Chemotherapy with low-dose bevacizumab and carboplatin in the treatment of a patient with recurrent cervical cancer

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Summary

Management of patients with recurrent or advanced cervical cancer is a challenge. Concurrent chemotherapy has become the mainstay of treatment and platinum remains the most effective single agent. Combinations of other agents have not demonstrated significant advantages. The application of angiogenesis inhibitors such as bevacizumab, an antibody inhibiting vascular endothelial growth factor, in metastatic or advanced cervical cancer remains to be evaluated. We present the case of a patient with platinum-resistant recurrent cervical cancer treated with low-dose bevacizumab and carboplatin, with resultant improved disease progression and tolerable toxicity profiles.

Key words: Bevacizumab; Cervical cancer; Metronomic.

Introduction

Carcinoma of the cervix is the second most common cancer among women worldwide, and was responsible for over 250,000 deaths in 2005 [1]. Surgery remains the primary treatment of early-stage cervical cancer, and locally advanced lesions are managed with concurrent chemoradiation. The recurrence rate of cervical cancer is 10% to 20% for FIGO Stages IB-IIA, and 50% to 70% in locally advanced Stage IIB-IVA disease [2]. Only 12% to 45% of patients with advanced stage (IIIA-IVB) disease completely respond to the primary treatment described above, compared to a complete response rate of 70% to 90% in early stages [2]. A low response rate and poor prognosis with a 1-year survival rate between 15% and 20% in patients with recurrent disease or pelvic metastases [3] remain ongoing problems in clinical practice.

The role of chemotherapy in cervical cancer has been proven [3], and concurrent chemoradiation therapy has become the standard treatment of patients with locally advanced or metastatic cervical cancer [4]. Of all the drugs tested, cisplatin is the only drug with sufficient response, and has been suggested as the standard for treatment [5]. There have also been many trials with combination therapies, but the results are not satisfactory. Thus, the development of new drugs is imperative. With an improved understanding of molecular events in tumor cells, targeted therapies have become an important modality in cancer treatment. Angiogenesis has been reported to be an important mechanism in cancer development, including cervical cancer [6-8].

Bevacizumab is a monoclonal antibody targeting vascular endothelial growth factor (VEGF) and has been shown to be effective in many solid malignancies [7]. Anti-angiogenesis is an appealing strategy for cervical cancer treatment, and there are several ongoing clinical trials. We herein report the case of a patient with advanced cervical cancer who was treated by the combination of low-dose bevacizumab and carboplatin, with encouraging clinical results.

Case Report

A 37-year-old Taiwanese woman (G2, P1) who worked in Korea had an abnormal Pap smear with atypical cells of undetermined significance in August 2006. Cervical biopsy revealed carcinoma in situ. Conization of the cervix done in September 2006 showed squamous cell carcinoma with invasion to 8 mm in depth, compatible with Stage IB1 disease. She underwent radical hysterectomy with bilateral pelvic lymph node dissection at a tertiary medical center in Taiwan in October 2006. Pathological examination demonstrated no lymph node involvement, but positive lymph-vascular space invasion and close margins. Thus, postoperative radiotherapy including whole pelvic radiation with a total dose of 5400 cGy and intravaginal brachytherapy with a total dose of 3000 cGy was delivered beginning November 2006. She received regular follow-up after treatment.

She developed low back pain in June 2007. A pap smear did not disclose evidence of recurrence; however, elevated anti-SCC (2.3 ng/ml) was noted. Computed tomography (CT) of the abdomen revealed paraaortic soft tissue masses and destruction of the L4 vertebra. Metastasis was proven by CT-guided biopsy, followed by palliative surgery with pedicle fixation, L3/4 laminectomy, and partial tumor excision for symptom relief in September 2007. Palliative radiotherapy for the residual metastatic lesions was advised.

The patient was then seen at our hospital for further management. Chemotherapy with weekly cisplatin (40 mg/m^2) was administered from October to November 2007. Her lower back pain improved and serum anti-SCC levels declined as shown in Figure 1.

Four months later, lower back pain and sciatica associated with elevation of anti-SCC recurred. CT of the abdomen and pelvis showed paraaortic soft tissue masses causing bony destruction of the L4 vertebra, suggesting recurrence. Weekly

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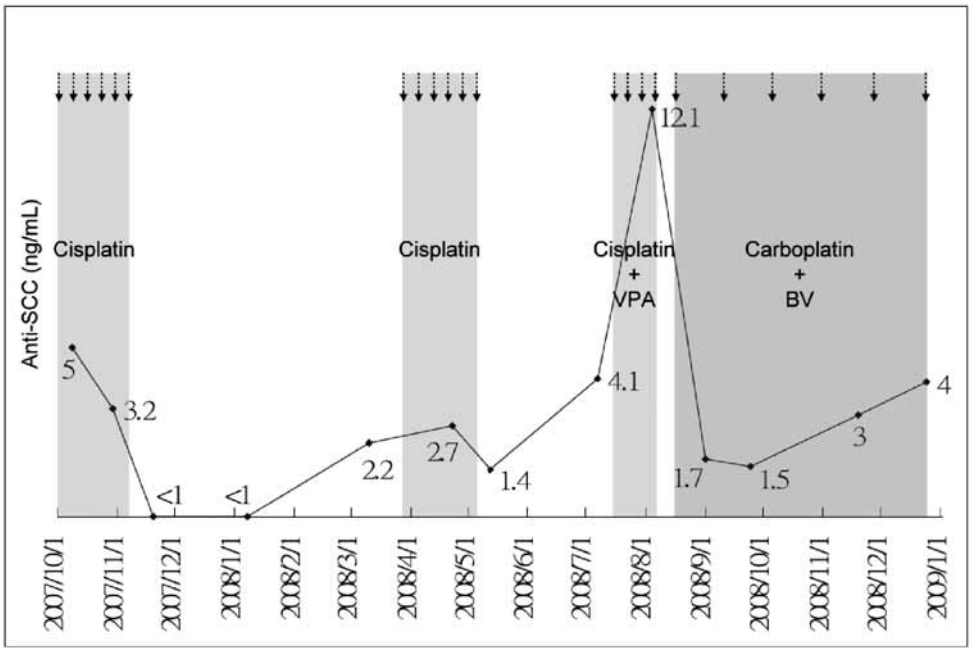

Figure 1. — Changes of anti-SCC in the course of treatment. VPA, valproic acid; BV, bevacizumab.

cisplatin for six cycles was administered again, with resultant mildly improved symptoms and declining anti-SCC (Figure 1).

Disease progression with worsening lower back pain, further destruction of L4 and L5 vertebrae, and elevation of anti-SCC was noted two months later. A histone deacetylase inhibitor, valproic acid, coupled with cisplatin for sensitization of chemoresistance was used for four weeks, which was ineffective as evidenced by a rising level of the tumor marker (Figure 1). A combination of low dose bevacizumab (3 mg/kg) and carboplatin (AUC = 5) every three weeks was tried. The response was dramatic with declining anti-SCC (Figure 1) and stable symptoms. Shrinkage of the paraaortic soft tissue mass was noted by CT four months later (Figure 2). Toxicity was assessed according to the National Cancer Institute's Common Toxicity Criteria, version 3.0, grade 1-2 leukopenia, grade 1-2 thrombocytopenia, and grade 2-3 anemia were noted, and overall, the regimen was well tolerated. However, disease progression with elevated anti-SCC, followed by worsening of pain developed again three months after the therapy. The patient received hospice care thereafter.

Discussion

Chemotherapy with single agent cisplatin at 50 mg/m^2 every three weeks has been used for advanced or recurrent cervical cancer with a response rate from 20% to 30% and overall survival of seven months [3]. No other single regimen has documented greater benefits than cisplatin. Carboplatin has also been tested in a phase II trial for recurrent or metastatic squamous carcinoma of the cervix, and showed a response rate of 15% and median progression-free survival of 3.4 months [9]. Combination therapy with cisplatin and topotecan was reported superior to single-agent cisplatin with response rates of 27% and 13%, median overall survival of 9.4 and 6.5 months, and median progression-free survival of 4.6 and 2.9 months, respectively [10]. Despite more common bone marrow suppression, this doublet did not worsen the quality of life [10]. Even so, the prognosis remains poor and identifying active chemotherapy regimens with tolerable adverse effects is of great importance to maximize the length and quality of life of these patients.

Angiogenesis has been proven to play an important role in solid malignancies. Increased angiogenesis contributes to the development and progression of cervical cancer, and is also associated with advanced disease and poor prognosis [8, 11]. The VEGF pathway is one of the major pathways involved in angiogenesis, and high VEGF expression was found to be associated with deep tumor invasion, pelvic node metastases, pelvic and distant failure, and impaired survival in cervical cancer patients [11].

With angiogenesis being a crucial pathway in cervical carcinogenesis and disease progression, the therapeutic strategy using the anti-VEGF antibody bevacizumab is theoretically rational. A number of phase II and III trials have documented the efficacy of bevacizumab for a variety of solid tumors [7]. In 2006, a retrospective study of bevacizumab combined with 5-fluorouracil or capecitabine in heavily pretreated patients with recurrent cervical cancer showed clinical benefit in 67% of the subjects, including one complete response, one partial response, and two patients with stable disease [12]. The progression-free interval of these four patients ranged from 2.5 to 5.9 months, suggesting potential activity in pretreated recurrent cervical cancer [12]. Since then, several phase II clinical trials of monotherapy or combination therapy with bevacizumab in cervical cancer have been initiated.

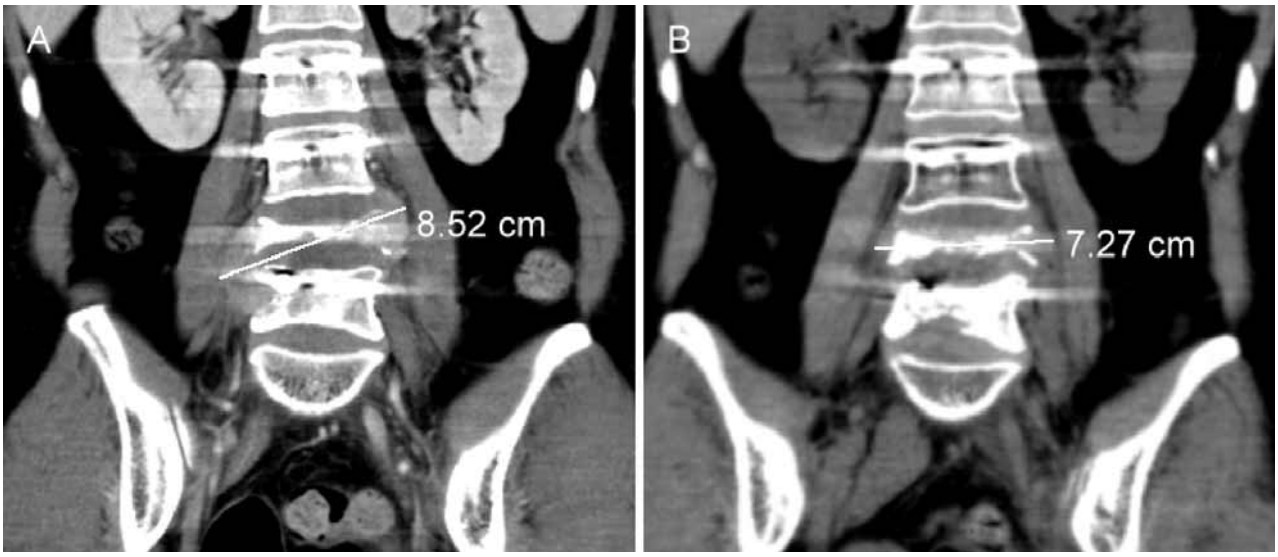

Figure 2. — CT films obtained before (A) and after (B) five cycles of chemotherapy with carboplatin and bevacizumab. The lesion is smaller but remains a stable disease after the treatment.

A recent report demonstrated an encouraging result using single agent bevacizumab at 15 mg/kg every 21 days in persistent or recurrent squamous cell carcinoma of the cervix [13]. Among the 46 patients enrolled, 23% survived without disease progression for at least six months, and 10.9% had a partial response. The median progression-free survival was 3.4 months, with a range of 2.53 to 4.53 months. However, many grade 3 or 4 adverse events were noted, including hematologic toxicity, hypertension, deep venous thrombosis, pulmonary embolus, and gastrointestinal and genitourinary/renal events. Additionally, one patient died of grade 5 infection, possibly due to the therapy [13].

Preclinical data have shown that bevacizumab not only has an anti-angiogenic effect, but may normalize tumor vasculature, thereby diminishing tumor hypoxia and promoting drug delivery [14]. Thus, combining an anti-angiogenic agent with cytotoxic chemotherapy is believed to enhance antitumor activity. Additionally, a new approach, metronomic chemotherapy, with low doses on a frequent schedule has demonstrated benefits in the treatment of several kinds of tumors. Unlike traditional chemotherapy using the 'maximum tolerated dose', this strategy provides not only efficacy, but reduced toxicity and improved quality of life.

In the present report, the combination of low-dose bevacizumab and carboplatin provided significant positive effects on symptoms, level of anti-SCC, and tumor size. The progression-free interval was approximately three months, comparable with the previously reported data of the trial, and this regimen was well tolerated with only minor hematologic toxicity. Recently, doubt has been cast on the application of traditional ways of measuring therapeutic responses in newly developed drugs [8, 15]. Surrogate biomarkers for therapeutic response may be needed for guidance regarding dose and schedule. Our report demonstrates that lower doses of bevacizumab in combination with carboplatin may work well in cervical cancer, an important implication considering the lower economic burden and toxicity.

With limited treatment options for advanced cervical cancer, we found low-dose bevacizumab combined with carboplatin to be possibly effective, with lower costs and side-effects than other options. Optimal dosing and markers for monitoring the treatment response using bevacizumab have not been well established. Further studies are warranted to investigate metronomic therapy using lower doses of bevacizumab and carboplatin in the setting of recurrent and advanced cervical cancer. The lower dose and lower cost of such a newly developed target therapy may help patients with cervical cancer, especially in developing countries.

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