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Case report

Docetaxel and cyclophosphamide induced remission in platinum and paclitaxel refractory ovarian cancer

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Platinum-based chemotherapy is the standard treatment for advanced ovarian cancer, with response rates of 40–60%. In patients who fail platinum treatment, paclitaxel has resulted in response rates of 10–48%. Docetaxel has partial non-cross-resistance with and is twice as potent *in vitro* as paclitaxel in inhibiting microtubule disaggregation. The combination of docetaxel and cyclophosphamide is synergistic in pre-clinical studies and clinically active in breast cancer. We present the case of a patient with platinum and paclitaxel refractory ovarian cancer who achieved a remission with docetaxel and cyclophosphamide. [© 1998 Lippincott-Raven Publishers.]

Key words: Cisplatin, cyclophosphamide, docetaxel, ovarian cancer, paclitaxel.

Introduction

Ovarian cancer is the leading cause of death from gynecologic malignancy in the US. It kills more women each year than all other gynecologic malignancies combined. Platinum-based combination chemotherapy regimens are the standard treatment for advanced ovarian cancer, with reported response rates of 40-60%.[1] Unfortunately, relapses occur within several years.

The advent of taxanes as salvage treatment has improved response rates and prolonged survival in ovarian cancer patients who fail platinum treatment. Paclitaxel has resulted in response rates of 10-48% in this group of patients.[2-4] Docetaxel (Taxotere), a new semisynthetic taxane extracted from the needles of the European Yew (*Taxus baccata* L),[5,6] is twice as potent *in vitro* as paclitaxel in promoting the assembly of tubulin and in inhibiting microtubule depolymerization.[7] Preclinical studies demonstrated only partial cross-resistance between paclitaxel and docetaxel.[8,9] A recent study indicated the absence of complete resistance to docetaxel in patients with paclitaxel-resistant breast cancer.[10]

Alkylating agents have been used in the treatment of ovarian cancer for many years and show some activity in patients with platinum and/or paclitaxel refractory ovarian cancer.[11-13] Preclinical studies showed the synergistic effect of docetaxel and cyclophosphamide against cancer cells, and 60-70% of maximum tolerated dose of each agent could be administered safely.[14,15]

We present the case of a patient with epithelial ovarian cancer who failed platinum-based chemotherapy and then paclitaxel salvage treatment, and who achieved a remission with docetaxel and cyclophosphamide.

Case report

A 49-year-old woman underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and optimal tumor reductive surgery in November 1995. The tumor was a high grade ovarian carcinoma with a mixed pattern, including undifferentiated and papillary serous carcinoma, and omental and lymph node metastases (stage IIIC, grade 3). The patient then received four courses of combination chemotherapy with carboplatin and cyclophosphamide. As a result of myelosuppression, the patient was placed on carboplatin alone for eight more courses until October 1996. There was no evidence of disease by physical examination, chest X-ray and computed

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tomography (CT) scan of her abdomen and pelvis. Her serum level of CA-125 was initially elevated to 335 U/ml and normalized after three cycles of chemotherapy. In November 1996, second look laparoscopy with peritoneal washings and multiple biopsies was performed. There was no pathologic evidence of cancer. Her serum levels of CA-125 were below 35 U/ml from the time of her last chemotherapy in October 1996 until early March 1997 when it was 80 U/ml. She had occasional abdominal cramps. Her physical examination, chest X-ray and CT scan of the abdomen and pelvis showed no evidence of recurrence. She was placed on a study of high-dose carboplatin (AUC 11 mg.min/ml) with thrombopoietin support for three cycles from April to June 1997.[16,17] Her serum levels of CA-125 were stable. In view of the lack of response and fatigue associated with high-dose carboplatin, the patient went on to receive standard-dose carboplatin for one cycle in the hope of maintaining stable disease. However, her CA-125 rose from 70 to 141 U/ml. There was no measurable disease by physical examination or imaging studies. The chemotherapy was changed to high-dose paclitaxel (250 mg/m^2) over 24 h every 3 weeks with granulocyte colony stimulating factor (G-CSF) support and monthly leuprolide acetate depot 7.5 mg by intramuscular injection. She received two courses of paclitaxel from July to August 1997 and her serum CA-125 rose from 141 to 174 U/ml. In September 1997 she was started on therapy with docetaxel at 75 mg/m^2 (85 mg/m^2 as of cycle number 2) preceded by cyclophosphamide 600 mg/m^2 i.v. infusion over 1 h every 3 weeks with G-CSF support. This regimen was based on a phase I study reported by Valero.[18] The patient was premedicated with 8 mg of dexamethasone by mouth for 5 days starting 1 day prior to chemotherapy, and i.v. cimetidine 300 mg and diphenhydramine hydrochloride 50 mg 30 min prior to chemotherapy.

To date, the patient has received 10 courses of docetaxel and cyclophosphamide. She tolerates the treatment well without major side effects. Her serum level of CA-125 has dropped from 174 to 11.1 U/ml in March 1998 (Figure 1) and her imaging studies reveal no evidence of recurrence.

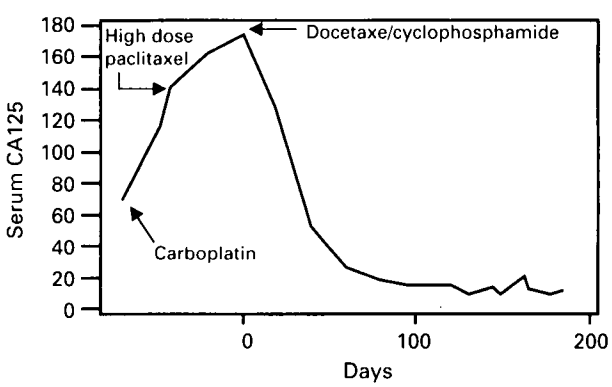

Figure 1. Serum CA-125 levels continued to rise during standard-dose carboplatin and then high-dose paclitaxel treatment. However, after initiation of the combination of docetaxel and cyclophosphamide, there was a dramatic drop in the serum CA-125 levels.

Discussion

Platinum-based combination chemotherapy regimens have led to higher response rates and longer survival for patients with advanced ovarian cancer than previous non-platinum-based regimens.[1] The advent of taxanes as salvage therapy has further prolonged overall survival. Unfortunately, relapse rates remain high and most women with advanced ovarian cancer will ultimately die of their disease.

Docetaxel is twice as potent *in vitro* as paclitaxel in inhibiting microtubule disaggregation.[7] Docetaxel showed greater *in vitro* cytotoxic potency than paclitaxel against murine and human cancer cell lines, and superior *in vivo* antitumor activity against B16 melanoma.[7,8,19] In nine human ovarian carcinoma cell lines studied *in vitro*, cytotoxicity was approximately two orders of magnitude greater for docetaxel than paclitaxel.[20] Piccart *et al.* conducted the largest phase II trial with docetaxel in advanced epithelial ovarian cancer who failed platinum-base chemotherapy and reported overall response rate of 23.5% in 76 assessable patients.[21] Three previous phase II trials, one in Europe[22] and two in the US,[23,24] have also shown encouraging response rates (up to 40%). In an *in vitro* study, some platinum-resistant ovarian cancer cell lines show no cross-resistance between paclitaxel and docetaxel.[9] A preliminary report of a phase II study indicated that docetaxel had significant activity in paclitaxel-resistant ovarian cancer.[25] Docetaxel may be active in platinum and paclitaxel refractory ovarian cancer.

Alkylating agents have a broad range of activity in a variety of solid tumors including ovarian cancer.[26] Some of these DNA-damaging agents have been used in patients who fail platinum and/or paclitaxel with response rates of 10–20%.[11–15] The preliminary results of a phase I study indicated that the combination of docetaxel and cyclophosphamide was quite active in many solid tumors and was well tolerated without any unexpected toxicities at the doses recommended for future trials.[18]

The patient whose case report is presented herein tolerated docetaxel and cyclophosphamide very well, and has a dramatic serologic remission with this treatment.

Conclusion

Docetaxel and cyclophosphamide should be considered for patients with platinum refractory ovarian cancer who fail paclitaxel. Trials of this combination are warranted.

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