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Case Report

Successfully Overcoming Carboplatin Hypersensitivity by Continuous 48-h Infusion of Cisplatin Plus Poly (ADP-Ribose) Polymerase Inhibitor for Heavily Pretreated Recurrent Ovarian Cancer

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Abstract

The success of ovarian cancer treatment is hampered by the recurrent nature and the resistance or hypersensitivity to a platinum regimen. The addition of poly (ADP-ribose) polymerase (PARP) inhibitors can increase the sensitivity to platinum-resistant tumors, although while increasing risk of hematologic toxicity. Substituting cisplatin for carboplatin could result in satisfactory outcomes in the case of carboplatin hypersensitivity. However, there are no efficacy and safety data regarding continuous low-dose cisplatin infusion combined with an oral PARP inhibitor for ovarian cancer patients with hypersensitivity to carboplatin. Herein, we report the case of a heavily pretreated ovarian cancer patient with carboplatin hypersensitivity who safely received low-dose cisplatin (30 mg/m^2 every 3 weeks) over a 48-h infusion combined with a PARP inhibitor for a total of 10 days (D_{-2}–D_7) and successfully achieved partial response after four cycles of treatment, the efficacy of which was further enhanced by the addition of deep regional hyperthermia.

Keywords: Carboplatin hypersensitivity, cisplatin infusion, heavily pretreated ovarian cancer, poly (ADP-ribose) polymerase inhibitor

Introduction

Carboplatin hypersensitivity can impede gynecologic cancer treatment despite prior tumor response to platinum. It is dose-dependent and ranges from <1% in the first cycle to 27%

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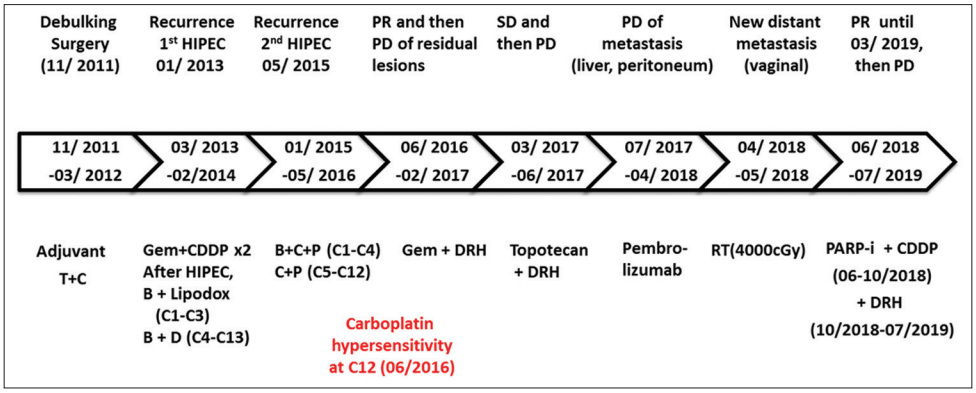

Figure 1: Time course of extensive clinical magagment HIPEC: Hyperthermic IntraPeritoneal Chemotherapy, B: bevacizumab, C: carboplatin, D: doxorubicin, lipodox: liposomal doxorubicin, T: docetaxel, P: paclitaxel, CDDP: cisplatin infusion, PARP-i: PARP inhibitor, DRH: Deep regional hyperthermia, PD: progression of disease, PR: Partial response, SD: Stable disease

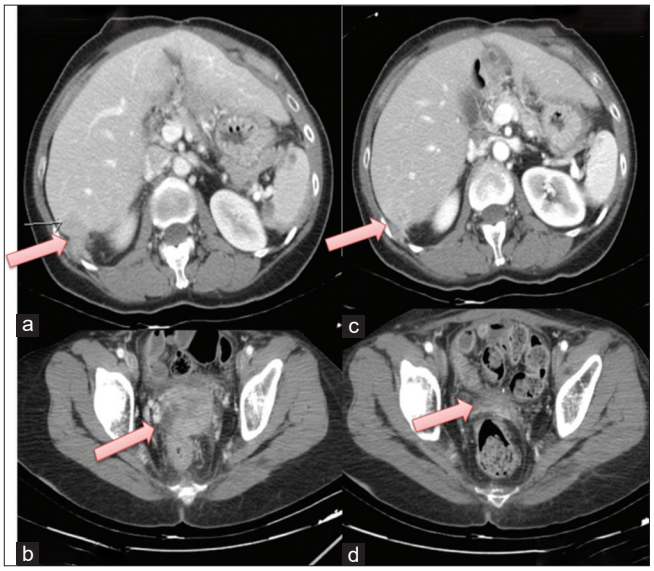

Figure 2: (a and b) Computed tomography of the abdomen and pelvis revealed liver metastasis and a pelvic tumor (May, 2018) before poly (ADP-ribose) polymerase-inhibitor and cisplatin treatment (c and d) Computed tomography of the abdomen and pelvis revealed partial regression of the liver metastasis and pelvic tumor (October, 2018) after poly (ADP-ribose) polymerase-inhibitor and cisplatin treatment

in patients who received more than seven cycles.[1] Substituting cisplatin for carboplatin resulted in satisfactory outcomes (no adverse events in 75%)[2] due to a lack of cross-reactivity.[3]

The addition of poly (ADP-ribose) polymerase (PARP) inhibitors to platinum exerts a synthetic lethality effect and improves survival, especially for breast cancer (BRCA) mutant tumors with homologous recombination (HR) repair deficiency.[4] Such a combination has less efficacy for HR repair proficient tumors when compared with BRCA mutant ones, while hyperthermia can induce a transient HR defect resembling BRCA-mutant status, thereby potentiating the efficacy.[5]

However, the safety and efficacy data of cisplatin infusion and PARP inhibitors for patients with carboplatin hypersensitivity is lacking. In this article, we report the clinical course of a patient with carboplatin hypersensitivity who had safely achieved a partial response with a low-dose cisplatin infusion and PARP inhibitor as shown in Figure 1.

Case Report

A 58-year-old postmenopausal woman was diagnosed with ovarian cancer, Stage IIIc, and had received optimal debulking surgery in November 2011. The pathology showed high-grade serous adenocarcinoma. She experienced unexplainable discomfort just after one cycle of cisplatin and paclitaxel infusion and visited another hospital where she received 5 other courses of adjuvant chemotherapy of docetaxel and carboplatin for a total of six cycles of adjuvant chemotherapy. In December 2012, re-elevation of cancer antigen (CA)-125 and left abdomen peritoneal seeding were noted; therefore, the second-line gemcitabine (1000 mg/m^2) and cisplatin (60 mg/m^2) every 3 weeks was performed for two cycles. The patient visited our oncology unit because of unexplainable general discomfort after the second cycle of cisplatin. As a positron emission tomography-computed tomography (PET-CT) scan revealed progressive peritoneal seeding, she received secondary cytoreductive surgery followed by hyperthermic intra peritoneal chemotherapy (HIPEC) with docetaxel intraperitoneally in January 2013.[6,7] She then received the third-line bevacizumab and liposomal doxorubicin (a platinum agent was omitted due to her refusal) combined with deep regional hyperthermia (DRH) every 3 weeks from March 2013 for three cycles.[8] Lipodox was changed to doxorubicin later due to severe hand-foot syndrome and was continued for an additional ten cycles up to February 2014.

There were several new recurrent peritoneal seedings found in January 2015 and three cycles of combined paclitaxel, carboplatin, and bevacizumab (paclitaxel [175 mg/m^2], carboplatin [AUC of 5 i.v.], and bevacizumab [5 mg/kg]) were administered every 3 weeks for four cycles before second HIPEC in May 2015. Residual disease was noted after operating, and a paclitaxel and carboplatin regimen without bevacizumab was continued for up to an additional eight

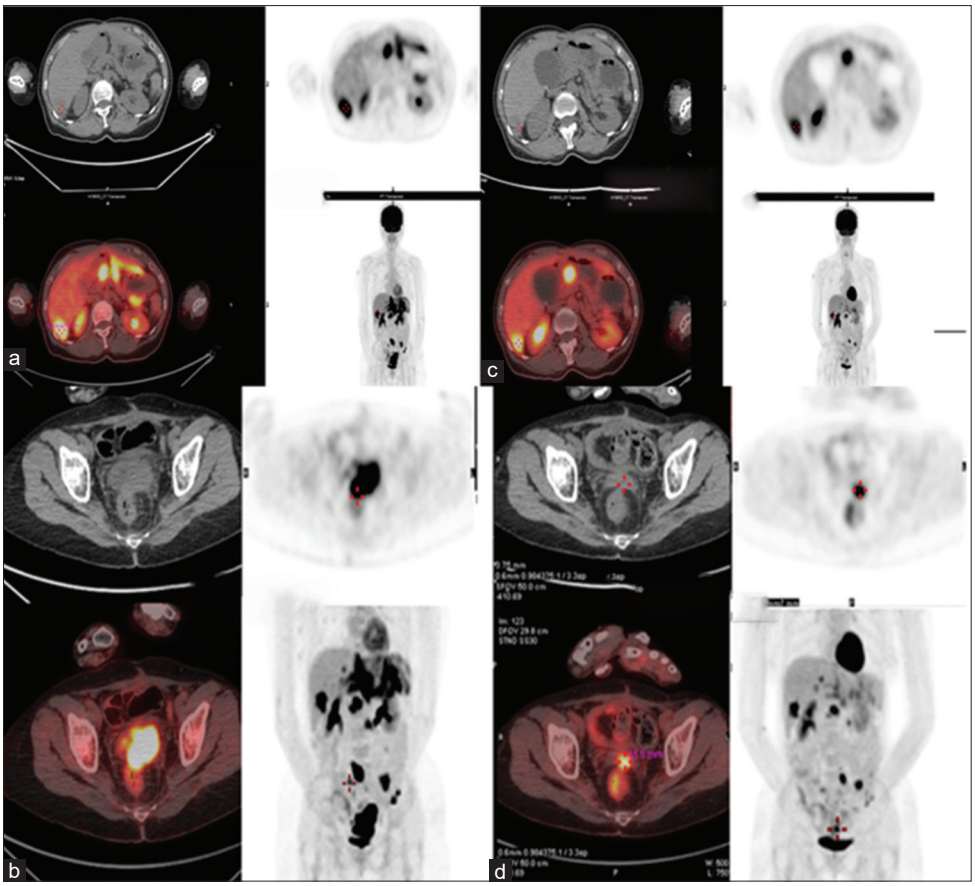

Figure 3: (a and b) Positron emission tomography-computed tomography of the abdomen and pelvis revealed a pelvic tumor and metastases (May, 2018) before poly (ADP-ribose) polymerase-inhibitor, cisplatin and deep regional hyperthermia (c and d) Positron emission tomography-computed tomography of the abdomen and pelvis revealed partial regression of the pelvic tumor, liver, and peritoneal metastases (December, 2018) after poly (ADP-ribose) polymerase-inhibitor, cisplatin and deep regional hyperthermia

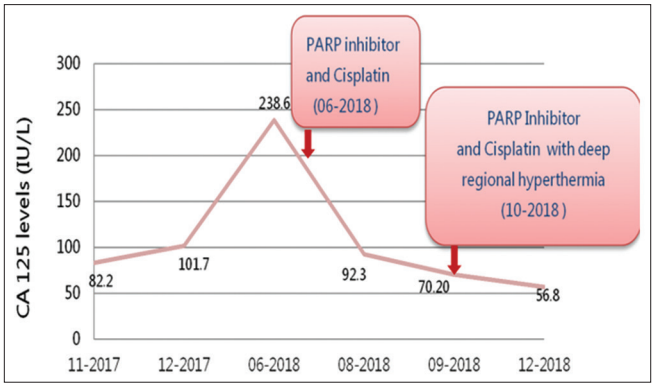

Figure 4: Tumor marker cancer antigen-125 declines after poly (ADP-ribose) polymerase-inhibitor and cisplatin and further declines upon being combined with deep regional hyperthermia in later cycles

cycles. Partial relapse determined by PET-CT scan was noted, but the patient developed anaphylactic shock to carboplatin on the 12th cycle in May 2016, after which we discontinued the regimen. Because of persistent residual lesions, weekly gemcitabine (1000 mg/m^2) was provided combined with DRH from June 2016 to February 2017. Due to elevated CA-125 and the increasing size of the metastatic nodules in the liver, abdominal, and pelvic organs with rectosigmoid colon invasion, she received salvage chemotherapy using topotecan (1.5 mg/m^2/day i.v. infusion on $D_{1\text{-}5,}$ a total of a 21-day course) under DRH beginning in March and lasting until June 2017. Tumor progression over the peritoneal area and left perirectal mass were noted along with progressive elevation of CA-125 therefore, immunotherapy with pembrolizumab (3 mg/kg) was given in July 2017 until April 2018.[9] Radiotherapy of 4000 cGy in 20 fractions was applied to a new vaginal metastatic nodule found in May 2018.

Considering the tumor was a partially platinum-sensitive one, substituting cisplatin for the patient's carboplatin hypersensitivity was a reasonable regimen in such a heavily pretreated case. Salvage chemotherapy using a low-dose cisplatin (30 mg/m^2) infusion over 24 h and olaparib 300 mg BID (D_{-2}-D_7) was initiated starting in June 2018. Since she experienced Grade IV neutropenia, the regimen was then adjusted by changing the infusion rate of cisplatin from 24 h to 48 h since the second cycle with granulocyte colony-stimulating factors support. She successfully achieved partial response after four cycles of the above regimen at the end of October 2018, as determined by an abdominal and pelvic CT scan as

shown in Figure 2. The response was further enhanced by the addition of DRH (D_2) that was reconfirmed by a PET-CT scan in December 2018 as shown in Figure 3. A further decline in the tumor marker was noted one month later, especially after combination with DRH as shown in Figure 4.

Discussion

The success of readministration of a platinum agent in relapsed ovarian cancer patients has been determined by the total platinum-free interval (Tpf): the interval between the first-line chemotherapy and disease relapse. Tpf is stratified as platinum-refractory (<1 month), resistant (1–6 months), partially sensitive (6–12 months), and fully sensitive (>12 months).[10] Our case behaved as a partially platinum-sensitive one, with the first Tpf at approximately nine months, allowing further platinum-containing regimens even after being heavily pretreated.

Management options of carboplatin hypersensitivity include desensitization, alteration of platinum salt, or, at worst, an avoidance of the offending agent.[11] Despite carboplatin hypersensitivity, our patient could tolerate further cisplatin replacement as reported by Callahan MB *et al*.[2] Administration by continuous infusion (i.e., 6–120 h) maintains a constant plasma level with better tolerance while preserving the efficacy of cisplatin (which acts in discrete phases of the cell cycle) compared with bolus infusions.[12]

The rationale for the addition of a PARP inhibitor to cisplatin is based on the fact that >50% of all high-grade serous ovarian cancers exhibit disruption of the BRCA pathway with a PARP inhibitor.[13] Previous studies on such combination regimens have raised concerns regarding an increased risk of myelotoxicity and recommended dose reduction of a PARP inhibitor combined with a standard dose of platinum chemotherapy.[14] We adjusted the duration of olaparib (limited to 10 days [D_{-2}-D_7] instead of prolonged daily use) was overcome by lower-dose cisplatin and a PARP inhibitor in the presence of DRH with tolerable toxicity profiles and an optimal synergistic effect, which led to a good clinical outcome. In addition to adjusting the dose and infusion rate of cisplatin (low-dose (30 mg/m^2) infusion over 48 h), thereby reducing myelotoxicities without compromising the clinical efficacy.

DRH can lead to apoptosis of rapidly dividing cells and potentiate cisplatin and a PARP inhibitor combination by transiently inducing a BRCA-deficient status.[5] In our case, despite the absence of data on BRCA status (due to the patient's financial situation), the addition of DRH to the combined PARP inhibitor and platinum regimen led to a favorable biochemical and radiologic response, indicating the feasibility of such a combination for heavily pretreated patients.

Conclusion

Combined low-dose 48-h cisplatin infusion every 3 weeks plus a periodic PARP inhibitor (D_{-2}-D_7) and DRH (D_2) could be an alternative and effective regimen for heavily pretreated patients with carboplatin hypersensitivity.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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