Complete remission of recurrent and refractory ovarian cancers using weekly administration of bevacizumab and gemcitabine/oxaliplatin: report of two cases

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Summary

Background: A combination therapy with gemcitabine and oxaliplatin (GEMOX) yielded a moderate activity in platinum-resistant ovarian cancers; however, frequent severe toxicities, such as thrombocytopenia and neurotoxicity, were observed. A certain modification of schedule might therefore facilitate the clinical application of the regimen. The authors report two cases that achieved complete response to a weekly administration of bevacizumab and GEMOX. *Materials and Methods:* Two patients with platinum-resistant recurrent ovarian cancers received a weekly regimen of GEMOX with bevacizumab: 2 mg/kg of bevacizumab, 300 mg/m^2 of gemcitabine, and 30 mg/m^2 of oxaliplatin, three weeks on and one week off, Q4 weeks. Complete remission was observed after three to four courses of therapy. Hematologic and non-hematologic toxicities more than grade 2 were not observed during chemotherapy. The patients are now without tumor progression more than 12 months after initiation of therapy. *Conclusion:* Weekly administration of bevacizumab and GEMOX had potential activity in recurrent and refractory ovarian carcinomas. These findings warrant necessity of further trial in such clinical settings.

Key words: Ovarian cancer; Recurrence; Weekly therapy; Bevacizumab; Gemcitabine/oxaliplatin.

Introduction

Although epithelial ovarian cancers are a chemo-sensitive disease that respond to initial platinum/paclitaxel chemotherapy with a high response rate, more than half of patients with advanced disease develop recurrence and require further therapy [1]. For the treatment of recurrent or refractory ovarian cancers, a single agent such as gemcitabine, pegylated doxorubicin, or topotecan is administered as a salvage treatment [2, 3]. However, the response is limited with median progression-free survival less than 12 months.

A combination therapy with gemcitabine and oxaliplatin (GEMOX) has been evaluated for recurrent ovarian cancers in several phase II studies. Overall response rates ranged from 20% to 37% [4], however, in patients with platinum-resistant disease, response was observed in less than ten percent of the cases. Additionally, frequent severe toxicities, such as thrombocytopenia and neurotoxicity, have been reported. Another phase II study of a combination therapy with bevacizumab (10 mg/kg), gemcitabine (1,000 mg/m^2), and oxaliplatin (65 mg/m^2) on days 1 and 15 in a 28-day cycle showed an extremely high response rate of 68.5% for platinum-sensitive ovarian cancers [5]. The response rate was approximately two times higher than previous reported rates with GEMOX. Thus, the authors attempted a weekly-based continuous regimen of bevacizumab combined with GEMOX (B-GEMOX) for heavily pretreated and refractory ovarian cancers. The present reports two cases with recurrent and refractory ovarian cancers that achieved complete remission by weekly B-GEMOX.

Case Report

Case 1

Case 1 is a 71-year-old patient with Stage IIIC ovarian serous cystadenocarcinoma who was referred to the Clinic because of refractory and recurrent disease located in the pelvis, para-aortic lymph nodes, and lungs (Figures 1A-C). Five years ago, the patient received two cycles of neoadjuvant chemotherapy with weekly paclitaxel and carboplatin (wTC) followed by primary debulking surgery. Subsequently, she received six cycles of wTC, however, recurrent disease was seen in the pelvis three years ago. The patient underwent debulking surgery for the pelvic mass, and since then all regimens she received did not show a response: ten cycles of combination with irinotecan and paclitaxel, four cycles of pegylated liposomal doxorubicin, and three cycles of irinotecan and cisplatin. After consultation in the Clinic, the patient received the following weekly regimen with B-GEMOX therapy: 2 mg/kg of bevacizumab, 300 mg/m^2 of gemcitabine, and 30 mg/m^2 of oxaliplatin, three weeks on and one week off, Q4 weeks. Grade 1 toxicities of neutropenia, nausea, fatigue, and skin pain were observed, but there were no toxicities greater than grade 2. Complete response (CR) was observed after four cycles of B-GEMOX (Figures 1D-F). Massive ascites and bilateral pleural effusion also completely disappeared. Eastern Cooperative Oncology Group (ECOG) physical status was improved as ascites decreased: two at the initiation of B-GEMOX, and none after three cycles of B-GEMOX. Additional four cycles were administered with 16 months from the initiation of B-GEMOX and the patient is now without tumor progression.

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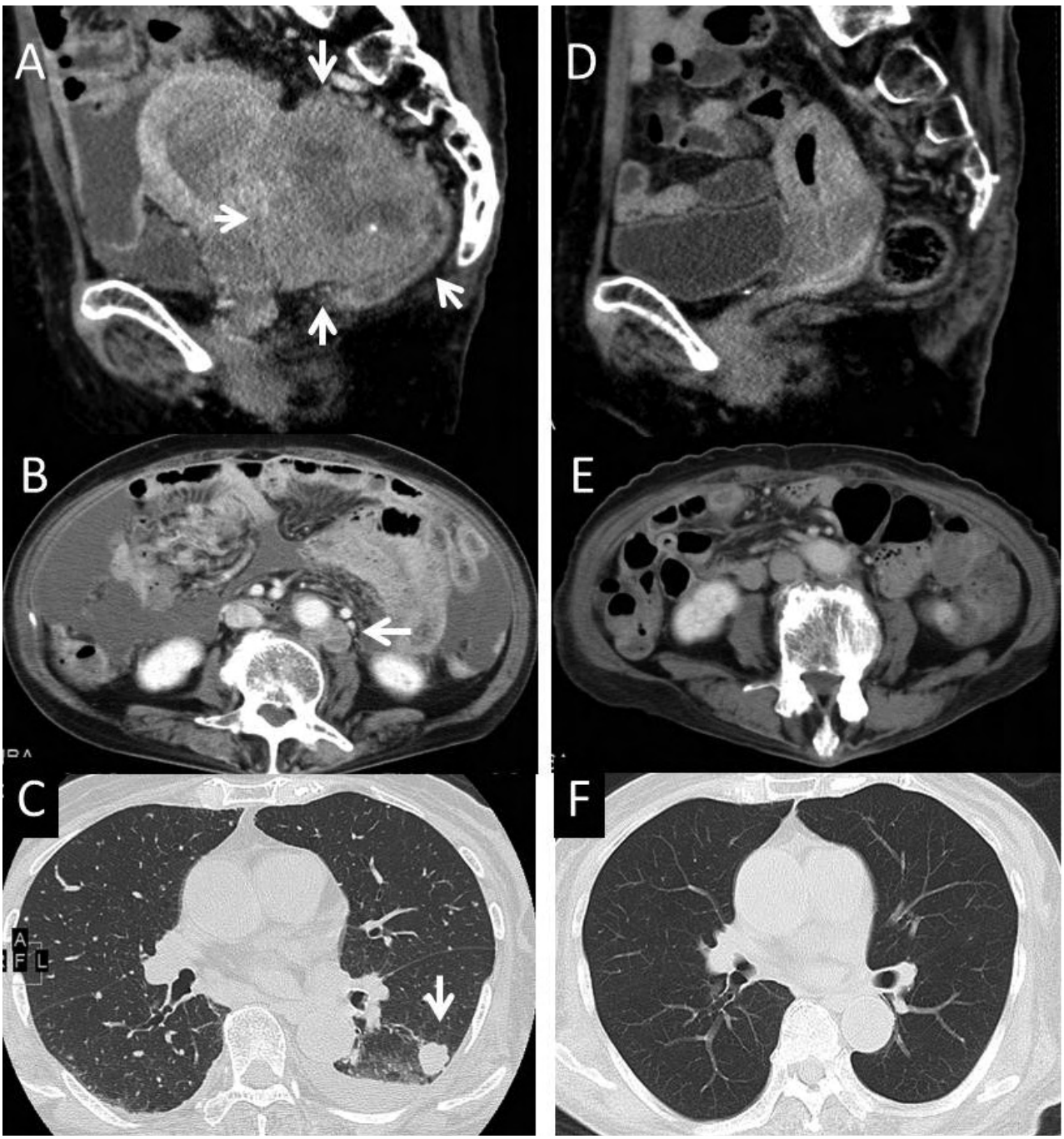

Figure 1. — CT images of recurrent and refractory ovarian cancers. A, B, and C: recurrent and refractory tumors before combination therapy with bevacizumab and GEMOX (arrow). D, E, and F: all refractory tumors, massive ascites, and pleural effusion were not detected by CT images after four cycles of the therapy, achieving CR. Images D, E, and F correspond with images A, B, and C, respectively.

Case 2

Case 2 is a 53-year-old patient with Stage IIIC ovarian serous cystadenocarcinoma who was referred to the Clinic because of refractory peritoneal dissemination. For the treatment of recurrent tumors, a combination using paclitaxel and carboplatin was not effective, and another regimen with ifosfamide, epirubicin, and cisplatin also failed. At consultation in the Clinic, positron emission tomography-computed tomography (PET-CT) images showed multiple peritoneal disseminations with a moderate amount of ascites. She received three cycles of weekly B-GEMOX at an equivalent dose as Case 1 and achieved CR by PET-CT images. The ascites also disap-

Table 1. — *Response of combination therapy with gemcitabine and oxaliplatin for platinum-resistant ovarian cancers*.

Authors Dose of drugs (mg/m^2)	Response rate CR	 PR	Major grade 3/4 toxicities
Raspagliesi *et al*. 2004 G: 1,000 d. 1.8 O: 130 d. 8 (every 3 w)	0%	0%	40% neutropenia; 70% thrombocytopenia; 5% nausea/vomiting, liver dysfunction
Germano *et al*. 2007 G: 1,000 d. 1 O: 100 d. 2 (every 2 w)	10%	14%	37% neutropenia; 19% anemia; 4% nausea/vomiting
Kakykaki *et al*. 2008 G: 1500 d. 1.8 O: 130 d. 8 (every 3 w)	4%	15%	42% neutropenia; 10% anemia; 24% thrombocytopenia; 12% nausea/vomiting; 12% asthenia 2% neurotoxicity, allergy, edema
Harnett *et al*. 2007 G: 1,000 d. 1.8 O: 130 d. 8 (every 3 w)	0%	9%	24% neutropenia; 11% thrombocytopenia 16% nausea; 9% neuropathy; 7% dyspnea
Ray-Coquard *et al*. 2009 G: 1,000 d. 1.8 O: 100 d. 1 (every 3 w)	CR + PR = 38%		51% neutropenia; 26% thrombocytopenia 12% anemia; 7% nausea/vomiting; 8% asthenia
Horowitz *et al*. 2011 G: 1,000 d. 1.5 O: 65 d. 1.5 B: 10 mg/kg d. 1 (every 4 w)	NA	NA	26% neutropenia; 11% nausea/vomiting; 16% fatigue, neuropathy; 5% pulmonary embolism, hypertention, liver dysfunction

CR = complete response; PR = partial response; G = Gemcitabine; O = Oxaliplatin; B = Bevacizumab; NA = not available; D = day; w = weeks.

peared. Grade 1 toxicities of nasal bleeding, nausea, and dysgeusia were observed, however, there were no other severe toxicities. The patient received three more cycles of the therapy. Twelve months from the initiation of B-GEMOX, the patient is now with no sign of tumor progression.

Discussion

Response and major toxicities of combination therapy using gemcitabine and oxaliplatin (GEMOX) for platinum-resistant ovarian cancers are summarized in Table 1. The rate of complete response ranged from 0% to 10%, suggesting that the efficacy of GEMOX was limited as several anti-cancer agents used for platinum-resistant ovarian cancers [6-9]. Grade 3 and 4 toxicities were frequently observed in the patients treated with GEMOX: neutropenia, thrombocytopenia, neuropathy, asthenia, and so on (Table 1). The only phase II study evaluating the efficacy of combination with bevacizumab and GEMOX (B-GEMOX) yielded a response rate of 68.5%, however, the patients eligible for this trial were only platinum-sensitive relapsed ovarian cancers [5]. The rates of severe toxicities, such as neutropenia and thrombocytopenia, were lower in the Horowitz study (oxaliplatin = 65 mg/m^2, biweekly) as compared with other studies (oxaliplatin = 100-130 mg/m^2, every two to three weeks), suggesting that both dose and schedule of oxaliplatin were key factors for toxicities. The two patients presented were heavily treated with more than three regimens; the authors selected a weekly regimen to reduce severe toxicities, and doses of three drugs were almost half of those used in the Horowitz study: 2 mg/kg of bevacizumab, 300 mg/m^2 of gemcitabine, and 30 mg/m^2 of oxaliplatin, three weeks on and one week off, Q4 weeks. The present cases showed toxicities of grade 1 only: neutropenia, fatigue, skin pain, nasal bleeding, and dysgeusia in one case and nausea/vomiting in both cases. The weekly regimen of B-GEMOX showed excellent tolerability with less toxicity.

The present two cases had recurrent disease that was platinum-resistant and refractory to previous chemotherapy. CR was obtained after three to four cycles of B-GEMOX, and ascites with or without pleural effusion completely disappeared. In addition to complete response observed in recurrent tumors, reduction of ascites improved the quality of life, especially in patients with recurrent ovarian cancers. Additive effects of bevacizumab might be explained by the evidence that a combination of bevacizumab and a low-dose cytotoxic regimen blocks vascular repair and survival, enhancing the effects of cytotoxic drugs [10]. Also, reduction of ascites was explained by inhibition of vascular endothelial growth factor (VEGF) pathway, as ascites and plasma samples of ovarian cancers showed significant up-regulation of VEGF. [11]. Bevacizumab, a humanized recombinant antibody binding to VEGF, may have the potential to suspend the ascites production resulting from peritoneal dissemination in solid cancers including ovarian cancers [12].

Conclusion

Weekly administration of bevacizumab and GEMOX had potential activity in recurrent and refractory ovarian carcinomas. These findings warrant necessity of further trial in such clinical settings.

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