SPANDIDOS PUBLICATIONS

MOLECULAR AND CLINICAL ONCOLOGY 4: 245-248, 2016

Curative effect of bevacizumab combined with chemotherapy in advanced or recurrent uterine sarcoma

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Received July 24, 2015; Accepted November 23, 2015

DOI: 10.3892/mco.2015.709

Abstract. The aim of this study was to investigate the clinical effect of bevacizumab (BEV) combined with chemotherapy in advanced or recurrent uterine sarcoma. The clinical data of 4 patients with advanced or recurrenct uterine sarcoma, who received treatment with BEV combined with chemotherapy in our hospital between May, 2006 and May, 2014, were retrospectively analyzed. We estimated the chemotherapy response rate [complete response (CR) + partial response (PR)], clinical benefit rate [CR + PR+ stable disease (SD)], progression-free survival (PFS) and overall survival (OS), and evaluated treatment safety and toxicity reactions. Of the 4 patients, 1 achieved CR, with a disease-free survival time of 96 months; 1 achieved PR, with a PFS of 13 months and an OS of 25 months; 1 achieved SD, with a PFS of 9 months and an OS of 24 months; and 1 developed progressive disease, with a PFS of 3 months and an OS of 9 months. The response rate (CR+PR) was 50%, and the clinical benefit rate (CR+PR+SD) was 75%. Treatment-related adverse reactions occurred in all 4 patients, including bone marrow suppression and gastrointestinal reactions. Of the 4 patients, 1 developed grade 4 bone marrow suppression (thrombocytopenia), whereas the remaining 3 patients developed grade 2 bone marrow suppression (leukopenia). Of the 4 cases, 2 developed grade 2 gastrointestinal reactions, and the remaining 2 patients grade 1 gastrointestinal reactions. Therefore, BEV combined with chemotherapy was able to effectively control advanced or recurrent uterine sarcoma, was well-tolerated, and is considered to be a safe and effective candidate treatment for this type of tumor.

Introduction

Uterine sarcoma is a rare malignant tumor of the female reproductive system. The incidence of uterine sarcoma among women is only 1.23-1.70/100,000 (1,2), comprising 1-3% of gynecological malignant tumors and 3.0-5.0% of malignant tumors of the uterine body (3). Uterine sarcoma is a highly aggressive malignancy; even if treated at its early stages, patients often develop local recurrence and distant metastasis. Total hysterectomy is the standard treatment for early-stage uterine sarcoma. There is currently no standard therapy for advanced or recurrent uterine sarcomas, but chemotherapy is the preferred approach. However, chemotherapy only achieves a 30% response rate in advanced or recurrent uterine leiomyosarcomas (3). Therefore, it is crucial to investigate other medications and therapeutic regimens for advanced or recurrent uterine sarcomas. This study retrospectively analyzed 4 patients with advanced or recurrent uterine sarcoma who were treated with bevacizumab (BEV) combined with chemotherapy in our hospital between May, 2006 and May, 2014, with the aim to determine the efficacy of this combination in uterine sarcoma.

Patients and methods

Patient characteristics. We retrospectively analyzed the clinical data of 4 patients with advanced or recurrent refractory uterine sarcoma who were treated with BEV combined with chemotherapy in our hospital between May, 2006 and May, 2014. Of the 4 cases, 2 had advanced-stage (IV) persistent uterine sarcoma (1 patient received BEV as first-line treatment and 1 patient as second-line treatment), whereas the remaining 2 patients had recurrent uterine sarcoma (1 patient received BEV as second-line treatment and 1 patient as third-line treatment). The pathological types were undifferentiated sarcoma of the uterus in 1 case, uterine carcinosarcoma in 2 cases and uterine leiomyosarcoma in 1 case. The mean age of the patients was 61 years (range, 44-79 years) and the Karnofsky performance status score was ≥80 prior to treatment. The patient characteristics are summarized in Table I.

Therapeutic method. BEV (Avastin; Genentech, South San Francisco, USA) 7.5 mg/kg with 100 ml 0.9% NaCl, 1 h prior to or following chemotherapy, as an intravenous drip over 60 min, repeated every 2 or 3 weeks. The chemotherapeutic drugs included dacarbazine (DTIC), cisplatin (DDP), etoposide (VP-16), adriamycin, paclitaxel and carboplatin. The patients received 4-12 cycles of BEV treatment, with a mean

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Key words: uterine sarcomas, bevacizumab, combined chemotherapy

of 8.3 cycles. The completed cycles of BEV combined with chemotherapy were 4-8, with a mean of 6 cycles. One patient received BEV 7.5 mg/kg as an intravenous drip every 2 weeks, for a total of 12 times (2 BEV administrations per 4-week cycle); the other 3 patients received BEV 7.5 mg/kg as an intravenous drip every 3 weeks, synchronously combined with chemotherapy. However, 1 patient was unable to tolerate treatment due to grade 4 bone marrow suppression (thrombocytopenia, platelet count 13 G/l) after 8 cycles of chemotherapy, and thus she was administered single-agent BEV maintenance therapy for 3 cycles (once every 3 weeks).

Therapeutic evaluation. All the patients were evaluated after receiving >2 cycles of treatment with BEV according to the World Health Organisation Response Evaluation Criteria In Solid Tumors, version 1.1 (2009). Response to treatment was classified as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). Chemotherapy response rate (CR+PR) and clinical benefit rate (CR+PR+SD) were also evaluated.

Toxicity evaluation. The adverse reactions to BEV combined with chemotherapy were evaluated according to the toxicity evaluation standards of the National Cancer Institute. Cardiovascular toxicity was evaluated with a sphygmomanometer, electrocardiogram (ECG) monitor and ECG examination; urinary system toxicity was evaluated with routine urine and kidney function tests. Toxicity was graded as 0-4.

Follow-up. The patients were followed up in an outpatient setting or telephonically, until death or until the last follow-up in October, 2014.

Statistical analysis. Statistical analysis was performed by SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). The x2 inspection was used for count data and PFS was estimated with the Kaplan Meier method, using the log-rank test. Of the 4 patients, 3 had succumbed to disease progression at the last follow-up, with a progression-free survival (PFS) of 13, 9 and 3 months. The PFS of the surviving patient was 96 months. The overall survival (OS) of the deceased patients was 25, 24 and 9 months, and of the surviving patient 96 months (Table I).

Results

Objective effect. The total chemotherapy response rate of BEV combined with chemotherapy (CR+PR) was 50% (2/4) and the clinical benefit rate was 75% (3/4). The clinical evaluation of the 4 patients was CR in 1 case, PR in 1 case, SD in 1 case and PD in 1 case. The mean PFS was 30.25 months and the mean OS 38.5 months. The one patient who achieved CR survived for 96 months and remained alive at the last follow-up; her computed tomography scans prior to and following treatment are shown in Fig. 1.

Toxicity reaction. The treatment-related adverse reactions mainly included bone marrow suppression; 1 patient had grade 4 thrombocytopenia [platelet (PLT) count 13 G/l], while the remaining 3 patients had grade 2 bone marrow suppression (leukopenia); the non-hematological toxicities included

Table I. Characteristics of the 4 patients.

N	Age (years)	Initial treatment	Pathology	Prior chemotherapy	Usage of BEV	Combined chemotherapy	RECIST	Toxicity (BM/ suppression GI reactions)	Follow-up PFS/OS (months)	Outcome
1	44	TAH + BSO	Undifferentiated endometrial sarcoma	IFO + Doxil	7.5 mg/kg every 2 weeks, 12 times	DTIC + VP-16 + DDP	CR	II/II	96/96	Alive
2	57	TAH + BSO	Carcinosarcoma	PEI, TI	7.5 mg/kg every 3 weeks, 11 times	DTIC + VP-16 + DDP	PR	IV/I	13/25	Deseased
3	63	TAH + BSO	Leiomyosarcoma	EI	7.5 mg/kg every 3 weeks, 4 times	DTIC + EPI + DDP	SD	II/II	9/24	Deseased
4	79	TAH + BSO	Carcinosarcoma	-	7.5 mg/kg every 3 weeks, 6 times	PC, IFO + EPI	PD	II/I	3/9	Deseased

BEV, bevacizumab; RECIST, Response Evaluation Criteria In Solid Tumors; BM, bone marrow; GI, gastrointestinal; PFS, progression-free survival; OS, overall survival; TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; IFO, ifosfamide; PEI, cisplatin, etoposide, and ifosfamide; TI, paclitaxel and ifosfamide; EI, epirubicin and ifosfamide; DTIC, dacarbazine; VP-16, etoposide; DDP, cisplatin; EPI, epirubicin; PC, paclitaxel and carboplatin; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

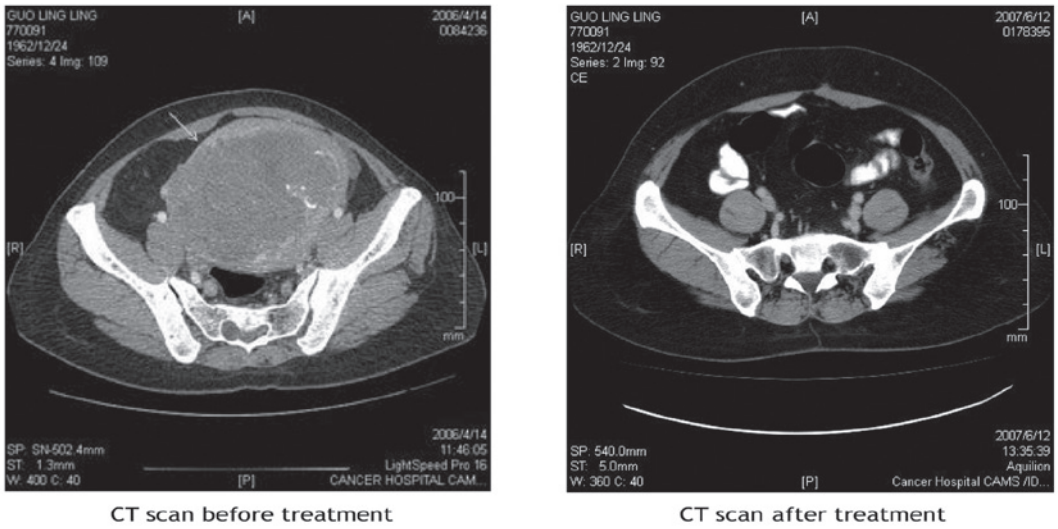

Figure 1. Pre- and post-treatment computed tomography (CT) scans of the surviving patient.

grade 2 gastrointestinal reactions in 2 patients and grade 1 in the remaining 2 patients.

Discussion

Uterine sarcomas are a group of heterogeneous malignant tumors derived from uterine mesenchymal tissue, and include leiomyosarcoma of the uterus, endometrial stromal sarcoma, uterine adenosarcoma and carcinosarcoma. At present, uterine carcinosarcoma is classified into endometrial carcinoma. The prognosis of uterine sarcoma is poor, with a 5-year survival rate of only 30% (4). Prognosis is poor, as this type of cancer may easily recur and metastasize following primary treatment. Furthermore, certain patients are not diagnosed until they are at an advanced stage (with distant metastasis), in which case the 5-year survival rate is <15% (5). The effect of treatment on persistent and/or recurrent uterine sarcomas is poor, particularly for patients who have recurred after first-line chemotherapy. When these patients receive >2 lines of chemotherapy, re-using mono- or combination chemotherapy (including ifosfamide, doxorubicin, cisplatin, topotecan, paclitaxel, docetaxel, gemcitabine and gemcitabine combined with docetaxel), the effectiveness of these regimens is only 5-27% (6-8). Several tumor treatment centers worldwide have been actively investigating treatment methods for uterine sarcomas, including novel chemotherapeutic drugs and molecular-targeted agents, but the results have not been satisfactory. Bernstein-Molho *et al* (9) reported that the efficiency rate was 0% with trabectedin as second- or third-line therapy for metastatic leiomyosarcoma, whereas the SD rate was 60%. Aghajanian *et al* (10) reported that the response rate with iniparib combined with paclitaxel and carboplatin (as first-line chemotherapy) was 23.5% (4/17) in late persisitent and/or recurrent uterine sarcomas, but 35.3% (6/17) of the patients only achieved SD. Hensley *et al* (11) reported that, according to the Gynecologic Oncology Group (GOG), the results of sunitinib used as single-drug therapy in a phase II clinical study to treat persistent and/or recurrent uterine sarcomas achieved a PR rate of 8.7% (2/23); the rate of grade 3 hematological toxicity was 17.4% and of grade 3-4 non-hematological toxicity ≤30% (11). Gynecological oncologists must continuously investigate effective agents for the treatment of uterine sarcomas, as the availability of relevant data is currently limited.

Inhibition of the vascular endothelial growth factor (VEGF) pathway has been used in cancer treatment in recent years. BEV is a type of humanized restructuring anti-VEGF monoclonal antibody, and a number of researchers have already confirmed that BEV is effective in treating a variety of solid tumors, such as colorectal, lung, breast and ovarian cancer; however, very few reports have been published to date on BEV as treatment for uterine sarcomas and/or other soft tissue sarcomas. It was previously demonstrated that VEGF is strongly expressed in the epithelium and stroma of uterine carcinosarcomas (12), and GOG is currently conducting a phase III randomized clinical study (12) to assess the curative effect of gemcitabine combined with docetaxel, with or without BEV, in patients with advanced or recurrent uterine leiomyosarcomas (12). In the present study, 4 cases of uterine sarcomas received BEV combined with chemotherapy; 2 cases had advanced-stage disease (IV) and persistent uterine sarcoma (1 case received BEV as first-line and 1 case as second-line therapy), whereas the other 2 cases presented with recurrent uterine sarcomas post-treatment (1 case received BEV as second-line and 1 case as third-line therapy). The pathological tumor type was undifferentiated sarcoma of the uterus in 1 case, uterine carcinosarcoma in 2 cases and uterine leiomyosarcoma in 1 case. The patients received 4-12 cycles of BEV treatment, with a mean of 8.3 cycles. The completed cycles of BEV combined with chemotherapy were 4-8, with a mean of 6 cycles. One patient received BEV 7.5 mg/kg as an intravenous drip every 2 weeks, for a total of 12 times (2 BEV administrations per 4-week cycle); the other 3 patients received BEV 7.5 mg/kg as an intravenous drip every 3 weeks, synchronously combined with chemotherapy. However, 1 patient was unable to tolerate treatment due to grade 4 bone marrow suppression (thrombocytopenia, PLT count 13 G/l) after 8 cycles of chemotherapy, and thus she was administered single-agent BEV maintenance therapy for

3 cycles (once every 3 weeks). The clinical evaluation of the 4 patients was CR in 1 case, PR in 1 case, SD in 1 case and PD in 1 case. Cases 1 and 2 achieved CR and PR, respectively, and received >6 cycles of DTIC + VP-16 + DDP chemotherapy combined with BEV, with a PFS of 96 and 13 months, and an OS of 96 and 25 months, respectively. This is consistent with the results of Olawalye *et al* (13), who reported that a patient with recurrent uterine epithelioid angiosarcoma achieved CR following treatment with BEV combined with chemotherapy for 6 cycles; the patient exhibited a disease-free survival for 12 months until the time the report was published.

In our study, 1 patient (case 3) was evaluated as SD after 4 cycles of BEV combined with chemotherapy; the pelvic recurrence completely disappeared after treatment, and the multiple metastases in her lungs were also evaluated as SD, with a PFS of 9 months. The patient eventually succumbed to morbidities associated with changing the therapeutic regimen and tumor progression. These findings demonstrated that BEV combined with chemotherapy may be an effective second- and/or third-line therapy to treat advanced persistent (case 1) and recurrent (cases 2 and 3) uterine sarcomas, and that patients with persistent or recurrent uterine sarcomas may achieve CR with appropriate dosage and dosing intervals of BEV combined with the appropriate chemotherapy regimens, with a PFS of up to 96 months. Of the 4 patients, only 1 (case 4) was clinically evaluated as PD after BEV combined with chemotherapy as first-line therapy. This PD may be associated with the fact that the patient had been irradiated radically for cervical cancer prior to the development of uterine sarcomas; therefore, the patient's uterus and surrounding tissues may have developed fibrosis and resulted in a different vascular distribution and tumor formation compared with the patients who only received chemotherapy. Furthermore, the patient's sarcoma comprised complex components (leiomyosarcoma, chondrosarcoma and endometrial stromal sarcoma). Thus, this patient did not benefit from BEV treatment combined with chemotherapy.

Treatment-related adverse reactions were mainly bone marrow suppression and gastrointestinal reactions in all 4 patients who received a mean of 8.3 cycles of BEV therapy in the present study. Grade 4 thrombocytopenia (PLT count 13 G/l) was only observed in 1 patient (case 2) and may have been associated with several factors: The patient was elderly (63-years old) and received a total of 13 cycles of chemotherapy (3 lines), while the remaining 3 patients exhibited grade 2 bone marrow suppression (leukopenia). The main non-hematological toxicity was grade 2 gastrointestinal reactions in 2 patients and grade 1 in the remaining 2 patients. There were no severe adverse reactions to BEV, such as bowel perforation, bleeding or blood vessel embolism, high blood pressure, or severe proteinuria (14). Thus, it may be safe to use BEV combined with chemotherapy to treat advanced persistent and/or recurrent uterine sarcomas.

In conclusion, BEV combined with chemotherapy exhibits efficacy in the treatment of advanced or recurrent uterine sarcomas, with a tolerable toxicity profile. Treatment with BEV may achieve a CR, and potentially long-term disease-free survival, and may be considered as a safe and effective candidate regimen for advanced or recurrent uterine sarcomas, in addition to providing a theoretical basis for further clinical research involving larger samples.

Acknowledgements

This study was supported by the Gynecologic Oncology of Cancer Institute and Hospital, Chinese Academy of Medical Sciences.

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