

Bevacizumab Treatment for Recurrent Ovarian Cancer with Isolated Metastasis to the Lymph Node

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Abstract

Bevacizumab (BV) has been used as an effective treatment option for advanced and recurrent cancers; however there are no reports till date on its usage in ovarian cancers with isolated metastasis to the lymph node. Here, we present two cases of ovarian cancer (OVCA) recurrence with isolated metastasis to the lymph node that showed complete response (CR) to BV. In the first case, a 60-year-old woman with OVCA, FIGO stage Ic(b), clear cell adenocarcinoma, exhibited recurrence of the disease with isolated metastasis to the right internal iliac lymph nodes approximately after a year. Eight cycles of paclitaxel/carboplatin therapy resulted in stable disease (SD) and six cycles of docetaxel/carboplatin/BV therapy resulted in CR in the patient without adverse effects. In the second case, a 34-year-old woman who presented with OVCA, FIGO stage IIIC, showed recurrence of ovarian cancer with periportal and external iliac lymph node metastasis after a year which showed CR with paclitaxel/carboplatin combination chemotherapy. Further recurrences in this patient with portal artery metastasis and hilar lymph node metastasis were treated with irinotecan/nedaplatin with surgery and adjuvant therapy and surgery respectively, resulting in SD. Recurrence with para-aortic and obturator lymph node metastasis was noted further, which was treated with 6 cycles of paclitaxel/carboplatin/BV therapy, resulting in CR without adverse effects. Hence, BV might be effective for OVCA recurrence with isolated metastasis to the lymph node and is useful in such cases with no dissemination refractory to prior regimens.

Keywords: Ovarian cancer; Recurrence; Bevacizumab; Lymph node; Complete response; Chemotherapy; Paclitaxel; Carboplatin

Introduction

Globally, ovarian cancer ranks third out of all the cancers occurring in women; however it is associated with highest mortality rates [1]. Bevacizumab has been reported as a primary treatment option for advanced or recurrent ovarian cancers and is found to prolong progression-free survival (PFS) and improve quality of life [2-7], regardless of histological type. As such, ovarian cancer commonly relapses in the abdominal cavity. However, in some cases, metastasis to the lymph node also occurs [8]. The efficacy of BV for recurrence ovarian cancer with metastasis to the lymph node alone has not been reported to date.

We are the first to report 2 cases of ovarian cancer recurrence with isolated metastasis to the lymph node which were effectively treated with BV and resulted in complete response (CR).

Case report 1

A 60-year-old, married, 0 gravida, 0 para, non-smoking woman (height, 150.0 cm; weight, 49.0 kg; body mass index, 21.8 kg/m²) with a history of endometriosis presented with edema and tenderness in the lower right leg. Ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) were performed. Deep vein thrombosis from the right femoral vein to the popliteal vein was observed, but no pulmonary embolism, was noted. Serum cancer antigen (CA)-125 level was 65.7 U/ml. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy were performed for this patient and optimal tumor debulking was achieved. Pathological findings indicated ovarian cancer, FIGO stage Ic (b). The histological type was clear cell adenocarcinoma. Adjuvant therapy with paclitaxel/carboplatin (intravenous infusion of 6 cycles of paclitaxel 175 mg/m² and carboplatin at 5 mg/mL·min of the area under the concentration-time curve [AUC] based on the Calvert formula) was administered [9]. One year and 3 months after surgery, routine CT showed recurrence with right internal iliac lymph node metastasis (Figure 1). CA-125 level was not elevated. Eight cycles of paclitaxel/carboplatin therapy

were administered, and stable disease (SD) was found according to the RECIST guideline (version 1.1). Intravenous infusion of 6 cycles of docetaxel/carboplatin/BV (docetaxel 70 mg/m²; carboplatin at 5 mg/mL·min of the AUC; BV 15 mg/kg) was administered, which resulted in CR without adverse effects (Figure 2). Seven months later, maintenance therapy with BV (15 mg/kg) was administered, and no recurrence was noted.

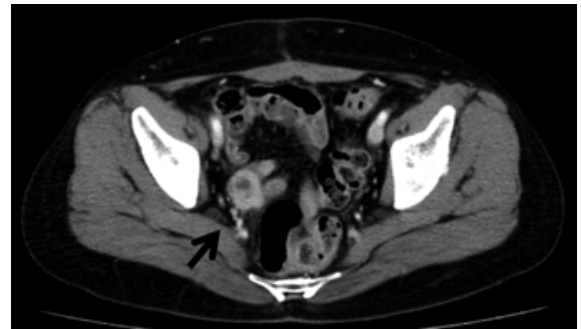


Figure 1: Computed tomography shows recurrence at the right internal iliac lymph node.

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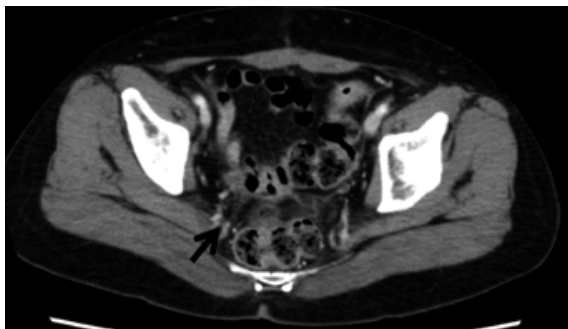


Figure 2: Disappearance of lymph node recurrence after 6 cycles of docetaxel/carboplatin/bevacizumab therapy.



Figure 3: Computed tomography shows lymph node recurrence at the para-aortic lymph node.

Case report 2

A 34-year-old, married, 0 gravida, 0 para, non-smoking woman (height, 163.0 cm; weight, 48.0 kg; body mass index, 18.1 kg/m²) presented with abdominal swelling. Vaginal examination showed a goose egg-sized pelvic tumor. Ultrasonography, CT, and MRI showed an ovarian tumor with a solid component. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy were performed, but peritoneal dissemination was noted. Pathological findings indicated ovarian cancer, FIGO stage IIIC. Histological type of the tumor was grade 3 serous adenocarcinoma. Six cycles of paclitaxel/carboplatin therapy were administered, which resulted in CR [9]. One year and 4 months after surgery, routine CT showed recurrence with portal and external iliac lymph node metastasis. CA125 level was not elevated. Intravenous infusion of 6 cycles of paclitaxel/carboplatin therapy (paclitaxel 175 mg/m²; carboplatin at 5 mg/mL•min of the AUC) was administered, which resulted in CR. She was then transferred to our institute. Five months after last treatment, CT showed recurrence with portal lymph node metastasis. Six cycles of irinotecan/nedaplatin (irinotecan 50 mg/m² on day 1, 8, and 15 after detection; nedaplatin 60 mg/m² on day 1) were administered; however, SD was noted. Laparoscopic lymphoidectomy and 3 cycles for adjuvant therapy with pegylated liposomal doxorubicin (50 mg/m²) were used for treatment. After 5 months, CT showed recurrence with hilar lymph node metastasis, for which abdominal lymphoidectomy was performed. Four months later, the CA-125 level increased to 40 U/ml and CT showed recurrence with para-aorta and obturator lymph node metastasis (Figure 3). Six cycles of paclitaxel/carboplatin/BV therapy (paclitaxel 175 mg/m²; carboplatin at 5 mg/mL•min of the AUC, BV

15 mg/kg) were administered, which resulted in CR without adverse effects (Figure 4) [10]. Maintenance therapy with BV (15 mg/kg) was soon administered. Seven months later, no recurrence was noted.

This study received ethical approval from the ethics committee of our institution, and informed consent was obtained from both the patients.

Discussion

We report two important clinical findings from this study. Firstly, BV was effective for ovarian cancer recurrence with isolated metastasis to the lymph node, and it might be useful in these patients with no dissemination refractory to prior regimens.

Previous reports on phase III trials have indicated that BV has prolonged PFS [2-7]. However, the efficacy of BV based on site of recurrence has not been evaluated. BV use is associated with a risk of gastrointestinal (GI) perforation; hence, its use is debated. The incidence of adverse effects of BV treatment for ovarian cancer, such as GI perforation, is higher than that in other cancers [11,12]. In a well-designed phase III trial, GI perforation was observed in 1.3-2.8% of patients treated with BV [2-7]. However, a phase II study of recurrent ovarian cancer showed that 23.8% patients developed GI perforation and patients receiving three prior chemotherapy regimens had more risk [11]. But in clinical practice, recurrent ovarian cancer needs to be treated with a combination of BV and other chemotherapeutic agents. In addition, a trend of higher incidences of GI perforation with bowel wall thickening or bowel obstruction in CT has been reported in recurrent ovarian cancer [11]. In patients with metastasis to the lymph node alone and no dissemination, bowel wall thickening or bowel obstruction might not occur, which in turn may not result in GI perforation; hence BV use might not result in this particular adverse event. Our first case was an ideal candidate for BV treatment because of isolated metastasis to the lymph node, which would be associated with a lower risk of GI perforation.

BV has been shown to be effective for recurrence with isolated metastasis to the lymph node. Studies have shown that vascular endothelial growth factor (VEGF)-3 expression is related to lymph node metastasis [12-14]. BV is a humanized monoclonal antibody, particularly targeting all VEGF subtypes. The VEGF-3 blocking effect by BV has been demonstrated previously [15]. One paper has reported treatment of colon cancer recurrence with isolated metastasis to the lymph node using BV that resulted in CR [16]. Based on these findings, we hypothesized that BV might be effective for ovarian cancer recurrence at the lymph node.



Figure 4: Lymph node recurrence size reduced to <5 mm after 6 cycles of paclitaxel/carboplatin/bevacizumab therapies.

Recently, Dao et al. [17] reported that patients with recurrent cancer treated with 12 cycles of BV are at a risk of lymph node metastasis, which suggests that BV is not the optimal treatment for lymph node metastasis from ovarian cancer. A high number of patients in that study had lymph node positive recurrent cancer (38-47%), but in our case, no lymph node metastasis was noted after first operation. Hence, the patients in their study were at a higher risk than was our patient, which explains the difference in findings. Isolated lymph node recurrence has a less aggressive peritoneal spreading pattern [18]. Chemotherapy, as well as BV, may be effective in cases of this pattern of recurrence. In other studies, ovarian cancer treated with conventional intravenous cytotoxic regimens tends to recur in the lower abdomen and pelvis, while that treated with intra-peritoneal therapy was more likely to relapse at extra-abdominal sites, specifically the extra-abdominal lymph nodes [19]. Therefore, patients on long-term maintenance therapy might experience recurrence with lymph node metastasis alone; hence, accumulation of cases on isolated lymph node recurrence is needed.

Conclusion

From our case studies, we found that BV was effective for recurrent ovarian cancer with isolated metastasis to the lymph node and it might be useful for such patients with no dissemination refractory to prior regimens. Accumulation of a large number of such cases is needed to confirm the efficacy of BV for isolated metastasis to the lymph node in recurrent ovarian cancer.

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