there were no significant differences between the two groups ($P > 0.05$). In addition, there were 5 cases of electrocardiogram (ECG) changes marked by T wave change, a slighter degree of ST-segment depression, and nodal tachycardia, but the symptoms returned to normal after drug discontinuance or symptomatic treatment.

Comparison of the level of VEGF between two groups

There were no statistically significant differences before treatment between the two groups ($P > 0.05$). The level of VEGF after treatment in both groups significantly decreased ($P < 0.01$). There were significantly

Table 3
Comparison of the level of VEGF between the two groups (mean ± SD).

Group	Time	VEGF (pg/ml)
Combined treatment group ($n = 27$)	Treatment before	685.56 ± 41.28
	After 2 cycles of treatment	528.09 ± 53.08[ab]
	After 4 cycles of treatment	389.64 ± 55.17[ac]
Control group ($n = 27$)	Treatment before	717.93 ± 48.27
	After 2 cycles of treatment	568.43 ± 56.19*
	After 4 cycles of treatment	438.86 ± 42.66*

Compared with treatment before, [a]$P < 0.01$; compared with control group after 2 cycles of treatment, [b]$P < 0.05$; Compared with control group after 4 cycles of treatment, [c]$P < 0.05$. SD: standard deviation.

Table 2
Comparison of the short-term efficacy between the two groups (n, %).

Groups	CR	PR	SD	PD	RR	TSR
Combined treatment group ($n = 27$)						
2 cycles	0 (0)	10 (37.0)	7 (25.9)	10 (37.0)	10 (37.0)[a]	17 (63.0)
4 cycles	3 (11.1)	14 (51.6)	8 (29.6)	2 (7.4)	17 (63.0)	25 (92.6)
Control group ($n = 27$)						
2 cycles	0 (0)	7 (25.9)	10 (37.0)	10 (37.0)	7 (25.9)†	17 (63.0)
4 cycles	0 (0)	8 (29.6)	9 (33.3)	10 (37.0)	8 (29.6)	17 (63.0)

Compared with the control group after 2 cycles of treatment, [a]$P > 0.05$; compared with control group after 4 cycles of treatment, †$P < 0.05$. CR: complete remission; PR: partial remission; SD: stability of disease; PD: progression of disease; RR: remission rate; TSR: total stability rate.

different ($P < 0.05$) between the two groups after 2 cycles of treatment. After 4 cycles of treatment, the VEGF level in the trial group was significantly lower than in the control group ($P < 0.01$) (Table 3).

Discussion

Most ovarian cancers are occult, about 75% patients have been found with advanced disease. For advanced ovarian cancer, cytoreductive surgery combined with chemotherapy, usually platinum/paclitaxel, can temporarily alleviate the condition, but the recurrence rate is as high as 85%.[6] Therefore, to explore a new treatment of high specificity, limited side effects, and with acceptable patient-tolerance is particularly important. In recent years, a rapid development of molecular targeted therapy for the treatment of advanced ovarian cancer at home and abroad has ushered in a new era.

Angiogenesis refers to the process of sprouting a system of new blood vessels, mainly blood capillaries, based on the existed microvascular bed. Under normal physiological conditions, angiogenesis occurs only in embryonic development and in the tissue injury repair period, while the aberrant angiogenesis is one of the pathological changes seen in tumors.[2] Angiogenesis is tightly regulated by a variety of angiogenic factors and angiogenesis inhibitors, including VEGF and its receptor (VEGFR), considered to be the strongest and the most specific key regulatory factors. It demonstrated that the VEGF expression in the tumor was lower in malignant tumors, borderline tumors, and benign tumors, and in lymph node metastasis it is significantly higher than in those without lymph node metastasis.[7] The VEGF expression in ovarian cancer is significantly higher than in normal ovarian tissue and benign ovarian tumors, suggesting that VEGF plays a key role in the development and progression of ovarian cancer.[8] These findings provide evidence for treating ovarian cancer by blocking VEGF expression. To determine the efficacy of anti-tumor angiogenesis therapy, there must be effective chemotherapy to decrease the tumor burden, and the activity of tumor was significantly decreased. The use of anti-tumor angiogenesis therapy can block tumor angiogenesis, reduce the vascular supply of the tumor, synergize with chemotherapy and prolong its effective time.[3] Bevacizumab is a new molecular targeted drugs for anti-angiogenesis in phase II and III clinical trials for the treatment of refractory and recurrent ovarian cancer and ovarian cancer associated with malignant ascites.[9,10] It has achieved a definite therapeutic effect.

Rh-endosta is recombinant human rh-endostatin developed in our country with multiple target points, the mechanism of which is an anti-tumor effect by inhibiting the migration of vascular endothelial cells and blocking the tumor cell nutrient supply by acting on the microenvironment of tumor cells, thus achieving the purpose of inhibiting tumor growth or metastasis.[11] Kisker et al[12] found that with single rh-endostar intraperitoneal injection in a mouse, tumor tissue could be cleared within 2 h. The use of a mini-osmotic pump for continuous administration would make the plasma concentration stable for a long time, and 1/8 of the amount of the injected dose can achieve the same anti-tumor effect. This might be due to the ongoing administration of the intravenous infusion, continuous uniform liquid input, and extended infusion time that maintained a stable blood concentration so that there was drug continually presentation and neovascular endothelial cells were exposed to a better anti-tumor effect.

This study compared the rh-endostar intravenous infusion pump in combination with chemotherapy with chemotherapy alone and compared the experimental group and the control group, and the efficiency and the overall stable rate have increased, and the difference was significant ($P < 0.05$). Another study confirmed that rh-endostar can inhibit ovarian cancer cells and tumor growth, but rh-endostar intravenous infusion studies on ovarian cancer therapy are few.[13]

Meanwhile, this study also measured patients' serum VEGF levels. After both treatments, serum VEGF levels were significantly lower than before ($P < 0.05$), which was consistent with some other findings that chemotherapy reduced the tumor burden and decreased VEGF levels.[14,15] This study found that after four cycles of treatment, serum VEGF levels in the experimental group decreased significantly more than in the control group. This is evidence of rh-endostar's anti-angiogenic effect via inhibition of VEGF expression. The therapeutic effect may be due to the anti-tumor effect of rh-endostar showing significant effect-time dependence. With the extension of treatment time, the anti-tumor effect was significantly higher. From a retrospective analysis, the length of the rh-endostar treatment period and sustaining its use would bring greater benefits.[16] Kubota[17] showed that insufficient anti-angiogenic drugs of a therapeutic dose could lead to the rapid growth of blood vessels and limit the effect of inhibiting tumor growth. Therefore, the long period of rh-endostar application and subsequent maintenance therapy may bring greater benefits to patients.

In conclusion, rh-endostatin intravenous infusion combined with the TP regimen can enhance the

efficacy of patients with advanced ovarian cancer and reduce the adverse reactions. Further study also needs long-term follow-up, a large-scale sample and a new standard for judging the clinical efficacy.

References

1. Gubbels JA, Claussen N, Kapur AK, Connor JP, Patankar MS. The detection, treatment and biology of epithelial ovarian cancer. *J Ovarian Res*. 2010;3:8.
2. Jemal A, Siegel R, Xu JQ, Ward E. Cancer statistics. *CA Cancer J Clin*. 2010;2010:277–300.
3. Folkman J. Angiogenesis: an organizing principle for drug discovery? *Nat Rev Drug Discov*. 2007;6:273–286.
4. Ohlund D, Ardnor B, Oman M, Naredi P, Sund M. Expression pattern and circulating levels of endostatin in patients with pancreas cancer. *Int J Cancer*. 2008;122:2805–2810.
5. Cao DD, Ge W, Wang HM, Zhang L, Zheng YF, Zhang JZ. Efficacy and safety of rh-endostain combined with chemotherapy versus chemotherapy alone for advanced NSCLC: a meta analysis review. *Chin J Lung Cancer (Zhongguo Fei Ai Za Zhi)*. 2011;14:404–413.
6. Krasner C, Duska L. Management of women with newly diagnosed ovarian cancer. *Semin Oncol*. 2009;36:91–105.
7. Li X, Liu B, Xiao J, et al. Roles of VEGF-C and Smad4 in the lymphangiogenesis, lymphatic metastasis and prognosis in colon cancer. *J Gastrointest Surg*. 2011;15:2001–2010.
8. Li L, Wang LM, Zhang W, Tang BJ, Zhang JQ, Song HL. Correlation of serum VEGF levels with clinical stage, therapy efficacy, tumor metastasis and patient survival in ovarian cancer. *Anticancer Res*. 2002;24:1973–1979.
9. Richard TP, Don SD, Stephen AC, et al. Phase II study of carboplatin, paclitaxel, and bevacizumab with maintenance bevacizumab as first-Line chemotherapy for advanced mullerian tumors. *J Clin Oncol*. 2010;28:154–159.
10. Aghajanian C. The role of bevacizumab in ovarian cancer-an evolving story. *Gynecol Oncol*. 2006;102:131–133.
11. Han B, Xiu Q, Wang H, et al. A multicenter, randomized, double-blind, placebo controlled study to evaluate the efficacy of paclitaxel-carboplatin alone or with endostar for advanced non-small cell lung cancer. *J Thorac Oncol*. 2011;6:1104–1109.
12. Kisker O, Becker CM, Prox D, et al. Continuous administration of endotatin by intraperitoneally implanted osmotic pump improves the efficacy and potency of therapy in a mouse xenograft tumor model. *Cancer Res*. 2011;6l:7669–7674.
13. Xin G, Du J, Zhu L, Yu YH, Li Y, Liu PS. Different anti-tumor effects for various regimens of endostar plus cisplatin in ovarian cancer. *Zhonghua Yixue Za Zhi*. 2011;91:3367–3370.
14. Townsley C, Oza A. Antiangiogenic therapies in ovarian cancer. *Therapy*. 2010;7:277–284.
15. Jazaeri AA, Slack-Davis JK. The promise of antiangiogenic therapy for ovarian cancer. *Cancer Biol Ther*. 2009;8:2273–2274.
16. Jiang XD, Dai P, Wu J, Song DA, Yu JM. The recombinant human endostatin improve the blood perfusion and hypoxia in non-small cell lung cancer. *Chin J Geriatrics*. 2011;30:737–741.
17. Kubota Y. Tumor angiogenesis and anti-angiogenic therapy. *Keio J Med*. 2012;61:47–56.

Edited by Xiu-Yuan Hao