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Case Report

Bevacizumab for malignant pleural effusion in ovarian clear cell carcinoma: a case report

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Objective: Malignant pleural effusion (MPE) is a major problem associated with late phase of epithelial ovarian cancer for which an optimum treatment consensus has yet to be determined. Although bevacizumab (Bev), a VEGF ligand inhibitor, has been shown to effectively control MPE, the clinical benefit of half-dose Bev treatment to control MPE remains unclear. *Methods*: We describe a patient with platinum-sensitive ovarian clear cell cancer (OCCC) and symptomatic MPE for whom tumor markers increased after one cycle of paclitaxel and carboplatin chemotherapy. After switching to five cycles of Bev plus paclitaxel/carboplatin chemotherapy, we observed the disappearance of MPE. *Conclusion*: The half-dose Bev therapy may be an effective treatment for MPE in OCCC. However, further investigation is still warranted to evaluate the therapeutic effectiveness of Bev.

Keywords

VEGF; Ovarian cancer; MPE

1. Introduction

Epithelial ovarian cancer (EOC) accounts for approximately 90% of ovarian cancer cases, the mortality of which is the highest among gynecologic malignancies [1, 2]. For the five histological subtypes of EOC, ovarian clear cell carcinoma (OCCC) is the second most common subtype, but its prognosis is worse than the first most common, high-grade serous carcinoma [3]. Previous studies have found that approximately 70% of patients present with terminal stage at diagnosis and more than 60% of patients experience recurrence after initial treatment [1].

Pulmonary metastasis is considered to be a common site of EOC recurrence [4]. Accumulation of malignant pleural effusion (MPE) is a major complication in pulmonary metastasis of terminal-stage EOC patients, with symptoms including dyspnea, respiratory distress and chest pain [5]. Moreover, 38–40% of patients with advanced ovarian cancer at diagnosis will present with MPE [6]. It is extremely important to effectively control development of MPE, thereby helping to treat pulmonary metastasis and relieve symptoms. However, the current treatment of MPE is generally unsatisfactory, such as intermittent outpatient thoracentesis, pleuroperitoneal shunt, or pleurodesis [7]. These treatments are associated with adverse events and only provide symptomatic relief, without addressing the tumor itself.

Vascular endothelial growth factor (VEGF), one of the key molecules for angiogenesis, is considered to play a critical role in MPE formation [8]. Previous studies have found that VEGF increases vascular permeability by making tumor vessels disorganized and convoluted [9]. It is noteworthy that inhibition of VEGF-mediated signaling for EOC patients has been reported to be a promising therapeutic option for the control of malignant ascites [10].

Herein, we described one OCCC patient who received anti-VEGF treatment for MPE and evaluated the clinical efficacy of half-dose Bev treatment.

2. Case report

A 59-year-old woman (2 gravida, 2 para) visited Beijing Obstetrics and Gynecology Hospital with pelvic masses. Chest computed tomography (CT) scan indicated right-sided adnexal masses and massive ascites. Her serum cancer antigen (CA)-125 (351 U/mL), CA19-9 (22.26 U/mL) and carcinoembryonic antigen (CEA) (2.35 ng/mL) levels were elevated. Based on a clinical diagnosis of ovarian cancer, the patient underwent cytoreductive surgery with hysterectomy, bilateral salpingo-oophorectomy, omentectomy and appendectomy. Histopathological examination revealed clear cell carcinoma with partial serous adenocarcinoma. We diagnosed primary ovarian clear cell carcinoma. She was administered six courses of first-line chemotherapy (paclitaxel and carboplatin).

Thirty months after the first-line chemotherapy, pelvic recurrence and pulmonary metastasis were detected. It is worth noting that pulmonary metastasis occurred with left intrathoracic mass and left-sided malignant pleural effusion. Chest CT scan revealed a left intrathoracic mass c. 5.9 $\times$ 7.0 $\times$ 8.5 cm in size and partial atelectasis of the left lung lower lobe caused by massive pleural effusion. Although the patient had severe symptoms of dyspnea and cough with viscous sputum, conservative therapy, not thoracic surgery, was recommended in surgical consultation in light of the high risk of surgery.

The tumor was deemed platinum-sensitive. Accordingly, the patient was administered paclitaxel and carboplatin as chemotherapy. After one cycle, the levels of CA-125, CA19-

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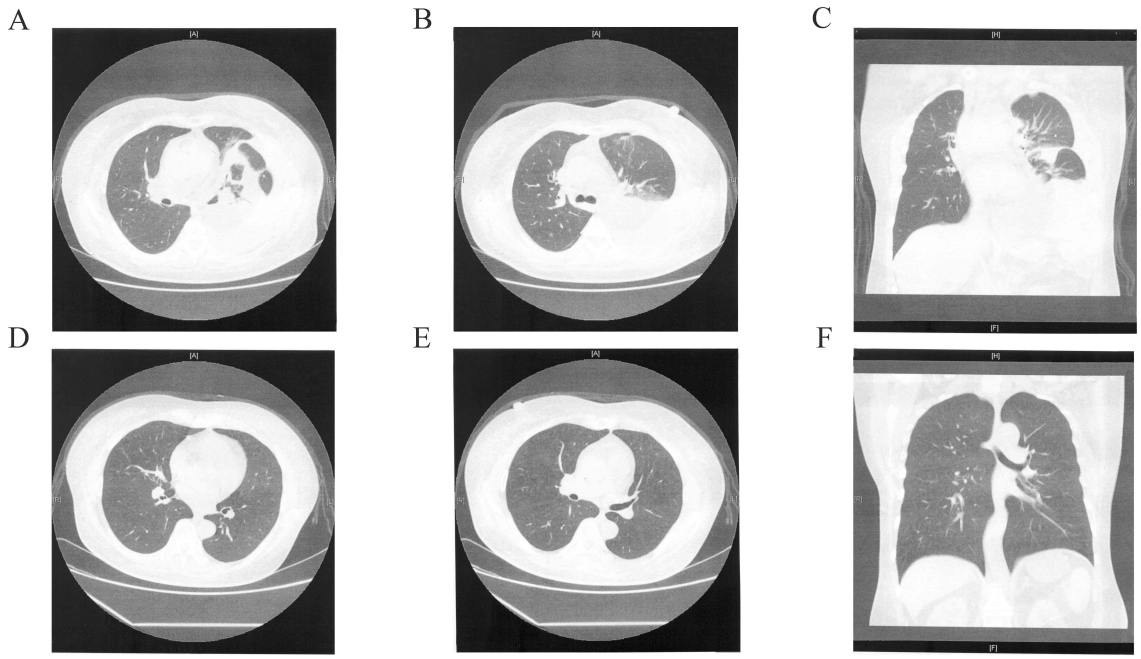

Fig. 1. Changes in MPE with treatment. (A–C) MPE at initiation of treatment. MPE appeared and progressive disease was confirmed. (D–F) MPE disappeared after 5 cycles of bevacizumab plus TC chemotherapy.

9 and CEA were increased. Subsequently, the patient was administered paclitaxel (Albumin Bound) (260 mg/m^2, q3 weeks), carboplatin (AUC6, q3 weeks) and Bev (7.5 mg/m^2, q3 weeks). After five treatment cycles, chest CT scan indicated a complete disappearance of the left-sided pleural effusion, and a diminishment in the tumor in left-sided thoracic cavity from 5.9 × 7.0 × 8.5 cm to 4.1 × 6.3 × 3.8 cm (Fig. 1). Given a second surgical evaluation, the patient underwent thoracoscopic lesionectomy surgery. The effect on pleural effusion was maintained for six months following administration of Bev plus TC combination therapy.

3. Discussion

We describe a case of successful improvement in the signs and symptoms of MPE following Bev therapy. Despite initial difficulty with surgery, Bev was effective in this case and provided a pathway for thoracoscopic surgical treatment of pulmonary metastasis and MPE.

One of the most commonly recurring complications of advanced ovarian cancer is pulmonary metastasis accompanied by the development of a pleural effusion. Although there are several palliative treatment options for MPE, pulmonary metastasectomy (PM) is the most effective treatment for pulmonary metastasis from ovarian cancer [7]. But PM can only provide favorable outcomes in highly selected patients meeting the following criteria [11]: (1) complete resection of metastases was considered achievable; (2) the metastatic lesions were limited to the lungs, or extra-pulmonary distant metastasis was already controlled or controllable if present; (3) the general condition of the patient was good, and the patient's respiratory function was sufficient to tolerate resection. In the present case, the recurrence of this patient is mainly pulmonary metastasis. Due to MPE, the patient's respiratory function could not tolerate surgery.

Bev was considered as a means to delay pleural fluid accumulation [12]. As cancer cells advance, increased VEGF secretion may facilitate tumor progression by promoting angiogenesis and augmented microvascular permeability, thereby causing significant pleural fluid and ascites [10]. Compared with nonmalignant pleural effusions, the significantly high level of VEGF has been shown in MPEs [13]. Thus Bev, a VEGF-A inhibitor, has proven to be an effective treatment of MPE. Previous report has demonstrated the clinical benefits of Bev (15 mg/kg, q3 weeks) in non-small cell lung cancer patients with MPE [12].

For the treatment of epithelial ovarian cancer, Bev is the first anti-angiogenic drug approved by the FDA. The GOG-218 and ICON-7 trials were two phase III trials of Bev plus chemotherapy versus chemotherapy alone in a first-line setting [14–16]. The OCEAN trial was a phase III trial in a platinum-sensitive recurrent setting [17, 18]. All results showed that Bev with chemotherapy could improve median PFS. In addition, The GOG-218 trial showed that patients with ascites significantly benefit from Bev therapy. Notably, the ICON-7 trial included ovarian clear cell carcinoma. The dose of Bev therapy was 7.5 mg/kg (q3 weeks) in the ICON-7 trial and 15 mg/kg (q3 weeks) in GOG-218. Further, previous reports have shown the clinical benefits of half-dose of Bev (7.5 mg/kg, q3 weeks) in OCCC patients with malignant ascites [10].

In the present study, our patient exhibited negative expression of PD-L1 and non-BRCA mutation. Considering the efficacy data of earlier trials, we selected half-dose Bev therapy plus chemotherapy for our patient. MPE was responsive to Bev (7.5 mg/kg, q3 weeks) plus TC combination chemotherapy. Therefore, the half-dose therapy of Bev may be to eradicate MPE from ovarian cancer. Based on our results, Bev can be considered as suitable for patients who do not meet the criteria of PM and improve whom respiratory function to tolerate surgery. Lastly, our patient was not observed to experience any complications such as bowel perforations or hemorrhage.

In conclusion, we present the efficacy of Bev in an ovarian cancer patient with MPE. Intravenous administration of half-dose of Bev might be a potential novel approach for MPE due to ovarian cancer. Further larger-scale studies are still warranted to evaluate the clinical benefits of this therapy.

Author contributions

DW collected data, analyzed the data and wrote the paper; YQZ collected data and analyzed the data; JWM analyzed the data and revised the paper. All authors have read and approved the manuscript.

Ethics approval and consent to participate

We certify that we have obtained the appropriate consent form the patient. All clinical information and images used in this paper were approved.

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Conflict of interest

The authors declare no conflict of interest.

References

[1] Suh DH, Kim HS, Chang S, Bristow RE. Surgical management of recurrent ovarian cancer. Gynecologic Oncology. 2016; 142: 357–367.

[2] Meinhold-Heerlein I, Fotopoulou C, Harter P, Kurzeder C, Mustea A, Wimberger P, *et al.* The new who classification of ovarian, fallopian tube, and primary peritoneal cancer and its clinical implications. Archives of Gynecology and Obstetrics. 2016; 293: 695–700.

[3] Kim SI, Lee JW, Lee M, Kim HS, Chung HH, Kim J, *et al.* Genomic landscape of ovarian clear cell carcinoma via whole exome sequencing. Gynecologic Oncology. 2018; 148: 375–382.

[4] Paik ES, Lee Y, Shim M, Choi HJ, Kim T, Choi CH, *et al.* Timing and patterns of recurrence in epithelial ovarian cancer patients with no gross residual disease after primary debulking surgery. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2016; 56: 639–647.

[5] Eitan R, Levine DA, Abu-Rustum N, Sonoda Y, Huh JN, Franklin CC, *et al.* The clinical significance of malignant pleural effusions in patients with optimally debulked ovarian carcinoma. Cancer. 2005; 103: 1397–1401.

[6] Mironov O, Ishill NM, Mironov S, Vargas HA, Zheng J, Moskowitz CS, *et al.* Pleural effusion detected at CT prior to primary cytoreduction for stage III or IV ovarian carcinoma: effect on survival. Radiology. 2011; 258: 776–784.

[7] Davies HE, Lee YCG. Management of malignant pleural effusions: questions that need answers. Current Opinion in Pulmonary Medicine. 2013; 19: 374–379.

[8] Grove CS, Lee YC. Vascular endothelial growth factor: the key mediator in pleural effusion formation. Current Opinion in Pulmonary Medicine. 2002; 8: 294–301.

[9] Masoumi Moghaddam S, Amini A, Morris DL, Pourgholami MH. Significance of vascular endothelial growth factor in growth and peritoneal dissemination of ovarian cancer. Cancer Metastasis Reviews. 2012; 31: 143–162.

[10] Shimizu Y, Kajiyama H, Yoshida K, Tamauchi S, Nakanishi T, Kikkawa F. The usefulness of bevacizumab for relief from symptomatic malignant ascites in patients with heavily treated recurrent ovarian cancer. Journal of Obstetrics and Gynaecology Research. 2019; 45: 2435–2439.

[11] Kanzaki R, Inoue M, Kimura T, Kawamura T, Funaki S, Shintani Y, *et al.* Role of pulmonary metastasectomy in colorectal cancer in the era of modern multidisciplinary therapy. Surgery Today. 2017; 47: 1111–1118.

[12] Mori R, Fujimoto D, Ito M, Tomii K. Bevacizumab for ramucirumab refractory malignant pleural effusion in non-small cell lung cancer: a case report and review of the literature. Oncotarget. 2017; 8: 48521–48524.

[13] Jia L, DU Y, Li T, Lv Y, Wang Y, Zhang Y, *et al.* Differential expression of vascular endothelial growth factor-A, -C and -D for the diagnosis and prognosis of cancer patients with malignant effusions. Oncology Letters. 2015; 10: 667–674.

[14] Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, *et al.* A phase 3 trial of bevacizumab in ovarian cancer. The New England Journal of Medicine. 2011; 365: 2484–2496.

[15] Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, *et al.* Incorporation of bevacizumab in the primary treatment of ovarian cancer. The New England Journal of Medicine. 2011; 365: 2473–2483.

[16] Oza AM, Cook AD, Pfisterer J, Embleton A, Ledermann JA, Pujade-Lauraine E, *et al.* Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomized trial. The Lancet Oncology. 2015; 16: 928–936.

[17] Aghajanian C, Blank SV, Goff BA, Judson PL, Teneriello MG, Husain A, *et al.* OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. Journal of Clinical Oncology. 2012; 30: 2039–2045.

[18] Aghajanian C, Goff B, Nycum LR, Wang YV, Husain A, Blank SV. Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. Gynecologic Oncology. 2015; 139: 10–16.