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Addition of bevacizumab to neoadjuvant chemotherapy for Stage IV ovarian serous adenocarcinoma with multiple lymph node metastases: a case report

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Summary

A 50-year-old female patient was diagnosed with Stage IV ovarian serous adenocarcinoma with multiple lymph node metastases. The CA-125 level normalized after four cycles of neoadjuvant chemotherapy (NACT) using paclitaxel, nedaplatin, and bevacizumab (BEV) before surgery. A positron emission tomography-computed tomography (PET-CT) scan showed significantly reduced bilateral adnexal masses after NACT fluorodeoxyglucose (FDG) metabolism in multiple lymph nodes was inhibited significantly, and the number and sites of metastatic lesions were decreased. The patient underwent optimal cytoreductive surgery. Chemotherapy was continued after surgery and image-guided radiation therapy (IGRT) (40 Gy) was applied for the remaining lymph nodes in the pelvic cavity and cervicothoracic region. No sign of recurrence has been observed in this patient nine months after surgery. The patient achieved a satisfactory outcome and no serious side effects were observed. Therefore, addition of BEV to NACT is a new method for the pre-operative treatment of advanced ovarian cancer.

Key words: Advanced ovarian cancer; Neoadjuvant chemotherapy; Bevacizumab.

Introduction

Currently, surgery is the standard treatment for ovarian cancer, and is supplemented by post-operative chemotherapy. Because of widespread metastasis and local invasion, only 20%-30% of patients with advanced ovarian cancer undergo optimal primary cytoreductive surgery (OPCS). Therefore, how to perform satisfactory cytoreductive surgeries for these patients is a difficult problem encountered by gynecologic oncologists. Neoadjuvant chemotherapy (NACT) is a new treatment method for advanced ovarian cancer. As with ovarian cancer chemotherapy, paclitaxel plus cisplatin therapy is the standard treatment for epithelial ovarian cancer in the NACT program. To improve the prognosis of patients with ovarian cancer, the vascular endothelial growth factor (VEGF) inhibitor, bevacizumab (BEV), is a major agent in biological therapy for ovarian cancer. The NICE guidelines recommend BEV plus paclitaxel and carboplatin as first-line chemotherapy for advanced ovarian cancer [1]. However, there have been few studies regarding the addition of BEV to NACT. The authors report a case of a 50-year-old patient with Stage IV ovarian serous adenocarcinoma who had multiple lymph node metastases and underwent OPCS after four cycles of NACT with BEV plus paclitaxel and nedaplatin. There were no serious or fatal side effects and the treatment outcome was satisfactory.

Case Report

On May 4, 2012, a 50-year-old female patient was admitted to the present hospital with a progressive mass in the left neck for one month. The pathologic examination in the local hospital showed that the lesion in the left neck was a lymph node metastasis from adenocarcinoma. The physical examination revealed an Eastern Cooperative Oncology Group (ECOG) of 1 and the blood pressure was 110/70 mmHg. In the root of the left neck, multiple enlarged lymph nodes fused into a hard mass with tenderness. The boundaries of the mass were unclear and the size was approximately 4 x 3 cm^2. The mass was essentially immobile. No abnormalities were noted in the heart, lungs, and abdomen. A hard mass (3 x 4 cm^2 in size) was palpable in the right adnexa, mobile, and non-tender. A mixed solid and cystic mass (5 x 4 cm^2 in size) was palpable in the left adnexa, mobile, and non-tender. A positron emission tomography-computed tomography (PET-CT) scan (May 4, 2012) showed multiple enlarged and clustered lymph nodes in the root of the left neck and the left shoulder (Figure 1). The fluorodeoxyglucose (FDG) uptake was abnormally increased, the maximum standardized uptake (SUV) value was 15.5, and the diameter of the largest lymph node was 1.4 cm. The lymph nodes in the right shoulder were also visualized with a maximum SUV value of 3.1 and the diameter of the largest lymph node was 0.9 cm. There were multiple enlarged lymph nodes on the left side of the aortic arch, the FDG uptake was abnormally increased, the maximum SUV value was 62, and the diameter of the largest lymph node was 1.3 cm. A lesion with abnormally increased FDG metabolism was observed in the left adnexa; the maximum SUV value was 14.1 and the size was 2.5 x 1.2 x 3.0 cm^3. In the right adnexa, a lesion with abnormally increased FDG metabolism was observed anterior to the rectum;

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the maximum SUV value was 27.7 and the size was 2.3 x 1.4 x 2.5 cm^3. There were multiple nodular lesions with abnormal FDG uptake located along the right uterine wall; the maximum SUV value was 12.6 and the diameter of the largest lesion was 1.4 cm. There were multiple enlarged, beaded lymph nodes located medial to the bilateral iliac blood vessels, which extended superiorly to the peripheral area of the abdominal aorta and extended further to the posterior space of the head of the pancreas. The total length of the beaded lymph nodes was approximately 23 cm, the diameter of the largest lymph node was 2.2 cm, and the maximum SUV value was 11.9. No abnormal activity in FDG metabolism was observed in other anatomic sites. The CA-125 level (1: before chemotherapy, Figure 2) was 164.40 U/ml. The patient was diagnosed with Stage IV ovarian serous carcinoma with multiple systemic lymph node metastases.

Between May 9, 2012 and July 11, 2012, the patient was treated with four cycles of NACT, including paclitaxel (175 mg/m^2 iv on d1), nedaplatin (80 mg/m^2 iv on d1), and BEV (7.5 mg/kg iv on d1). The interval between each cycle was 21 days. Stage II hypertension, according to the Common Toxicity Criteria (NCI-CTC) criteria (version 3.0), occurred during chemotherapy and the blood pressure was controlled using oral felodipine. Subsequently, grade I bone marrow suppression occurred, which improved after appropriate treatment. Thirteen days after the third cycle of chemotherapy (July 5, 2012), a repeat PET-CT was obtained (Figure 1). No abnormal FDG uptake was observed in the bilateral shoulders and the neck. Multiple lymph node images were observed on the left side of the aortic arch; the diameter of the largest lymph node was 0.8 cm, but no FDG sign was observed. The FDG uptake mildly increased in the left adnexa; the maximum SUV value was 5.4 and the diameter was 0.8 cm. No lesions with abnormal FDG uptake were observed in the right adnexa, uterus, or pelvis. In addition, no abnormal activity of FDG metabolism was observed in other anatomic sites. After NACT, the sizes of the lesions in the bilateral adnexa were reduced significantly; the FDG metabolism of the lymph nodes in multiple sites of the body was inhibited, and the number and sites of tumor metastases were significantly decreased.

An exploratory laparotomy was performed on August 1, 2012. No ascites was noted during surgery. Adhesions involving loops of bowel and intestinal adhesions to the left pelvic wall were present. The left ovary adhered to the left pelvic wall and the posterior lobe of the broad ligament. The left ovary was slightly enlarged, the surface was rough, and scant necrotic tumor tissue was observed. No abnormalities were observed in the right ovary and fallopian tube. The size of the uterus was normal and some small intramural myomas were observed. The inferior diaphragm, liver capsule, omentum, appendix, small intestine, and mesentery were smooth without obvious tumor lesions (Figure 3A). The pelvic and para-aortic lymph nodes were significantly enlarged bilaterally, the texture was hard, and the adhesions were abundant. A left salpingo-oophorectomy was performed first. The results of the frozen biopsy revealed poorly differentiated serous adenocarcinoma in the left ovary and fallopian tube. Then, ovarian cancer cytoreductive surgery, including a total hysterectomy, right salpingo-oophorectomy, omentum resection, appendectomy, pelvic lymph node dissection, aortic lymph node sampling, and enterolysis) was performed. The standard of satisfactory cytoreductive surgery is defined as no gross residual tumor after surgery (Figure 3B). The post-operative pathologic examination showed a small area with cancer tissue in the right ovary, but no cancer in the endometrium or right fallopian tube. Intramural leiomyomas and retention cysts in the cervix were observed. No cancer lesions were present in the appendix and omentum. Cancer metastasis was identified in the right common iliac lymph nodes (1 of 3), left internal iliac and obturator lymph nodes (1 of 2), and right ventral aortic lymph nodes (1 of 3). No cancer metastasis existed in the remaining lymph nodes.

A partial ileus occurred six days after surgery, which improved after continuous gastrointestinal decompression, acid suppression, and nutritional support. Vaginal bleeding was noted 14 days after surgery (August 15, 2012). The estimated blood loss was 60 ml. Hemostasis was achieved by packing gauze into the vagina. The second and third episode of vaginal bleeding occurred on August 18 and 22, 2012. The estimated blood loss was 300 ml during each episode. Active bleeding in the left apex of the remnant vagina was observed during a gynecologic examination, which stopped after packing gauze into the vagina, hemostatic medications, and rehydration. The coagulation profile showed that the PT, APTT, and TT were normal, and the D-dimer and FDP were slightly increased. The fifth cycle of chemotherapy using paclitaxel (175 mg/m^2 iv on d1) and lobaplatin (40 mg/m^2 iv on d1) was administered on August 27, 2012 without BEV. The sixth cycle of chemotherapy was administered on October 9, 2012 using paclitaxel (175 mg/m^2 iv on d1), lobaplatin (40 mg/m^2 iv on d1), and BEV (7.5 mg/kg iv on d1). Before the sixth cycle of chemotherapy, the CA-125 level was 10.76 U/ml. A PET-CT scan was obtained on October 15, 2012 (six days after the sixth cycle of chemotherapy). The result showed that there were multiple lymph nodes (0.2 - 0.3 cm in diameter) located in the roots of the neck bilaterally near the thoracic aortic arch, the peripheral area around the major retroperitoneal blood vessels, and the inguinal regions bilaterally. No increased FDG metabolism was observed. No sign of abnormal activity of FDG metabolism was observed in other anatomic sites. Between November 6, 2012 and December 5, 2012, the authors performed IGRT (40 Gy) in the remaining lymph nodes in the abdominal and pelvic cavities and the thoracic and cervical areas. No tumor recurrence was observed during nine months of follow-up visits after chemotherapy and radiotherapy (until September 2013). The patient has survived for 16 months.

Discussion

In the past few decades, a number of approaches have been attempted to deliver systemic treatment to improve the prognosis of patients with ovarian cancer. However, addition of a third drug to the paclitaxel and cisplatin chemotherapy regimen did not improve the prognosis, rather increased the side effects. Currently, many scholars have added molecular targeted therapy to paclitaxel and cisplatin-based chemotherapy in the treatment of ovarian cancer. Angiogenesis is an important factor of tumor invasion and metastasis and a necessary condition for tumor development. It has been reported that VEGF is highly expressed in ovarian cancer, and is related to ascites formation and a poor prognosis [2-4]. Previous studies have shown that anti-VEGF therapy can reduce the tumor load, inhibit the formation of malignant ascites, and there is a synergistic effect between anti-VEGF therapy and cytotoxic drugs [5]. Two large-scale randomized controlled clinical trials (GOG218 and ICON7) have captured the authors' attention. It has been reported that the addition of BEV to standard chemotherapy and use of BEV as

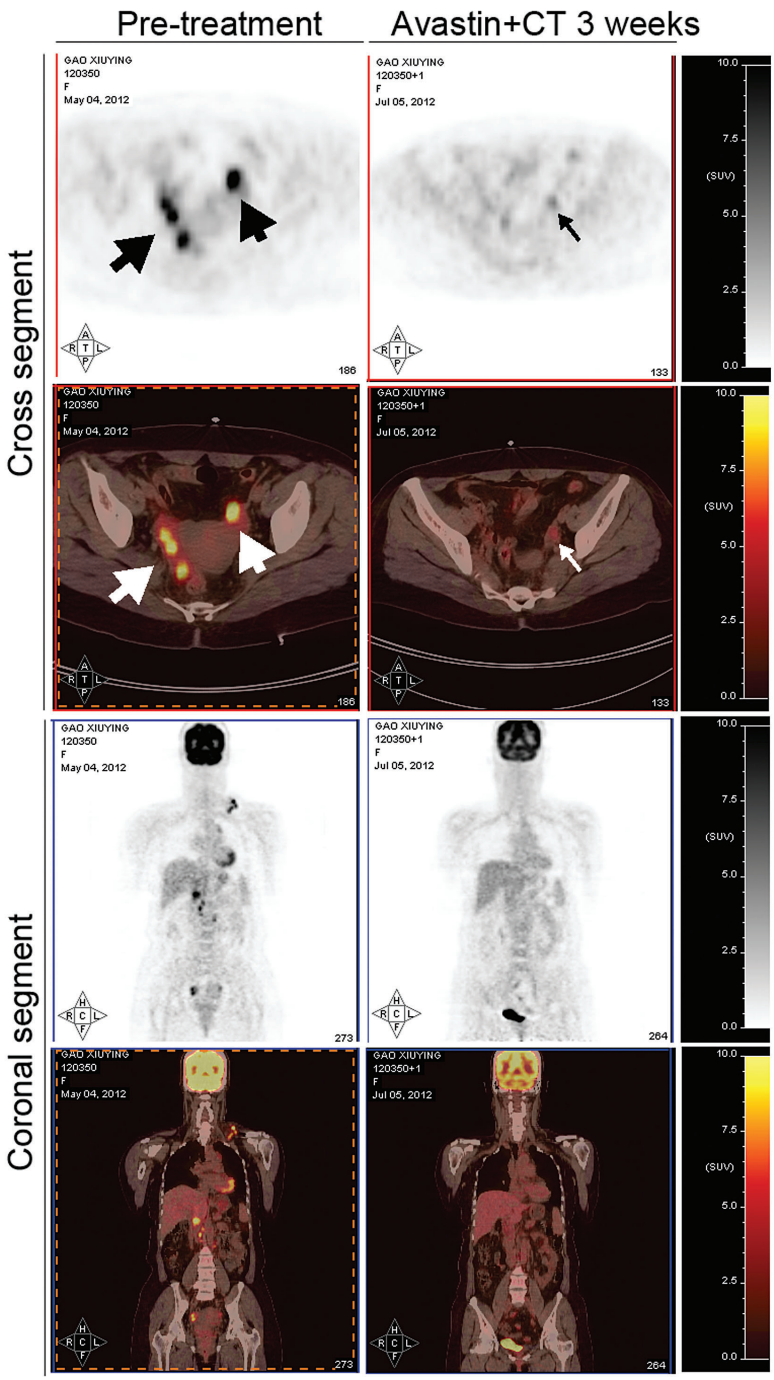

Figure 1. — PET-CT views of pre-treatment and avastin plus chemotherapy treatment at three weeks.

maintenance therapy can significantly improve the progression-free survival (PFS) of patients with advanced ovarian cancers [6-7]. BEV has been widely used in pre-operative NACT for breast, colon, and prostate cancers. Van *et al.* [8] used BEV in pre-operative NACT for 50 patients with colon cancer and related liver and lung metastases. Radical surgery was performed on 36 patients (72%); the two-year overall survival was 80%, and the two-year recurrence rate was 64%. Clavarezza *et al.* [9, 10] used BEV in pre-operative NACT for patients with breast cancer and achieved a satisfactory disease response rate and pathologic complete response rate whether or not the receptors were positive or negative. Ross *et al.* [11] used BEV in NACT for patients with high-risk localized prostate cancer and observed that the tumor diameter and plasma PSA level decreased significantly. Nevertheless, there have been few studies involving the use of BEV in pre-operative NACT for advanced ovarian cancer. The

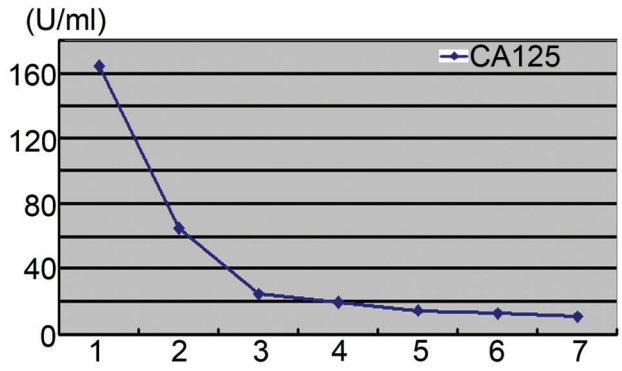

Figure 2. — Time course of changes in CA-125 levels. 1: before chemotherapy; 2: after one cycle of chemotherapy; 3: after two cycles of chemotherapy; 4: after three cycles of chemotherapy; 5: after four cycles of chemotherapy; 6: after one cycle of post-op chemotherapy; 7: after two cycles of post-op chemotherapy.

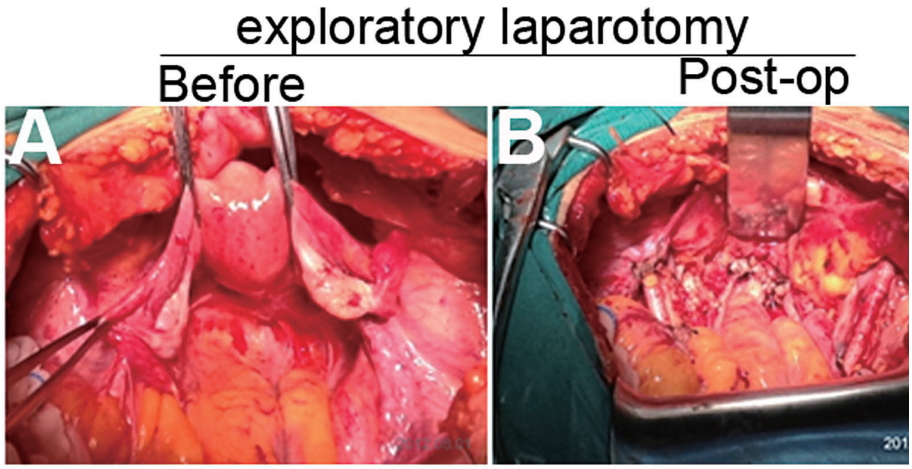

Figure 3. — An exploratory laparotomy was performed on August 1, 2012. A: Before operation; B: post-operation.

present authors have reported a 50-year-old patient with Stage IV ovarian serous adenocarcinoma with multiple lymph node metastases who received NACT using BEV, paclitaxel, and nedaplatin.

The authors administered four cycles of NACT using BEV, paclitaxel, and nedaplatin. After three cycles of chemotherapy, a PET-CT scan showed that a decrease in the tumor diameter > 50%. Furthermore, the FDG value was significantly inhibited, and the maximum SUV value was reduced from 27.7 to 5.4. All enlarged lymph nodes shrank obviously after treatment and the diameter of the largest lymph node was reduced from 2.2 to 0.8 cm. There were no obvious abnormal signs of FDG and the CA-125 level normalized after two cycles of NACT. According to the NCI-CTC criteria (version 3.0), only a grade I gastric response, grade I bone marrow suppression, and Stage II hypertension occurred, but no serious side effects, including proteinuria, gastrointestinal perforation, and venous thrombosis, were noted during NACT. After NACT, the number and anatomic sites of metastatic lesions decreased significantly, metabolism was inhibited, and OPCS was successfully performed. The estimated intra-operative blood loss was only 150 ml and primary wound healing was achieved after surgery. However, three episodes of grade II vaginal bleeding occurred 14 days after surgery, which was related to the addition of BEV to NACT. VEGF has a normal physiologic effect on embryonic development, repair of damaged endothelial cells, and wound healing. Anti-VEGF therapy induces VEGF-mediated damage during the repair of the endothelial cell surface, which results in bleeding. Based on a meta-analysis, the administration of BEV significantly increases the incidence of high-level bleeding, the risk is dose-dependent, and differs in various tumor types [12]. The risk of delayed wound healing decreased when BEV was withdrawn six to eight weeks before surgery and administered again > 28 days after surgery [13-14]. In a recent study regarding the safety of surgery after NACT using BEV, paclitaxel, and carboplatin, four of five patients were FIGO Stage IV. All patients received six cycles of NACT; the mean number of cycles with BEV was three and the mean interval between the last pre-operative dose of BEV and surgery was 54 days (range, 34-110). Grade 3 complications occurred in one patient, and CT-guided lymphatic cyst aspiration was performed on this patient [15]. In the current study, vaginal bleeding after NACT using BEV might be related to

the short interval between the last BEV dose and surgery (only 20 days). The half-life of BEV is relatively long (approximately 20 days). It has been reported that BEV is still active after surgery in patients with colon cancer and related liver metastases, even if NACT using BEV is withdrawn six weeks before surgery. BEV inhibits VEGF in the circulation and local tissues, but does not increase the peri-operative mortality, which suggests that VEGF is not the most important factor during the acute recovery stage after surgery [8]. Thus, there should be a proper interval between the last administration of BEV and surgery because post-operative complications may occur within a long period after surgery. Stage II hypertension occurred after NACT using BEV, which may be related to the fact that BEV inhibits vascular endothelial cells from synthesizing nitric oxide, reduces the number of arterioles and capillaries, and thereby increases vascular resistance. Thus, blood pressure should be monitored routinely in patients treated with BEV.

Conclusion

NACT using paclitaxel, nedaplatin, and BEV achieved an excellent outcome in the treatment of a patient with Stage IV ovarian serous adenocarcinoma and multiple lymph node metastases. The patient underwent OPCS. Despite side effects, including hypertension, vaginal bleeding, gastric response, and bone marrow suppression, all these symptoms improved after symptomatic treatment. The addition of BEV to NACT did not increase the toxicity of chemotherapy drugs nor did BEV increase the incidence of surgery-related fatal complications after NACT.

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