Docetaxel in the Treatment of Ovarian Cancer

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Docetaxel (Taxotere) has extended the armamentarium of agents with significant activity in the treatment of ovarian cancer. As a single agent in advanced ovarian cancer patients previously treated with a platinum agent, docetaxel at 100 mg/m² every 3 weeks yields a 30% overall response rate and a 6-month duration of response.

Epithelial ovarian cancer is a major source of mortality of women in the United States. It is the leading cause of gynecologic cancer death.[1] The disease is unusual in women below the age of 40, and gradually increases to a peak rate of 57 per 100,000 in the 8th decade. The median age of diagnosis is 63 years of age.[2] Although genetic factors have been noted, approximately 90% of the cases do not have an identifiable genetic predisposition. There are no early signs or symptoms of the disease, and most patients are diagnosed in an advanced state. Following surgical bulk reduction, chemotherapy is generally given. The prognostic factors for the disease remain the nature of the histology, the amount of residual disease following primary surgery, and the stage of the disease.[3] The disease is staged according to the International Federation of Gynecology and Obstetrics (FIGO) nomenclature.

Chemotherapy for advanced ovarian cancer has evolved over the years into combination regimens that generally included cisplatin or carboplatin (Paraplatin). The introduction of paclitaxel/platinum-based chemotherapy has resulted in a prolongation of the median progression-free survival and overall survival of patients. In the benchmark trial, Gynecologic Oncology Group (GOG)-111, the taxane/cisplatin arm had a median survival of 38 months vs 24 months ($P < .001$) for the cisplatin/cyclophosphamide arm. Superiority of the paclitaxel/cisplatin regimen over the cisplatin/cyclophosphamide regimen in terms of both progression-free survival and overall survival were later confirmed in a European trial.[4] The long-term impact on survival is not yet known. The cisplatin/paclitaxel combination has the major side effects of myelosuppression and neuropathy. The substitution of carboplatin for cisplatin has generally lessened, but does not eliminate, neuropathy. Furthermore, depending on the administration schedule of paclitaxel, hematologic toxicities may be less frequent.[5] Taken together, the trial results indicate that the more convenient paclitaxel/carboplatin combination is generally better tolerated than paclitaxel/cisplatin and appears to be equally efficacious. When used as a 3-hour infusion, paclitaxel is associated with significant neurotoxicity, however, and questions remain about the possibility that longer schedules of paclitaxel may be somewhat more efficacious as first-line therapy. As a result of this ambiguity, and based upon the results of docetaxel (Taxotere) in preclinical and clinical trials, numerous studies have investigated the substitution of docetaxel for paclitaxel in combined use with the platinum salts in the treatment of ovarian carcinoma. The remainder of this article will review preclinical and clinical trials of docetaxel in ovarian cancer, concluding with the preliminary results of a large, phase III randomized trial comparing docetaxel- and paclitaxel-based regimens in the first-line setting.

Preclinical Data

The relative activity of paclitaxel vs docetaxel in ovarian cancer cell lines has been the subject of several studies. Aapro et al compared the in vitro sensitivities of paclitaxel and docetaxel in bone marrow, head and neck, sarcoma, colon, and ovarian cancer cell lines.[6] In a sulforhodamine or tetrazolium salt 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay, 13 ovarian cancer lines were two- to fourfold more sensitive to docetaxel as compared with paclitaxel and up to 6,500-fold more potent than cisplatin. Alberts et al conducted an in vitro study comparing the relative cytotoxicities of paclitaxel and docetaxel against 50 fresh ovarian cancers obtained at surgery prior to chemotherapy.[7] A human tumor cloning assay was used to evaluate the degree of drug-induced inhibition of tumor colony formation (TCF) from the ovarian cancers. The achievable and median IC50 values (ie, 50% inhibition
of TCF compared with control) were 47.8% achievable and 19.0 µM median IC50 for paclitaxel vs 48.5% achievable and 3.28 µM median IC50 for docetaxel. On the basis of this data, it was concluded that docetaxel had at least equivalent cytotoxicity to paclitaxel against fresh ovarian cancers. Hanauske et al compared the antiproliferative action of docetaxel and paclitaxel against a variety of freshly explanted human tumor specimens using an in vitro soft agar cloning system.[8] Cytotoxicity was observed against breast, lung, ovarian, colorectal cancer, and melanoma tumor colony-forming units. In a head-to-head comparison, 29 specimens were found more sensitive to docetaxel than paclitaxel, while only 13 were more sensitive to paclitaxel than docetaxel. At 10 µg/mL, significant cytotoxicity was observed in 41% of specimens tested with docetaxel and 33% of specimens tested with paclitaxel. The authors concluded that cross-resistance between the two agents was incomplete, and that, on a concentration basis, docetaxel was more cytotoxic than paclitaxel in the majority of human primary tumor specimens evaluated.

Silverstrini et al compared paclitaxel and docetaxel in three established cell lines and in 19 primary cultures of ovarian neoplasms.[9] The assay used was clonogenic with a proliferative index based on tritiated thymidine incorporation. Both docetaxel and paclitaxel were more potent than cisplatin or doxorubicin in all three established cell lines. In addition, docetaxel was two to four times more cytotoxic than paclitaxel in two of the established cell lines and showed similar activity in one cell line. In primary culture systems, however, the taxanes were less active than cisplatin and doxorubicin. Cell lines that were sensitive to the taxanes generally had a higher labeling index (ie, higher proliferative activity) than those observed in resistant cultures. The authors suggested that preclinical determination of the inherent sensitivity of individual tumors to taxanes and of the tumor cell population proliferation rate could be useful in identifying patients who could benefit from taxane treatment.

Untch et al used the adenosine triphosphate cell viability assay in 14 cell lines, including 12 gynecologic and 2 breast cancer cell lines.[10] On a concentration basis, docetaxel was more active than paclitaxel in 5 cell lines and paclitaxel was the more active drug in 6 cell lines. Of interest, total cross-resistance to cell lines between the taxanes was not demonstrated. The authors concluded that both compounds were quite active and showed partial non-cross-resistance. The authors indicated that paclitaxel and docetaxel appear to have a different spectrum of activity in gynecologic and breast cancers, both of which are diseases where tumor heterogenicity remains a challenging therapeutic problem.

Nicoletti et al reviewed the activity of both taxanes in human ovarian carcinoma xenografts.[11] Intravenous drug was given once every 4 days for three consecutive doses in the nude mouse model. Xenografts were transplanted subcutaneously or intraperitoneally. Both taxanes cured all animals in early stage peritoneal implantation of HO22 tumor lines. Of note, both docetaxel and paclitaxel were more effective than cisplatin, which was used as the reference compound. The authors concluded that both docetaxel and paclitaxel were highly effective in four human ovarian carcinoma xenograft models.

In summary, both taxanes have been found to be extremely active in a variety of human ovarian cancer models. Docetaxel and paclitaxel demonstrated varying degrees of activity in preclinical ovarian carcinoma models and did not demonstrate total cross-resistance. The research indicates that human tumor cell lines that are resistant to paclitaxel are not necessarily resistant to docetaxel. Taken together, the information provided an interesting avenue for the clinical investigation of docetaxel in ovarian carcinoma.

**Docetaxel in Refractory, Platinum-Pretreated Ovarian Cancer**

The role of docetaxel in the treatment of refractory or recurrent ovarian cancer has been well described.[12-16] Four major trials of single-agent docetaxel have been conducted in advanced, pretreated ovarian cancer patients. A total of 340 patients were treated in two European and two US trials (Table 1).[12-16] The dose of docetaxel used in these studies was 100 mg/m² every 3 weeks. All patients had received prior platinum salt-based therapy. The time interval from previous platinum therapy, as well as the definition of "platinum resistance," was variable in the trials. When analyzed together, the overall response rate in the four phase II studies combined was 30% among 315 evaluable patients (95% confidence interval[CI]: 25%-36%) as shown in Table 2.[12-16] This level of antitumor activity was maintained among the 155 patients who had the most refractory disease (defined as a treatment-free interval of less than 4 months), where the overall response rate was 28% (95% CI: 19%-36%).

The most common side effects were grade 4 neutropenia and fluid retention. The incidence of febrile...
neutropenia among patients varied from 8% to 44%. These studies confirmed the activity of docetaxel in platinum-pretreated patients. In addition, there was a trend demonstrating that longer treatment-free intervals and platinum-free intervals were associated with higher response rates. It was also noteworthy that even the most refractory cases demonstrated a significant response rate to docetaxel.

**Docetaxel in the Treatment of Paclitaxel-Resistant Patients**

As discussed above, preclinical data indicated a lack of complete cross-resistance between docetaxel and paclitaxel; however, information concerning their clinical cross-resistance in epithelial ovarian cancer was lacking. Anecdotally, it had been reported that patients may respond to the alternative taxane upon relapse. Still, the characteristics and nature of these patients, along with the duration of the response, have not been well documented. A provocative paper published by Verschraegen et al. partially addressed this question.[17]

Thirty-two patients with ovarian carcinoma were treated with docetaxel at 100 mg/m² (n = 27) or 75 mg/m² (n = 5) after having failed paclitaxel-based therapy. The definition of paclitaxel failure was progression while on therapy or evidence of persistent disease after four courses of paclitaxel-based therapy (absolute paclitaxel resistance) or clinical remission followed by relapse within 6 months of completing paclitaxel-based therapy (relative paclitaxel resistance). Patients demonstrating paclitaxel resistance did not necessarily receive docetaxel treatment immediately and, in fact, may have been treated first with other, potentially non-cross-resistant regimens. Although the largest subgroup of patients (14/30) had received just one prior chemotherapy regimen, nine patients had received two prior regimens, five patients had received three prior regimens, three patients had received four prior regimens, and one patient had received five prior chemotherapy regimens. In 30 assessable patients, an overall response rate of 23% was documented, with 1 complete and 6 partial responses. An additional 6 patients demonstrated stable disease. Of the 19 patients who had disease progression while on paclitaxel (absolute paclitaxel resistance), 11% responded to docetaxel therapy. Docetaxel responders had a median taxane-free interval of 73 weeks, compared with 19 weeks in nonresponders (Table 3).[17] The implication of this report is that taxane resistance, similar to platinum resistance, may be a time-dependent phenomena. One criterion for analysis of taxane re-treatment studies, therefore, should be the time interval from prior taxane therapy. It is possible that re-treatment with taxanes is not necessarily schedule- or dose-dependent but may be most influenced by time from previous therapy. Further confirmation of this observation will be necessary. The authors concluded that docetaxel had definite antitumor activity in paclitaxel-resistant ovarian carcinoma—findings supported by previous preclinical observations as well as data concerning docetaxel sensitivity in paclitaxel-refractory breast cancer.[18] The authors indicated that docetaxel appears to be at least as effective as other approved second-line treatments for recurrent ovarian cancer (ie, topotecan [Hycamtin], liposomal doxorubicin [Doxil]), and its level of activity, ease of administration, and known safety profile warrant serious consideration in the first-line setting.

**The Role of Docetaxel as Primary Therapy for Ovarian Carcinoma**

**Docetaxel/Cisplatin Combination Therapy**

In untreated ovarian cancer, docetaxel has been investigated in dose-finding combination studies and in fixed-dose combinations aimed at identifying activity in larger patient populations. Two of the most notable dose-finding studies involved combinations of docetaxel with cisplatin and with carboplatin.

The largest study combining docetaxel with cisplatin was published by Vasey et al.[19] A total of 100 patients with FIGO stage IC to IV epithelial cancer were divided into two cohorts for treatment with docetaxel, 75 mg/m² or 85 mg/m², plus cisplatin, 75 mg/m², every 3 weeks, with an anticipated total number of six cycles. All patients received premedication with oral dexamethasone 8 mg two times per day for 5 days, starting the day prior to chemotherapy. The primary end point of the study was incidence of severe fluid retention that necessitated treatment withdrawal. Additional objectives were to gather data on the potential efficacy of the combination in terms of objective tumor responses, duration of response, progression-free survival, and overall survival.

In the first cohort, 49 patients received 258 cycles of therapy with cisplatin, 75 mg/m², and docetaxel, 75 mg/m². In the second cohort, 51 patients received 254 cycles with cisplatin, 75 mg/m², and docetaxel, 85 mg/m². Activity was notable, with an overall response rate of 69% and a clinical complete response rate of 38% in 39 patients assessable for response after three and six cycles. In 85 patients assessable by the serum marker CA-125, 73% demonstrated a response.
progression-free survival for the group was 12 months (95% CI: 10-14 months).
Results demonstrated that no patients were taken off study because of fluid retention. On the other hand, only 66 patients received the planned six cycles of therapy, and 16 patients withdrew from therapy early because of toxicity. Patients in cohort 2 experienced more profound nadir neutropenia and more frequent fatigue/lethargy compared with cohort 1 ([Table 4]).[19] In both cohorts combined, grade 2 or 3 neuropathy was reported in 17% and 6% of patients, respectively. There were five treatment-related deaths, all occurring in cohort 2. Three patients died of neutropenic complications and two patients died as a result of upper gastrointestinal hemorrhage related to premedication with the 5-day corticosteroid regimen. The authors concluded that the combination of docetaxel and cisplatin can be safely administered at doses of 75 mg/m² per drug given every 3 weeks, but they did not recommend increasing the dose of docetaxel to 85 mg/m² because of unacceptable hematologic complications and poorly tolerated fatigue/lethargy. In an effort to attenuate cisplatin-induced toxicities, the investigators subsequently investigated the substitution of carboplatin for cisplatin in combination with docetaxel.

**Docetaxel/Carboplatin Combination Therapy**

Vasey et al combined docetaxel and carboplatin as first-line therapy for ovarian cancer patients in a prospective, nonrandomized feasibility study.[20] The aim was to establish whether patterns of toxicity differed from those experienced with paclitaxel/carboplatin, with particular reference to myelotoxicity and neurotoxicity. One hundred and thirty-nine eligible patients with FIGO stage IC to IV epithelial ovarian cancer received a total of 750 cycles of chemotherapy in five cohorts at varying dose levels of carboplatin (at an area under the concentration-time curve [AUC] of 5-7) and docetaxel (60-85 mg/m²) every 3 weeks. Patients received a 3-day prophylactic regimen of oral dexamethasone 8 mg twice a day. In total, 110 patients received all six planned cycles of docetaxel and carboplatin for a 79% completion rate, and only 12% of patients came off therapy early because of toxicity.

Toxicities included grade 4 neutropenia in 75% of patients; however, febrile neutropenia was reported in only 4% of patients. Significant nonhematologic toxicities were infrequently reported. Although fatigue or lethargy were reported in more than 50% of patients, it was grade 3 in only five patients (4%). Also notable was the especially low incidence of significant neurotoxicity. Thirty-six patients (26%) experienced a treatment-related neuropathy; however, it was grade 1 in the vast majority (20%). No patients stopped protocol therapy because of neurotoxicity, and no significant neuromotor toxicity was reported. Overall, the clinical response rate was 66%, with a CA-125 response of 75%. The median progression-free interval was 16.6 months (95% CI: 13.3-19.1 months), and the estimated 1-year overall survival rate was 84%.

The authors concluded that the tolerable dose was carboplatin at an AUC of 5 and docetaxel, 75 mg/m² every 3 weeks. It is pertinent that carboplatin was dosed according to the Calvert formula, where the glomerular filtration rate was measured by $^{51}$CrEDTA. If clearance is calculated mathematically by the Cockcroft-Gault formula, then carboplatin at an AUC of 6 is recommended. At this recommended dose, 91% of patients completed six cycles of therapy. Although myelosuppression was commonly observed, complications were rare, and neither prophylactic antibiotics nor growth factors were required routinely. The authors reported evidence of a platelet-sparing effect with the docetaxel/carboplatin combination. Another interesting observation was the relative lack of significant neurotoxicity. The authors suggested that these findings may represent a toxicity advantage for docetaxel plus carboplatin, which may be particularly important for longer treatment durations.

The group from the Cleveland Clinic also conducted a study of combination carboplatin/docetaxel for malignancies of the ovary and fallopian tube and primary carcinoma of the peritoneum.[21] Eligible patients were those with no prior chemotherapy or a treatment-free interval of more than 2 years. The doses chosen for study were docetaxel, 60 mg/m², and carboplatin at an AUC of 6 (Cockcroft-Gault formula) once every 3 weeks for a maximum planned number of six cycles of treatment. Prophylactic medication was given with oral dexamethasone 8 mg twice daily beginning 24 hours before chemotherapy and continuing for a total of five doses. Prophylactic oral antibiotics were allowed if the clinician thought that grade 4 neutropenia would last more than 3 days. A total of 50 patients were entered in the study, with all but three patients (6%) having received no prior chemotherapy for their malignancy. Among the total patient population, 67% received all six planned treatment courses. Similar to other studies was the report of severe, but usually brief, neutropenia. Thrombocytopenia was distinctly uncommon, and there were no episodes of grade IV nonhematologic toxicities. Hypersensitivity reactions occurred in approximately one-third of patients higher than the incidence reported in other clinical trials of the combination. In all cases,
however, patients were able to continue therapy without further incidence by utilizing a protocol of diphenhydramine (50 mg IV) and hydrocortisone (50 mg IV) after discontinuation of the initial infusion. The chemotherapy was continued upon resolution of the hypersensitivity reaction and the administration of prophylactic compounds. It is also of interest that there was only a 6% incidence of grade 2 peripheral neuropathy, with no cases of grade 3 neuropathy observed. In 42 patients assessable for response, 32 patients (81%) were considered objective responders. At the time of the report, the median duration of progression-free survival had not been reached; it would exceed 16 months. The authors concluded that the combination of carboplatin at an AUC of 6 and docetaxel at 60 mg/m² was a highly active regimen with manageable hypersensitivity reactions and a very low incidence of neurotoxicity.

**Docetaxel/Carboplatin vs Paclitaxel/Carboplatin Therapy**

The largest trial of docetaxel in the first-line treatment of ovarian cancer has been the phase III SCOTROC trial comparing the docetaxel/carboplatin combination with the paclitaxel/carboplatin combination.[22] The preliminary results of the study were presented at the 2001 annual meeting of the American Society of Clinical Oncology. Eligible patients had FIGO stage IC to IV epithelial ovarian cancer and primary peritoneal cancer, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and had received no prior chemotherapy or radiotherapy. The primary end point of the study was progression-free survival, and secondary end points were overall survival, toxicity, quality of life, and response rate.

The treatment programs randomized 1,077 patients to either docetaxel at 75 mg/m² plus carboplatin at an AUC of 5 (Calvert formula) or paclitaxel at 175 mg/m² over 3 hours plus carboplatin at an AUC of 5 (Figure 1). Treatment courses were repeated every 3 weeks for up to six cycles. Patient characteristics were well balanced in terms of median age, ECOG performance status, FIGO stage, and postoperative residual disease. In a total of 586 patients evaluable for clinical response, the response rates were similar in both arms, with an overall response rate of 65% in the docetaxel/carboplatin arm (n = 297) and 62% in the paclitaxel/carboplatin arm (n = 289) (Table 5). Using CA-125 serum marker as a criterion of response, there was a 75% response rate in the docetaxel/carboplatin arm (n = 354) and 76% response in the paclitaxel/carboplatin arm (n = 355).

There was no significant difference in progression-free survival or overall survival at the time of this report.

A major issue of discussion concerning the trial has been the incidence of hematologic vs nonhematologic toxicities. The incidence of hematologic toxicities was higher in the docetaxel/carboplatin arm, although the complications were manageable and patients usually completed therapy as planned. Importantly, there were no differences between the arms in incidence of septic mortality or treatment discontinuations as a result of neutropenic complications (Table 6).[22] In contrast, the paclitaxel/carboplatin arm was associated with a greater incidence of neurologic toxicities that led to early treatment discontinuation. The overall rates of peripheral neuropathy were significantly higher for the paclitaxel/carboplatin arm (77% vs 45%, *P* < .001), and the incidence of grades 2 to 4 peripheral neuropathy also was significantly higher in the paclitaxel/carboplatin arm (30% vs 11%, *P* < .001) as compared with the docetaxel/carboplatin arm. Similarly, the paclitaxel/carboplatin arm had a significantly higher incidence of motor neuropathy, both overall (17% vs 8%, *P* < .001) and for grades 2 to 4 (8% vs 3%, *P* < .001), in comparison with the docetaxel/carboplatin arm (Table 7).[22] Finally, a much greater percentage of patients in the docetaxel/carboplatin arm did not develop neurotoxicity (Figure 2).

The preliminary conclusion of this large randomized trial was that the docetaxel/carboplatin and paclitaxel/carboplatin combinations were equally effective in regards to clinical and CA-125 response. Further analyses will be necessary to determine whether there is any difference in progression-free and overall survival between the study arms. The docetaxel/carboplatin arm was associated with a higher incidence of neutropenia, which did not result in a higher incidence of discontinuation of therapy or treatment-related deaths, however, and was generally managed on an outpatient basis. In contrast, the paclitaxel/carboplatin arm had significantly more neurotoxicity that led to early treatment discontinuation. To date, the findings suggest that docetaxel may represent a new alternative to paclitaxel for combination with carboplatin as first-line chemotherapy for advanced ovarian cancer.

**Conclusions**

Docetaxel has unequivocal and definite activity in platinum-refractory ovarian cancer patients, with a response rate of 30% and a response duration of 6 months. The activity of docetaxel in
platinum-pretreated patients is related to the treatment-free interval, with higher response rates being reported in patients with longer treatment-free intervals. The currently available clinical data do not support a conclusion about whether docetaxel or paclitaxel is a superior drug in treating patients who have had prior therapy, particularly platinum-based therapy. However, it has been demonstrated in a phase III trial that docetaxel has activity equal to paclitaxel as first-line therapy, as well as activity in patients who have had prior paclitaxel-based chemotherapy. The evidence suggests that the longer the taxane-free interval, the more likely the response to docetaxel. Because of our lack of understanding about the mechanisms of resistance to taxanes in the clinic, the optimum drug, dosing, or schedule for a taxane reinduction strategy remains unclear. Several studies combining docetaxel with the platinum salts have been conducted. The combination of cisplatin and docetaxel yields high antitumor activity. However, as was reported with the paclitaxel/cisplatin combinations, neurotoxicity and fatigue limit therapy. In contrast, the docetaxel/carboplatin regimen is a functional combination when used in doses of carboplatin at an AUC of 5 (51CrEDTA determination) or 6 (Cockcroft-Gault formula) and docetaxel doses ranging from 60 to 75 mg/m². This combination has been well tolerated when given every 3 weeks for six cycles. Of interest, the combination of docetaxel and carboplatin suggests a platelet-sparing effect in terms of the cumulative toxicity of carboplatin and a low incidence of neurotoxicity. The results of the large SCOTROC randomized trial comparing docetaxel/carboplatin with paclitaxel/carboplatin demonstrated that the docetaxel/carboplatin combination therapy had a significantly lower incidence of treatment-limiting neuropathy. Although the docetaxel/carboplatin combination demonstrated a higher incidence of neutropenia, this side effect was manageable and did not result in early treatment discontinuation. Preliminary results show similar overall response and survival rates, and the data await further analyses. In combination with carboplatin, docetaxel may represent a new alternative to paclitaxel as first-line chemotherapy for advanced ovarian cancer.

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