Long-term results of paclitaxel in FIGO stage III ovarian carcinoma

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The combination of platinum and paclitaxel is the standard treatment of advanced ovarian carcinoma; however, recent studies have questioned the actual role of the combination as compared to either of the two agents alone. We report an open-label, two-center, phase II study of upfront paclitaxel for patients with histological diagnosis of stage III ovarian carcinoma. Treatment consisted of paclitaxel at 175 mg/m^2 administered in a 3-h infusion every 21 days. Response was evaluated after the third course by either laparoscopy or exploratory laparotomy. Patients with stable or progressive disease discontinued treatment, whereas responding patients continued treatment until a maximum of six courses. Response, toxicity, time to progression (TTP) and survival were evaluated. From November 1993 to December 1995, 30 patients were accrued. All patients underwent primary cytoreduction; 17 (57%) and 13 (43%) patients had residual tumors <2 and >2 cm, respectively. Of 27 patients evaluable, objective responses were seen in 18 (66.4%) (95% CI 49.5–83.2)—12 complete (45%) and six partial (22%). Four patients had stable disease (15%) and five (18%) patients progressed. A total of 149 courses were administered to 30 patients, median 4 (range 1–6). Grade 3/4 neutropenia was seen in 13% of courses, peripheral neuropathy, myalgia and arthralgia were frequent, but transitory and relieved with analgesics. At a median follow-up time of 44.5 months (0–99) the TTP and median survival were 16.6 and 43.1 months, respectively. We conclude that single-agent paclitaxel is an effective and well-tolerated first-line treatment for advanced ovarian carcinoma. *Anti-Cancer Drugs* 14:347–352 © 2003 Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2003, **14**:347–352

Keywords: ovarian carcinoma, paclitaxel, single-agent

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Sponsorship: Taxol and complete funding for this investigation were provided by Bristol-Myers Squibb Company through its Pharmaceutical Research Institute.

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Received 3 December 2002 **Revised form accepted** 25 February 2003

Introduction

Ovarian cancer is one of the leading causes of death from gynecological malignancies worldwide [1]. As ovarian cancer is frequently asymptomatic in its early stages, approximately two-thirds of patients have advanced disease at presentation; hence, these patients are not amenable to cure with surgery and/or radiation therapy. Standard treatment for patients with ovarian carcinoma consists of an initial debulking surgery followed by adjuvant chemotherapy; however, long-term follow-up of suboptimally debulked stage III and IV patients revealed a 5-year survival rate of less than 10% even with platinum-based combination therapy [2]. Based on the results of GOG 111, the combination of paclitaxel and cisplatin is now the standard of care for ovarian cancer patients in stages III and IV. GOG 111 compared paclitaxel and cisplatin with cyclophosphamide and cisplatin in sub-optimally debulked stage III and stage IV patients who had no prior chemotherapy [3]. There was a statistically significant improvement in the clinical response rate in the experimental arm (73%) versus the control arm (60%) with a median survival of 24 versus 38 months. These results were further confirmed by a European–Canadian trial [4]. Because of the neurotoxicity of paclitaxel when associated with cisplatin, carboplatin has frequently been substituted for cisplatin in this regimen. Clinical trials assessing the efficacy of this substitution indicate no loss of efficacy [5,6]. Thus, many investigators consider the 3-h regimen of paclitaxel plus carboplatin (AUC 5–7) as an alternative to the paclitaxel and cisplatin as the preferred initial chemotherapy for patients with ovarian cancer.

Despite the superiority of the platinum/paclitaxel combination over cisplatin/cyclophosphamide, the GOG 132 [7] study randomized suboptimally debulked patients to receive either single-agent cisplatin at 100 mg/m^2 or paclitaxel at 200 mg/m^2 by 24-h infusion or both at standard dose (135–24 h/75). Interestingly, there were no differences in terms of overall survival for either of the three arms, although about 90% of patients in the

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single-agent arms eventually received salvage therapy and almost 50% crossed over from the single agent prior to clinical progression. However, neutropenia and febrile episodes were more severe in the high-dose single-agent paclitaxel arm. These data have led to reconsideration of the role of single agents, either a platinum or taxane, as an alternative to the recommended combination in the treatment of advanced ovarian cancer. Herein we report our long-term results of paclitaxel as a single agent administered at 175 mg/m^2 by a 3-h infusion in a group of untreated patients with the diagnosis of stage III ovarian carcinoma. At the time this study was initiated, there were no reported data on its activity and the long-term survival of patients when the drug is used as monotherapy as first-line treatment in advanced ovarian cancer.

Patients and methods

This open phase II study was performed at the Instituto Nacional de Cancerologia, Mexico City and Centro Médico del Potosí, SLP, Mexico. Thirty untreated patients with histological diagnosis of ovarian carcinoma were included. The inclusion criteria were: (i) staged III according to the FIGO classification; (ii) bi-dimensionally measurable lesion; (iii) aged 18–75 years; (iv) ECOG performance status 0–2; (v) normal hematological, renal and hepatic function as determined by: hemoglobin ≥ 10 g/l, neutrophil count > 1500/mm^3, platelet count $\geq 100\,000$ mm^3, total bilirubin $< 1.5\times$ the normal upper limit (NUL), transaminases $< 1.5 \times$ NUL and normal levels of creatinine in serum; and (vi) informed consent. The exclusion criteria included pregnant or lactating patients; previous chemotherapy or radiotherapy; borderline ovarian tumor; abdominal adenocarcinoma of unknown origin; and previous or concomitant malignancies except non-melanoma skin cancer. Patients with bowel obstruction, pre-existent motor or sensory neurotoxicity (WHO grade > 2), serious active infection, prior allergic reactions to drugs containing Cremophor, history of atrial or ventricular arrhythmia or congestive heart failure, documented myocardial infarction within the 6 months preceding the enrollment, or history of second- or third-degree heart blocks were also excluded. The study was approved by local ethics Committees and was conducted in accordance with The Declaration of Helsinki.

Treatment

Study medication consisted of paclitaxel at 175 mg/m^2 administered as a 3-h infusion in either 5% dextrose solution or normal saline in glass containers with polyethylene tubing with in-line cellulose acetate 0.22 μm. filters. Patients were premedicated with oral dexamethasone (20 mg at 12 and 6 h prior to paclitaxel) and with i.v. chlorpheniramine (10 mg) and cimetidine (300 mg), 30 min prior to paclitaxel. Courses were administered every 3 weeks. Dose reductions were considered in the event of hematological and non-hematological toxic effects as follows: when grade 3 neutropenia or thrombocytopenia (0.5–0.99 and 50–99×10^9/l, respectively) lasted at least 2 weeks, the dose was reduced to 135 mg/m^2 (one-level reduction) in the subsequent courses and when it was grade 4 (< 0.5 and $< 50 \times 10^9$/l) with or without febrile neutropenia or bleeding, the dose was reduced to 110 mg/m^2 (two-level reduction) in subsequent courses. For non-hematological toxicity, the dose was reduced to 135 mg/m^2 with grade 3 mucositis. Paclitaxel was not longer administered when intolerable paresthesias and/or marked motor loss occurred.

Interruption of paclitaxel infusion was required in the presence of significant hypersensitivity reactions (defined as hypotension requiring medication, angioedema, respiratory distress requiring bronchodilator therapy and generalized rash). Patients received full supportive care, including transfusions, antibiotics, antiemetics, steroids, anti-diarrheals and analgesics when appropriate. The prophylactic use of colony stimulating growth factors was not allowed. During chemotherapy, complete blood cell counts were performed weekly and biochemistry blood profiles only at day 1 of each course.

Evaluation of response

Tumor response was evaluated after the third course of chemotherapy by either laparoscopy or exploratory laparotomy, unless patients had clinical evidence of progression. In the latter case, a computed tomography scan was performed to confirm progression. Complete response was defined as the complete disappearance of all measurable disease. Partial response was recorded as a $> 50\%$ reduction in the sum of the product of the two longest perpendicular diameters of all measurable lesions. No change or stable disease was defined a $< 50\%$ decrease or $< 25\%$ increase in the sum of the product of the two longest perpendicular diameters of all measurable lesions. Progressive disease was defined as a $> 25\%$ increase in the sum of the product of the two longest perpendicular diameters of one measurable lesion (even with the regression of the other lesions) or the appearance of new ones. The decision regarding continuation of taxol treatment was made on the basis of tumor response. Patients with stable or progressive disease discontinued the treatment protocol. Patients in complete or partial response continued treatment until a maximum of six courses.

Toxicity

The toxicity to chemotherapy was recorded after each course of chemotherapy according to WHO criteria. Survival was considered from the date of diagnosis until death or last visit and progression-free survival from the date of diagnosis until the time of first progression. Curves were constructed according to the Kaplan–Meier method [8] and comparisons between groups were performed with the log-rank test [9].

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Results

Patient characteristics

From November 1993 to December 1995, 30 patients were accrued into this study. Twenty patients were recruited at the Instituto Nacional de Cancerología, México City, and 10 at Centro Médico del Potosí, San Luis Potosi. The clinical characteristics of patients are shown in Table 1. The mean age was 49.84 years (19–70); most had a ECOG 0–1; the most frequent histological variety was serous adenocarcinoma in 56% of cases and most tumors had a differentiation grade of 2 (47%) and 3 (37%). All patients underwent primary cytoreduction; 17 patients (57%) had a residual tumor < 2 cm and in 13 patients (43%) the residual tumor was > 2 cm.

Clinical response

Response could be evaluated in 27 patients. Three patients were not evaluated because of the following: one patient received only one course of paclitaxel because of severe paresthesia, another patient had a severe soft tissue infection unrelated to study medication and the third patient had sudden death at day 2 of the third course. Objective responses were seen in 18 patients (66.4%) (95% CI 49.5–83.2). Of these, 12 were complete (45%) and six were partial (22%) responses. Four patients had stable disease (15%) and five patients progressed to chemotherapy. Ten (83%) of the 12 complete responses occurred in patients with residual tumors < 2 cm, whereas this type of response was seen only in two (17%) patients with residual tumors > 2 cm.

Toxicity

A total of 149 courses with taxol was administered to 30 patients. The median number of courses administered was 4 (range 1–6). Hematological toxicity was manifested as neutropenia in 21 of 30 patients (71%), grade 3/4 in 13%. Only two patients presented a single episode of neutropenic fever without confirmed infection. No severe thrombocytopenia or anemia was observed (Table 2). With regard to non-hematological toxicity, some degree of alopecia was observed in almost all patients. Peripheral neuropathy, myalgia and arthralgia were frequent, but transitory and relieved with analgesics. Only one patient developed severe myalgia and arthralgia requiring hospitalization and i.v. analgesics; this patient was discontinued from the study. Dose reductions were not required for this toxicity. Cardiac toxicity grade 1 was observed in 3.5% of the courses. The dose was reduced to 135 mg/m^2 in three patients. There were two deaths during this study. One of them was a patient that developed a gluteal abscess followed by toxic shock and died while she was off therapy; another patient died at home on day 2 of the third cycle, but it was not possible to establish a causal association of her death with the study medication. No hypersensitivity reactions were reported.

Table 1 Patient characteristics

Patients entered	30
Evaluable for toxicity	30
Evaluable for response	27
Age [years (range)]	49.8 (19–70)
ECOG performance status [*n* (%)]	
0	22 (73.3)
1	5 (16.3)
2	3 (10.3)
Histology [*n* (%)]	
serous	17 (56.6)
endometroid	4 (13.3)
mucinous	3 (10.0)
mixed	4 (13.3)
other	2 (6.60)
Differentiation grade [*n* (%)]	
1	5 (16)
2	14 (47)
3	11 (37)
Residual disease (cm) [*n* (%)]	
<2	13 (43)
>2	17 (57)

Table 2 Toxicity to chemotherapy expressed as percentage of courses (149 courses)

Toxicity	Grade 1/2	Grade 3/4
Mucositis	39	0
Diarrhea	2	0
Nausea/vomiting	29	0.9
Allergic	0	0
Peripheral neurotoxicity	61	4.5
Pain: myalgia/artralgia	18.5	0
Cardiac rhythm	3.5	0
WBC/neutropenia	58	13
Anemia	18	0
Thrombocytopenia	31	0

Salvage treatment

A total of 19 patients received second- or third-line chemotherapy. In all cases it was based on cisplatin (cisplatin/cyclophosphamide in 17 cases and cisplatin/vinorelbine in two cases). Second-line therapy because of no response or progression was offered in two and five cases, respectively; however, five patients who only achieved partial response to first-line paclitaxel also received second-line therapy before clinical progression. Third-line salvage treatment was used in nine patients (two platinum-based, five non-platinum-based and one tamoxifen).

Time to progression (TTP) and survival

Follow-up was available to all patients—the median follow-up time was 44.5. months (0–99). In the intention-to-treat analysis of the 30 cases, a TTP of 16.6 months and median survival of 43.1 months were observed (Fig. 1). Thus, 28 and 36% of patients were progression-free and alive, respectively. The analysis of survival with regard to the status of residual disease showed a highly significant difference for both TTP and survival between patients with < 2 and > 2 cm tumors. The median TTP was 38 versus 5.4 months ($p = 0.0004$), respectively (Fig. 2); whereas for survival the median has

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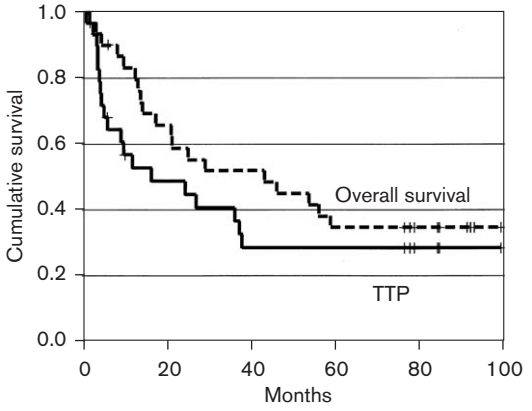
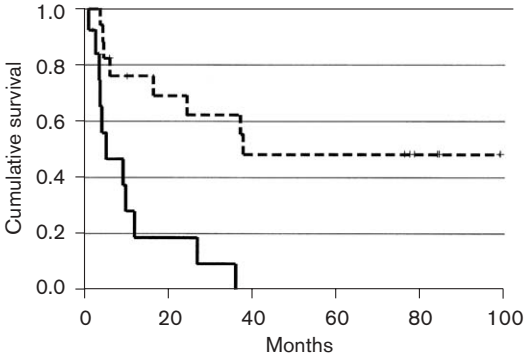
Fig. 1



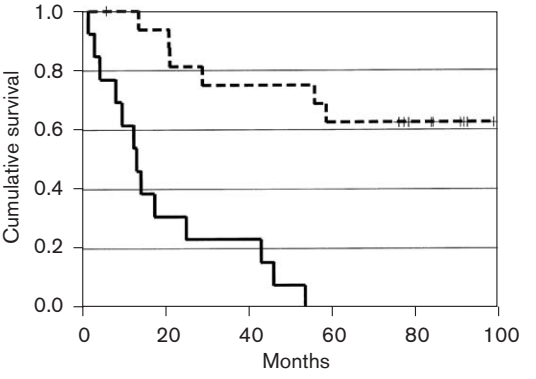
Overall survival and TTP. At a median follow-up of 44.5 months (0–99) in the intention-to-treat analysis, the TTP was 16.6 months and the median survival 43.1 months. At a maximum follow-up of 99 months, 28 and 36% are progression-free and alive respectively

Fig. 2



TTP according to residual disease. TTP stratified for residual disease <2 (dotted line) and >2 (solid line) cm. There was a statistically significant difference between both groups: 38 versus 5.4 months ($p=0.0004$), respectively.

Fig. 3



Overall survival according to residual disease. Overall survival stratified for residual disease <2 (dotted line) and >2 (solid line) cm. There was a statistically significant difference between both groups: 13.4 months for patients with >2 cm tumors, whereas the median survival has not been reached for those with <2 cm tumors ($p<0.00001$).

not been reached for patients with <2 cm tumors and was 13.4 months for patients with >2 cm tumors ($p<0.00001$) (Fig. 3). There were no statistically significant differences in TTP and survival when the analysis excluded the five patients in partial response who received second-line therapy before clinical progression (data not shown).

Discussion

Since the late 1980s, paclitaxel has been recognized as a promising drug in the treatment of ovarian cancer [10]. Several clinical studies using paclitaxel as a single drug in pretreated ovarian cancer have reported substantial activity with objective responses rates that range from 21 to 37% and complete responses in around 6% of patients [11–13]. The effectiveness of taxol as second-line and salvage therapy for ovarian carcinoma patients led to its combination with cisplatin. The GOG 111 and OV-10 studies showed the superiority of the paclitaxel/cisplatin combination over cisplatin/cyclophosphamide [3,4]; latter on, carboplatin was substituted for cisplatin with no loss of efficacy [5,6]. Thus, paclitaxel carboplatin has become the new standard of treatment in advanced ovary carcinoma.

However, recent studies have raised questions concerning the efficacy of this combination as compared to either of the two agents alone. The ICON III study failed to show significant benefit for paclitaxel combinations in 2075 previously untreated patients with ovarian cancer [14]. In this three-arm study, the paclitaxel/carboplatin combination was no more effective in terms of survival than the arm of single-agent carboplatin or the cyclophosphamide/cisplatin/doxorubicin combination. In addition, the GOG 132 study found no differences in the overall survival among single-agent cisplatin, single-agent paclitaxel or the combination of both agents [7]. The latter study has been interpreted as a comparison of combined versus sequential therapy.

The long-term results of our present study using single-agent paclitaxel administered at 175 mg/m^2 in the classical 3-week schedule further support the high efficacy of this drug when used as a single agent for advanced ovarian carcinoma. Response rate, progression-free and survival obtained in this study in stage III patients are comparable to those results obtained in the randomized trials of paclitaxel combined with platinum

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compounds. We obtained responses in 67% of patients with median progression-free and survival of 16.6 and 43.1 months, respectively, as compared to 73%, 18 and 38 months respectively from the GOG 111 study, [3] and 78%, 15.5 and 35.6 months respectively in the OV-10 study [4]. Of note, our results and those from the GOG 111 and OV-10 studies are similar in progression-free survival when compared to the patients receiving single-agent paclitaxel in the GOG 132 study [7].

Few studies have evaluated paclitaxel as a single agent in untreated patients with ovary cancer. Einzig *et al.* treated 34 stage IV ovarian cancer patients with paclitaxel at 180–250 mg/m^2 by 24-h infusion. They observed a response rate of 20% and a median survival of 27 months for the responding patients [15]. In another study performed on stage IV patients using paclitaxel at 225 mg/m^2 every 3 weeks, the overall response rate in 33 patients was 39.4%; interestingly, the response rate to carboplatin in those patients failing within 1 year was 57% and the median survival for all patients was 17.2 months [16]. Only one study of first-line paclitaxel has been reported on suboptimally resected stage III patients [17]. In that study, the schedule used was 175 mg/m^2 infused over 3 h every 3 weeks, as in the present report. The response rate and the median survival observed in the 34 evaluable patients were 55% and 6.1 months, respectively. The response rate and the median survival were shorter than those obtained in the present report; these differences could be explained on the basis that we included patients with optimal and suboptimal residual disease. These different survival probabilities are well established for both groups of patients as observed in this report, where the median TTP for optimal and suboptimal residual disease patients was 38 versus 5.4 months ($p = 0.0004$), respectively.

Highly heterogeneous patients have been accrued in studies using single-agent paclitaxel, including different doses and schedules of this agent; various proportions of patients in stages III and IV were used, and also variable status of disease after cytoreduction. These conditions preclude valid comparisons among these studies; however, all the results together strongly suggest that single-agent paclitaxel is at least as effective as the combination with a platinum compound in terms of survival. However, in many trials including the present one—where 19 out of 27 patients received cisplatin—patients were changed to platinum at relapse, which suggests that the sequential therapy is as effective as the combined one.

In a background of comparable efficacy, toxicity turns out to be a central issue. It is remarkable that when paclitaxel is administered at 175 mg/m^2 by a 3-h infusion the myelosuppression is not as severe as when it is used at 200 mg/m^2 by a 24-h infusion. In the latter case, grade 3/4 neutropenia was observed in only 13% of the patients and usually had a brief duration. Only one patient required the use of colony stimulating factor and dose reduction. No severe thrombocytopenia or anemia was observed.

In summary, our results show that single-agent paclitaxel is an effective first-line therapy in advanced ovarian carcinoma. Alternative schedules for its administration are actively being pursued to reduce its toxicity and increase its efficacy. In particular, the dose-dense approach of paclitaxel is very effective and turns out to be a well-tolerated treatment even for platinum/paclitaxel refractory patients [18]. Also, dose-intense paclitaxel combined with cisplatin/cyclophosphamide is promising in poor-prognosis advanced ovarian cancer [19]. In addition, it is possible that the dose-dense schedule may have anti-angiogenic effects that can potentially overcome tumor resistance [20]. All these data suggest that single-agent paclitaxel is a valid schedule of chemotherapy for advanced ovarian cancer and can be the first choice in patients with compromised renal function or with impaired hearing, and that dose-dense paclitaxel should be explored as first-line therapy and compared to triplets or sequential doublets incorporating newer drugs such as gemcitabine, liposomal doxorubicin and topotecan, among others.

Acknowledgments

We are in debt to Dr Steven Haworth for his comments, suggestions and support during the preparation of this manuscript.

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