

ORIGINAL ARTICLE

CARBOPLATIN COMBINED WITH DOCETAXEL AS A FIRST-LINE CHEMOTHERAPY IN EPITHELIAL OVARIAN CANCER

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Background – To evaluate the feasibility, efficacy, and toxicity of the combination of carboplatin plus docetaxel as a first-line treatment in advanced epithelial ovarian cancer.

Methods – Between February 1999 and December 2001, a prospective nonrandomized open study was done. Of the patients referred to two cancer clinics in Tehran, those in stage Ic-IV were selected. Combination of carboplatin plus docetaxel was given every 3 weeks for 6 cycles. Forty-two eligible patients (median age, 49 years; age range, 24 to 72 years) were given a total of 224 cycles of chemotherapy with carboplatin at AUC = 5 and docetaxel 80 mg/m². Thirty-five patients completed 6 cycles.

Results – The major toxicity was hematological with 50% of the patients developing grade II-IV neutropenia. Three patients developed grade IV thrombocytopenia. Four patients experienced clinical (sensory) neuropathy. Fluid retention was a significant clinical problem in 5 patients. The overall response rate was 71% (25/35). Four out of 12 previously inoperable cases showed complete pathologic remission in their second laparotomy. From the onset of the study the median follow-up for living patients was 21 months and the survival rate at 1 year was 80%.

Conclusion – This combination looks well tolerated and in addition to offering less toxicity, its efficacy seems comparable to the other standard regimen.

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Keywords • carboplatin • docetaxel • ovarian cancer

Introduction

Epithelial ovarian cancer ranks fourth among the leading causes of cancer death in women in the United States.¹ Most patients have advanced disease at the time of diagnosis. Until a few years ago, the combination of cisplatin plus cyclophosphamide was considered as the best treatment for this cancer.² In 1996 and 1998, two large prospective randomized trials showed that the combination of cisplatin-paclitaxel had significantly higher response rates, longer progression-free survival, and overall survival periods compared to the previous standard treatment of cisplatin and cyclophosphamide.

However, this higher efficacy was at the cost of greater toxicity, particularly neurotoxicity.³ In later studies, carboplatin replaced cisplatin. Data, collecting from many studies, demonstrated that carboplatin was equally effective with less neurotoxicity but greater myelosuppression.⁴ In all of these studies the dose of carboplatin was area under the curve (AUC) 5 – 8 and that of paclitaxel was 120 – 200 mg/m². These trials suggested that the combination of carboplatin plus paclitaxel was not only both more convenient and more tolerable for patients but it also appeared as effective as cisplatin plus paclitaxel. Docetaxel (Taxotere) has showed single agent efficacy equivalent to paclitaxel with an overall response rate of 25% in platinum refractory ovarian cancer. Moreover, docetaxel is generally delivered as a convenient 1-hour infusion.⁵ These advantages of docetaxel and carboplatin led the big oncology centers to

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initiate docetaxel-carboplatin as a first-line therapy for ovarian cancer patients.^{6,7}

The goal of the present study was to evaluate the efficacy and toxicity of the combination of docetaxel and carboplatin in our patients.

Patients and Methods

Forty-two patients, referred to two oncologic clinics, were enrolled without randomization in this trial between June 99 and September 2001. Eligible patients had histologically proved epithelial ovarian cancer in stage Ic-IV of International Federation of Gynecology and Obstetrics (FIGO) with or without successful debulking surgery at laparotomy. The patients had performance status < 2 in East Cost Oncology Group (ECOG) scale and normal liver and renal function. No one had received any prior radiotherapy or chemotherapy. Pregnant, lactating women, and those with a history of prior serious allergic reaction were also ineligible. Docetaxel, 80 mg/m² and carboplatin, AUC 5 were administered consecutively on day 1, every 3 weeks for 6 cycles. The dose remained fixed throughout cycles unless reduction was required due to toxicity. The interval cytoreduction surgery was determined on an individual basis. Premedication consisted of dexamethasone, 8 mg BID for 3 days, starting the day before chemotherapy. Docetaxel was diluted in 200 mL of normal saline or dextrose water 5% solution and administered over 1 hour by intravenous infusion. Carboplatin was diluted in 300 mL of normal saline and infused over 1 hour.

The prophylactic intravenous antiemetic consisted of granisetron (kytril) 3 mg, metoclopramide 20 mg, and dexamethasone 16 mg for all patients immediately prior to chemotherapy infusion. The full doses of cytotoxic agents were administered for neutrophil counts above 1500/ μ L, and platelet counts above 100,000/ μ L. Dose reductions were based on nadir blood counts. Any grade IV neutropenia was treated with granulocyte-colony stimulating factor (G-CSF). The patients underwent full physical examination, tests of biochemical profile, chest X-ray, and CT-scan of abdomen and pelvis prior to the treatment. Response to chemotherapy was assessed after 3 and 6 courses of chemotherapy by the same imaging technique used at baseline. A complete response was defined as complete disappearance of gross evidence of the disease. Partial response

was defined as a 50% or greater reduction in the product obtained from measurement of each lesion. Stable or progressive disease was considered as no response. Following completion of the protocol, patients were followed-up every 2 months for 1 year and every 3 months afterwards. The patients and their families were informed of the major complications of combination chemotherapy while a consent form was signed by a first degree relative.

Results

Forty-two patients were enrolled in this trial. All patients had proved epithelial ovarian adenocarcinoma. The median age was 49 years (age range, 24 to 72 years). Ninety percent had performance status of 0 – 1 ECOG. Overall, 224 cycles of chemotherapy were delivered. The major side effects were hematological; 21 patients (50%) developed grade II-IV neutropenia; despite the high incidence of grade IV neutropenia, there were only a few episodes of febrile neutropenia documented in 4 patients. Only 3 patients developed grade IV thrombocytopenia while no thrombocytopenic hemorrhage was seen. Anemia was commonly observed (14 patients) but the decision for transfusion was based on the clinical symptoms and hemoglobin level. Significant non-hematological toxicities were uncommon. Severe diarrhea was observed in 2 patients. Grade III-IV mucositis was seen in 3 patients. Overall, 4 patients experienced peripheral neuropathy; no motor toxicity was observed. Hypersensitivity reaction to docetaxel was seen in 3 patients; it always occurred in the first cycle and was controlled with more steroid and antihistamine injections. Fluid retention was a significant clinical problem in 5 patients. Of 42 patients, 35 were eligible for clinical and imaging response evaluation. The overall response rate was 71% with complete remission in 10 and partial remission in 15 cases. Only 2 patients had progression of the disease under chemotherapy. Four out of 12 previously inoperable patients showed complete pathologic remission in their second laparotomy. From the onset of the study the median follow-up for living patients was 21 months and survival rate at 1 year was 80%.

Discussion

From the advent of single alkylating agents to

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the present time when modern combinations are used, we have witnessed successive well-documented survival prolongations. Estimated 5- and 10-year overall survival rates for platinum-base combination chemotherapy without paclitaxel are approximately 25% and 10%, respectively.⁸ The median overall survival has been prolonged from 24 – 25 months to 35 – 38 months using a combination of paclitaxel and cisplatin compared to the previously used reference regimen containing cisplatin and cyclophosphamide.⁸

Preliminary results from randomized trials indicate that carboplatin may be an attractive alternative to cisplatin since it offers better tolerability while having the same response rates.⁸ In the current Gynecology Oncology Group (GOG) trial for early-stage disease, all patients initially received 3 cycles of paclitaxel-carboplatin and then were randomized between observation and 26 weekly injection of paclitaxel (GOG 175).^{9, 10} The most notable point of this study was the low incidence of clinically significant neurotoxicity. As a single agent, docetaxel produces neurotoxicity in 11% of patients and docetaxel-induced neuropathy does not generally appear until cumulative doses of docetaxel exceed 600 mg/m². The etiology of docetaxel-induced neurotoxicity is not completely understood; it is thought to be an effect on neuronal and Schwann cell microtubules with subsequent axonal degeneration and demyelination. It is not clear why docetaxel and paclitaxel differ in the degree of neurotoxicity.^{11, 12} On the whole, tolerance to the carboplatin-docetaxel combination was excellent. There were no treatment withdrawals due to fluid retention. Grade II or III neutropenia occurred in 60% of all patients. This level of myelosuppression was not accompanied by a higher rate of sepsis. In prior trials (Vasey and his colleagues) carboplatin, AUC 5 and docetaxel, 75 mg/m² were thought to be the best dosage combination offering a balance between efficacy and toxicity.¹³ However, in order to truly determine whether the combination of docetaxel and carboplatin can be recommended as a routine first-line therapy for epithelial ovarian cancer, large prospective randomized trials are needed. Further studies are in progress looking at the possibility of combining other noncross-resistant agents with carboplatin-docetaxel to improve the activity of the regimen. In all prior studies the overall response rates were between 49% and 75% with median follow-up of 19 months and the survival rate at 1 year in 85%. Our

results are comparable with the above mentioned studies and the most notable point of this study is the low incidence of clinically significant neurotoxicity (10% versus 24%).¹⁴ In conclusion, this study demonstrates that docetaxel plus carboplatin can be combined safely and with feasible efficacy as a first-line chemotherapy for advanced ovarian cancer. The recommended doses seem to be carboplatin, AUC 5 or 6 in combination with docetaxel, 80 mg/m². Although myelosuppression is commonly observed, sepsis is rare. Moreover, the incidence of neuropathy is also low and may confer a significant toxicity advantage over paclitaxel-cisplatin to these patients population.

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