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Docetaxel in Advanced Ovarian Cancer: Preliminary Results from Three Phase II Trials

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Docetaxel has been evaluated in 293 patients with advanced ovarian cancer in three phase II trials. All patients had previously received cisplatin and/or carboplatin as first-line treatment. In all three studies, treatment comprised docetaxel 100 mg/m^2 as a 1 h intravenous infusion every 3 weeks, without premedication for hypersensitivity reactions or emesis. To date, 200 patients are evaluable for response. Of these, 63 patients achieved complete or partial response, giving an overall response rate of 31.5% (95% confidence interval 24–39%) for all evaluable patients, or 21.5% for all patients entered in the studies. Of the 57 patients whose disease had progressed either during previous therapy or within 4 months of discontinuing previous therapy, 13 (23%) responded to docetaxel (EORTC data). Major adverse effects of docetaxel observed in approximately half the patients (particularly those who received more than four courses) included skin reactions and fluid retention. Grade III or IV neutropenia was common but short-lived. Severe acute hypersensitivity reactions occurred in approximately 5% of patients. Docetaxel now warrants evaluation as part of first-line therapy. Studies aimed at reducing the incidence of fluid retention and skin reactions with docetaxel are ongoing.

Key words: docetaxel, phase II clinical trials, iatrogenic disease, ovarian neoplasms
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INTRODUCTION

DOCETAXEL (Taxotere®) is a semisynthetic taxoid compound prepared from the needles of the European yew tree (*Taxus baccata* L.) [1]. It inhibits microtubule depolymerisation and has demonstrated a broad spectrum of activity in preclinical studies [2]. *In vitro*, docetaxel is approximately twice as potent as paclitaxel, and results from an *in vivo* study suggest that it has a therapeutic index superior to that of paclitaxel [3]. In another *in vivo* study, both docetaxel and paclitaxel showed superior activity to cisplatin in ovarian cancer xenografts [4]; similar findings have been observed against various cell lines in a wide range of *in vitro* studies [5].

Phase I trials of docetaxel have been conducted employing a range of doses and administration schedules. Clear-cut responses were seen in several patients, including those with ovarian or breast cancer. Neutropenia was the dose-limiting adverse effect, and mucositis was a complicating factor with prolonged infusion times and 5 day protocols [6–10]. Acute hypersensitivity reactions (HSRs) were reported occasionally, but these were rarely severe. It was, therefore, considered appropriate to proceed to phase II studies without routine prophylaxis.

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PATIENTS AND METHODS

Patients reported in this review were entered into one of three phase II studies; these have previously been published in abstract form [11–13]. The studies were performed by the Early Clinical Trials Group (ECTG) of the European Organization for Research and Treatment of Cancer (EORTC), the Clinical Screening Group (CSG) of the EORTC and the MD Anderson Cancer Center (MDACC), U.S.A. Patients were eligible for inclusion if they had bidimensionally measurable advanced epithelial ovarian cancer with haematological and biochemical parameters within preset limits, and evidence of progressive disease during or after previous platinum therapy. In both EORTC studies, patients were grouped according to the response to, and interval since, prior chemotherapy, although slightly different criteria were used in each study (Table 1). In the MDACC study, all patients were essentially refractory to cisplatin- or carboplatin-containing regimens administered as first- or second-line therapy.

Docetaxel 100 mg/m^2 was administered as a 1 h intravenous (i.v.) infusion, repeated at 3 week intervals. No routine premedication was given. However, patients who experienced an acute HSR to docetaxel generally received prophylaxis (with H_1- and H_2-antagonists and corticosteroids) before administration of subsequent courses. Response was assessed after two courses; responding patients continued therapy until either objective

Table 1. Patient stratification in EORTC studies according to either the response to, or interval since, prior chemotherapy with cisplatin and/or carboplatin

	ECTG Study	CSG Study
Group	Interval since previous chemotherapy (No. of patients)	Response to previous chemotherapy (No. of patients)
I	<4 months (43)	Relapse <4 months after first-line treatment (44)
II	4–12 months (55)	No response after first-line treatment or relapse after second-line treatment (43)
III	>12 months (25)	Relapse >4 months after first-line treatment (39)

disease progression or unacceptable adverse events occurred. Dose reductions of 25% were prescribed in the event of either neutropenia (neutrophil count $<0.5 \times 10^9/l$) lasting longer than 7 days, or fever requiring antibiotics in association with neutropenia. Dose escalation to 115 mg/m^2 was possible in the MDACC study provided that neutropenia was absent; however, this occurred in only 3 patients.

Response criteria were those accepted by UICC. Although CA 125 measurements were made with every course of treatment, the results were not used in the response assessment. A separate evaluation of the potential contribution of CA 125 measurements to the response assessment is currently underway.

RESULTS

At the time the analysis was performed, a total of 293 patients had been entered into the studies (Table 2). 43 patients were not yet evaluable for response, and the responses in a number of other patients had yet to be subjected to external review. The results, must, therefore, be regarded as preliminary.

Following external review, the responses of 31 patients were considered to be unevaluable because of equivocal radiological findings. A further 19 patients were considered to be ineligible for evaluation for various reasons.

Of the remaining 200 patients, 10 were considered to have achieved a complete response and 53 patients achieved a partial response, giving an overall response rate (OR) in evaluable patients of 31.5% (95% confidence interval (CI) 24–39%) (Table 3). 85 patients (42.5%) had disease stabilisation (DS) and 46 (23%) had progressive disease (PD). When expressed as the proportion of total patients entered into the study (n = 293), these results were 21.5% (OR), 29.0% (DS) and 15.7% (PD), respectively. For patients in groups I, II and III in the combined EORTC studies (Table 1), the overall response rates for the patients evaluable so far are 23% (13 of 57); 30% (20 of 67) and 44% (16 of 37), respectively.

Responses were seen at all disease sites, including liver, pelvis, lung and lymph nodes. At present, the data are too preliminary to assess response duration; currently this ranges from 2 to 8 months. In many patients, responses are continuing to be observed.

The adverse event profile of docetaxel is summarised in Table 4. In some instances data are not yet complete, but the overall percentage incidences reflect the general experience which is consistent throughout the studies. Grade III–IV neutropenia occurred frequently but was generally uncomplicated, and <10% of neutropenic episodes were febrile. No deaths due to myelosuppression were recorded. As in other studies, weight gain was related to the development of peripheral fluid retention. This, together with pleural effusions and ascites, has been a frequent finding in studies of docetaxel, especially in patients receiving multiple cycles of therapy. The problem is of particular concern in trials with ovarian cancer, where development of ascites is generally taken to represent disease progression. 94 patients experienced weight gain in the ECTG trial. This was

Table 2. Patient details for phase II studies of docetaxel

	Study			
	ECTG	CSG	MDACC	Total
Total No. of patients entered	123	126	44	293
Median age (years; range)	54 (30–75)	57 (26–69)	52 (26–69)	
Total No. of evaluable patients	85	75	40	200
Total No. of other cases				
Too early to evaluate	7	33	3	43
Not evaluable	24	6	1	31
Not eligible	7	12	0	19

ECTG, Early Clinical Trials Group of the EORTC; CSG, Clinical Screening Group of the EORTC; MDACC, MD Anderson Cancer Center, U.S.A.

Table 3. Results of phase II trials of docetaxel by study and type of response

Response	Study				% of total evaluable patients* (n = 200)	% of total patients entered (n = 293)
	ECTG	CSG	MDACC	Total		
CR (No. of patients)	3	6	1	10	5	3.4
PR (No. of patients)	23	17	13	53	26.5	18.1
PD (No. of patients)	21	22	3	46	23	15.7
OR (% of total evaluable patients)	31	31	35	31.5		
OR (% of total patients entered)	21	18	32	21.5		

CR, complete response; PR, partial response; PD, progressive disease; OR, overall response rate. For other abbreviations see legend to Table 2.
*Response in many patients was too early for analysis, but these patients were not unevaluable *per se*.

Table 4. Incidence and severity of major adverse effects of docetaxel

Adverse effect	Incidence
Neutropenia (grade III or IV)	83/99 patients (84%)
Acute hypersensitivity (grade II–IV)	13/207 patients (6%)
Skin reactions (grade II–IV)	98/188 patients (52%)
Fluid retention or effusions	102/181 patients (56%)*
Neuropathy (grade II–III)	11/95 patients (12%)

*Incidence was 66% in patients who received six courses of docetaxel.

severe in only 7/43 (16%) patients receiving up to four courses of docetaxel; however, in 53% (27/51) of those receiving more than four courses, weight gain amounting to >5% of the baseline weight occurred.

Skin reactions to docetaxel occurred frequently, but these were usually mild to moderate in severity. The reactions were characterised by pruritus, urticaria with maculae, and erythema with or without vesiculae or desquamation or nail changes. In the MDACC trial, affected patients experienced any or all of these symptoms, often in association with weight gain; however, skin reactions could be ameliorated by use of topical and/or systemic corticosteroids. As regards other adverse effects, acute HSRs occurred rarely in all the trials, and significant nausea and/or vomiting were negligible. Alopecia was virtually universal.

DISCUSSION

The interim results of these three phase II trials are relatively consistent and clearly show that docetaxel is an active drug for the treatment of refractory ovarian cancer. Although preliminary, the results already suggest that efficacy is related to the response to prior therapy but the response rate is still over 20% in the refractory patients. This is particularly encouraging, since patients whose initial therapy is ineffective have little prospect of responding to further treatment with cisplatin or carboplatin [14].

It is inevitable that attempts will be made to compare these results to those obtained with paclitaxel [15]. At present it is clear that the adverse event profile of docetaxel, which is characterised by the development of fluid retention and skin reactions, differs from that of paclitaxel. However, in contrast to the studies of docetaxel in which routine prophylaxis was not employed, patients in virtually all clinical trials of paclitaxel were routinely premedicated with a combination of dexamethasone and H_1- and H_2-antagonists. It is possible, therefore, that the adverse effects seen with docetaxel represent an unusual type of delayed HSR. Ongoing phase II trials of docetaxel, in which routine prophylaxis is being administered, will address this important issue. Evidence to support the view that premedication will be effective in reducing the development of these adverse effects has come from a subgroup analysis of patients treated with docetaxel in one ECTG centre. Patients receiving prophylactic therapy after the development of an acute HSR in the first and second courses experienced less subsequent fluid retention than patients who did not receive such therapy [16].

Present data are, as yet, insufficient to enable reliable comparisons of efficacy between docetaxel and paclitaxel. The overall response rate for paclitaxel, obtained by pooling the results of three published phase II trials in patients with previously treated ovarian cancer, is 30% (33/111 patients) [17–19]; this is similar to the response rate achieved with docetaxel. In due course, randomised comparative studies between the two drugs, either alone or in combination, will be conducted. If these involve previously treated patients, it will be important to pay particular attention to their response to prior therapy. In addition, dosages and schedules for each drug investigated in a comparative study must be chosen carefully. Extrapolation from *in vitro* comparisons of potency suggests that a dose of 100 mg/m^2 of docetaxel is equivalent to 200–250 mg/m^2 of paclitaxel. However, this dose of paclitaxel is considerably higher than the maximum dose tolerated when the drug is administered as a 24 h infusion in the absence of colony-stimulating factors.

At present, it can only be concluded that docetaxel is a promising new drug with significant activity in the treatment of ovarian cancer. Its precise role in the management of this disease will depend on the results of studies investigating combined docetaxel/cisplatin therapy. A recently reported study suggested significant superiority of paclitaxel/cisplatin over cyclophosphamide/cisplatin as first-line therapy for ovarian cancer [20]. Combination feasibility trials of docetaxel/cisplatin are ongoing, and the results are awaited with great interest.

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