Bevacizumab has more toxic in the era of ovarian cancer than colon cancer

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Case Report

Abstract

Three of the phase III randomized trials (GOG-0218, OCEANS, and AURELIA) evaluating the role of bevacizumab in ovarian cancer used a dose of 15 mg/kg every 3 weeks. ICON7 used a dose of 7.5 mg/kg. Together, these independent phase III trials show a benefit in the dose range of 7.5 mg/kg to 15 mg/kg. The existing data suggest that at this time the main role of bevacizumab in the treatment of ovarian cancer may be in the setting of recurrent disease in combination with chemotherapy. However, bevacizumab is associated with some side effects. Gastrointestinal or spontaneous bowel perforations and delayed postoperative fistulae have been described for metastatic colorectal cancer. Few data are available on its use as a treatment for ovarian cancer. In this letter we report the first enterocutaneous fistula and rectovaginal fistula due to use of bevacizumab in the setting of platin refractory epithelial ovarian cancer.

Keywords: Bevacizumab; Ovarian Cancer; Fistula

Introduction

Ovarian cancer is the most lethal gynecologic cancer and fifth leading cause of cancer death in the United States.1 Current management of advanced stage disease includes surgical tumor debulking, followed by adjuvant platinum- and taxane-based chemotherapy.2 Based on increasing knowledge of key biologic pathways driving tumor progression, several targeted therapies have been recently investigated in recurrent ovarian cancer. Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that targets vascular endothelial growth factor (VEGF)-A, and is indicated in the treatment of metastatic colorectal cancer, non-small cell lung cancer, renal cell carcinoma, and glioblastoma multiform. This antibody binds to and neutralizes all biologically active forms of VEGF-A, and then suppresses tumor growth and inhibits metastatic disease progression. In addition, VEGF-targeting agents are thought to enhance the effects of chemotherapy by normalization of primitive tumor vasculature, leading to decreased interstitial fluid pressure, increased tumor oxygenation, and enhanced delivery of cytotoxic drugs.3 Three (GOG-0218, OCEANS, and AURELIA) of the phase III randomized trials evaluating the role of bevacizumab in ovarian cancer used a dose of 15 mg/kg every 3 weeks. ICON7 used a dose of 7.5 mg/kg. Together, these independent phase III trials show a benefit in the dose range of 7.5 mg/kg to 15 mg/kg. The existing data suggest that at this time the main role of bevacizumab in the treatment of ovarian cancer may be in the setting of recurrent disease in combination with chemotherapy.3 However, bevacizumab is associated with some side effects. Gastrointestinal or spontaneous bowel perforations and delayed postoperative fistulae have been described for metastatic colorectal cancer.4 Few data are available on its use as a treatment for ovarian cancer. In this letter we report the first enterocutaneous fistula and rectovaginal fistula due to use of bevacizumab in the setting of platin refractory epithelial ovarian cancer.

Cases presentation

Case 1

A 54-year-old woman who had a history of ovarian cancer for five years came our clinic for fatigue and loss of appetite. The first diagnosis of ovarian cancer was revealed from ascites fluid five years ago. After diagnosis curative surgery had been performed and the patient’s surgical stage was stage IIIC because of positive peritoneal findings. The patient had adjuvant chemotherapy with paclitaxel and carboplatin for six courses. Six months after adjuvant treatment, the patients had a second surgery for new peritoneal masses, and pathology report showed the relapse. The patient had six courses chemotherapy with same agents for relapsed disease. The first progression was four months after the second chemotherapy, so that the patient had been treated as platin refractory ovarian cancer after this progression. Patient had several chemotherapy courses with different agents such as gemcitabine, liposomal doxorubicin.
and paclitaxel for three years. Six months ago the patient had third palliative surgery for bowel obstruction due to disease progression. 6 weeks after the last surgery a new chemotherapy course with docetaxel and bevacizumab (7.5 mg/kg per 21 days) had been administered for four courses. After the fourth course the patient had complained from fatigue and loss of appetite, and the patient administered to clinic for palliative care. The abdominal imagines and tumor markers of patients showed that a partial response to treatment. In the hospital the patient had complained from right side pain, in the clinical examination external orifice of enterocutaneous fistula and intestinal discharge had been found. The magnetic resonance imaging of lower abdomen had showed the fistula’s tract. The patient’s performance wasn’t good enough for a new surgical intervention so the fistula has put off for primary wound healing and the bevacizumab treatment quitted. The patient has refused another chemotherapy and leave the hospital for home care.

Case 2

The second case is a 44-year-old woman who has ovarian cancer diagnosis for three years. Three years ago patient had a curative surgery for malignant ovarian mass. The final pathological stage of patient was stage IIIC because of peritoneal implants and metastatic paraaortic lymph nodes. After surgery patient had taken six courses of chemotherapy with paclitaxel and carboplatin. 9 months after from the adjuvant treatment the disease relapsed in abdominal cavity and patient had taken the same chemotherapy schedule one more time. 4 months later the progression had been showed in abdominal cavity and liver, then patients had chemotherapy with gemcitabin. On the sixth month of gemcitabine treatment, progression had been occurred and then the fourth line chemotherapy had been started with topotecan but there was no improvement with topotecan therapy. Then fifth line chemotherapy with docetaxel and bevacizumab (7.5 mg/kg per 21 days) had been administered for three courses and partial regression was revealed, but the patient had complained for lower abdominal pain and stool discharging from vaginal cavity. The lower abdominal computed tomography showed that a fistula between rectum and vaginal cuff. The patient went to surgery for colectomy and colorectal anastomose. After the surgery, complaints of patients has relieved.

Discussion and Conclusion

In North Eastern German Society of Gynaecologic Oncology Ovarian Cancer Study Group trial, the most severe side effect of bevacizumab in heavily pre-treated and platinum resistant ovarian cancer was the occurrence of fistula (3 of 15 treated patients; %20). Since the mechanism of bevacizumab involves decreasing blood supply to tumor implants, it is plausible that this drug may cause necrosis and microperforation of the bowel wall. However, patients with recurrent ovarian cancer have other risk factors for gastrointestinal perforation including previous gastrointestinal surgery, intermittent or chronic bowel obstruction and poor nutrition. Both the two cases were platin refractor and both of them had multiple chemotherapies and surgeries. Also they had partial responses to taxane and bevacizumab therapy. The major factor for fistula pathophysiology in these cases is antiangiogenic effects of bevacizumab rather than other factors. In several trials bevacizumab therapy has an acceptable safety profile, but this complication has detrimental effects on quality of life and apart from colon cancer that most of oncologists have more experience with bevacizumab gastrointestinal tract complications are more significantly in the era of ovarian cancer. Clinical oncologists must be aware of the risks when the making therapy choice.

Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References