Recurrent Small Cell Carcinoma of the Uterine Cervix Responding to Combined Therapy with Paclitaxel, Cisplatin, and Bevacizumab: A Case Report

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We report a patient with recurrent refractory small cell carcinoma of the uterine cervix, in whom combined therapy with paclitaxel, cisplatin, and bevacizumab (TP + Bev) was effective. Small cell cervical carcinoma is a rare malignancy and its outcome is reported to be poor. The patient was a 45-year-old woman who visited a local hospital with the chief complaint of irregular vaginal bleeding and was referred to our department. The results of a smear test and examination of a tissue biopsy specimen suggested small cell carcinoma. FIGO stage II A disease was diagnosed by MRI and CT. She underwent radical hysterectomy with bilateral adnexectomy, and pelvic and para-aortic lymph node dissection. Although postoperative adjuvant chemotherapy was performed, local recurrence was found at three years after surgery. She received radiation therapy to the whole pelvis, bilateral inguinal regions, and site of recurrence. However, multiple liver metastases were detected and the tumor was considered to be refractory. Subsequently, she received TP + Bev as systemic chemotherapy, after which the local recurrence disappeared and the liver metastases became smaller.

Key words: Bevacizumab, Uterine cervical cancer, Small cell carcinoma, Liver metastasis, Immunohistochemical analysis

INTRODUCTION

Small cell carcinoma of the uterine cervix is an aggressive subtype of uterine cervical carcinoma, in which lymph node metastasis and hematogenous metastasis can occur at an early stage and the outcome may be very poor. The 5-year survival rate was reported to be 36.8% in patients with Stage 1–2A disease (confined to the pelvic cavity) and 0% in patients with extensive metastases [1–2]. It is also difficult to treat recurrent small cell carcinoma, and the life expectancy of patients with recurrence is only 7–8 months [3].

In Japan, small cell carcinoma of the uterine cervix is diagnosed in 70–80 patients per year and is a rare histologic type that accounts for only 1.0–1.2% of cervical carcinoma [4]. Because it is a rare tumor, no prospective clinical study has yet been conducted to assess treatment for this disease.

Bevacizumab is a monoclonal antibody targeting vascular endothelial growth factor-A (VEGF-A). In Japan, the national health insurance scheme has covered use of bevacizumab combined with paclitaxel for treatment of advanced recurrent / refractory uterine cervical carcinoma since 2016. This indication was approved on the basis of the results of the GOG240 study, which was an international, collaborative, phase III study that evaluated the effect of adding bevacizumab to chemotherapy (paclitaxel + cisplatin or paclitaxel + topotecan) in patients with unresectable / refractory uterine cervical carcinoma. It was shown that the over-
0–1.50), and neuron-specific enolase (NSE) was 8.9 ng/ml (normal range: 0–16.3).

Small cell carcinoma was suspected from the results of a smear test and examination of a tissue biopsy showed malignancy. Therefore, MRI and CT were performed. MRI revealed an irregular, poorly-defined mass (15 mm in diameter) on the right side of the uterine cervix. On T2-weighted images, the mass contained a faint high signal intensity area, while it was isointense on T1-weighted images. On contrast images, enhancement of the lesion was slightly fainter than the surrounding parenchymal tissues, and invasion of the vaginal wall was observed. CT scans showed no distant metastasis. Therefore, the diagnosis was FIGO stage II A disease, and she underwent radical hysterectomy with bilateral adnexectomy, pelvic lymph node dissection, and para-aortic lymph node dissection.

Histopathological examination of the resected specimen showed a tumor measuring 15 × 10 mm with 7-mm invasion of the uterine wall. While lymph node metastasis was positive, no invasion of the parametrium was observed and the surgical margin was negative (Fig. 1).

Although a ductal component was observed in part of the tumor, most of the lesion consisted of small round cells that formed rosettes. Invasion of lymphatics adjacent to the tumor was observed. On immunohistochemical analysis, CD56 was positive, chromogranin A was positive, synaptophysin was positive, p16 was positive, VEGF was positive, and p55 was positive (in the small cell component). In addition, the SSTR2a score was 2 +, the MIB-1 index was 90%, and keratin (AE1/3 and CAM5.2) was positive (Fig. 2). Thus, the pathological diagnosis was FIGO stage II A2 small cell carcinoma of the uterine cervix (pT1b1N1M0). She received six cycles of etoposide + cisplatin therapy as postoperative adjuvant chemotherapy.

At three years after surgery, PET-CT showed increased uptake by a lesion with a long diameter of approximately 25 mm (SUVmax = 9.2) near the upper left side of the vaginal stump, and NSE was increased to 3.2 ng/ml. Therefore, local recurrence was diagnosed.

Radiation therapy was performed targeting the whole pelvis and the bilateral inguinal regions (45 Gy/25 fractions), as well as the recurrent tumor (12 Gy/5 fractions). However, NSE increased further to 160 ng/ml and multiple liver metastases were detected by PET (SUVmax = 20.2) at three months after initiation of radiation therapy. Therefore, the tumor was considered to be refractory.

Accordingly, systemic chemotherapy was initiated with TP + Bev (at thirty-nine months after surgery). Paclitaxel (175 mg/m²) was administered intravenously on Day 1 of each cycle, followed by cisplatin (50 mg/m²), with standard medications to suppress emesis and hypersensitivity. Bevacizumab (15 mg/kg) was also administered intravenously on Day 1. One cycle was performed every three weeks.

After four cycles of TP + Bev, NSE was normalized (10.3 ng/ml) and CT scans showed that the tumors had diminished. After eight cycles of TP + Bev, the local recurrence was no longer detected and some of the liver metastases also disappeared (Fig. 3), while the other liver tumors were reduced in size. TP + Bev was continued until Cycle 11 and was discontinued at the patient’s request. At two months after discontinuation, NSE increased to 164 ng/ml and enlargement of the liver metastases was observed. The patient is currently alive at 16 months after recurrence was detected.

DISCUSSION

Small cell carcinoma is known to have the potential for neuroendocrine differentiation and it is more often detected as a primary lung tumor than in the cervix. It was reported that small cell carcinoma accounts for only 1–6% of uterine cervical carcinoma, making it a rare disease, and that it is relatively more frequent among younger women in their 30s and 40s [4, 7]. It has been suggested that human papillomavirus (HPV) infection may be involved in the pathogenesis of small cell carcinoma of the cervix. In fact, Stoler et al. and Wolber et al. reported that HPV-16 and HPV-18, which are high-risk HPV types for uterine cervical carcinoma, were detected in ≥ 85% of small cell carcinomas of the cervix [8, 9].

In patients with small cell carcinoma of the cervix, distant metastasis and lymph node metastasis often occur at an early stage, while advanced recurrent disease is associated with a life expectancy of only 7–8 months, so the prognosis is very poor [3]. As with other types of cervical carcinoma, the initial symptom is usually vaginal bleeding. The present patient had irregular vaginal bleeding for a number of years, but cancer screening did not identify any abnormalities.

On histopathological examination using Grimelius staining, Ki-67 (MIB-1) was positive, synaptophysin was positive, p16 was positive (in the small cell component), in addition, the SSTR2a score was 2 +, VEGF was positive, CD56 was positive, chromogranin A was positive, and keratin (AE1/3 and CAM5.2) was positive (Fig. 2). Thus, the pathological diagnosis was FIGO stage II A2 small cell carcinoma of the cervix (pT1b1N1M0). She received six cycles of etoposide + cisplatin therapy as postoperative adjuvant chemotherapy.
Fig. 2 Histologic findings in uterine cervix.
   a) Most of the lesion was observed small round cells that formed rosettes. (Hematoxylin and Eosin staining, low power view)  
   b) chromogranin A  
   c) synaptophysin  
   d) VEGF (high power view).

Fig. 3 CT findings.
   a) Liver metastases at the time of relapse.
   b) Remarkable reduction of the metastasis to liver after the eight cycles of Paclitaxel + Cisplatin + Bevacizumab therapy.
stain and immunohistochemical techniques, small cell carcinoma is often positive for neuroendocrine markers (such as NSE, synaptophysin, chromogranin A, and CD56), and it has been reported that the positive rates are in the range of 50–70% [10, 11]. In our patient, NSE was within the normal range at diagnosis, but test results for the other markers were positive. NSE is often elevated in patients with small-cell lung cancer, and it has been reported that this marker can be useful for both diagnosis and evaluation of the response to treatment [12]. In our patient, NSE increased to 23.2 ng/ml at the time of local recurrence and it increased further to 218 ng/ml as the disease progressed. Subsequently, NSE was normalized when the patient responded to TP + Bev. This suggested that TP + Bev can be a useful therapeutic option for patients with small cell carcinoma of the uterine cervix.

The GOG240 study reported by Tewari et al. showed that adding bevacizumab to paclitaxel + cisplatin prolongs overall survival. That study evaluated two primary endpoints, which were the usefulness of adding bevacizumab to chemotherapy (paclitaxel + cisplatin or paclitaxel + topotecan) and the usefulness of non-platinum-based combination chemotherapy. The authors reported that adding bevacizumab to chemotherapy reduced the risk of death by 29% without having an adverse impact on health-related QOL, with median overall survival being 13.3 months and 17.0 months in the groups without and with bevacizumab, respectively (hazard ratio = 0.71; p = 0.004) [5].

Tokumo et al. detected expression of VEGF in the tumors of 72.6% of Japanese patients with uterine cervical carcinoma, while Cheng et al. and Loncaster et al. reported that outcomes were worse for cervical carcinoma patients with high tumor expression of VEGF than for patients with low tumor expression of VEGF [13–15]. Furthermore, Tangjitgamol et al. reported that VEGF was overexpressed in the vast majority (95%) of patients with small cell carcinoma of the uterine cervix [6]. Therefore, we selected TP + Bev to treat the present patient. After four cycles of this therapy were performed, both the recurrent tumor and the liver metastases showed reduction in size. After eight cycles of this therapy, the recurrent tumor was no longer detectable and the liver metastases became even smaller or disappeared. Grade 1 anemia and Grade 3 leukopenia occurred during treatment with TP + Bev, but these adverse effects could be managed by administration of G-CSF and supportive therapy. There were no adverse effects specific to bevacizumab, such as hypertension, proteinuria, or thrombosis. In this patient, administration of TP + Bev was discontinued because the patient requested discontinuation due to treatment-related malaise and peripheral neuropathy. Enlargement of the liver metastases was observed at two months after discontinuation.

We encountered a patient in whom paclitaxel, cisplatin, and bevacizumab were effective for small cell carcinoma of the cervix, which is a rare type of uterine cervical carcinoma, so we decided to document the case in this report. Small cell carcinoma of the uterine cervix is a disease that tends to have a poor prognosis, since hematogenous metastasis and lymphatic metastasis can occur at an early stage. Because it is a rare tumor, no prospective clinical studies have been conducted in patients with small cell carcinoma of the cervix and standard treatment has not yet been established. In patients with ovarian cancer and breast cancer, it has been established that continuing treatment with bevacizumab after chemotherapy is useful for maintaining disease control. In our patient, exacerbation was observed after we discontinued treatment with TP + Bev. To establish more effective treatment regimens for small cell carcinoma of the cervix, such as continuation of bevacizumab therapy, we data from more patients with this disease should be collected and analyzed in the future.

REFERENCES