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Review

Phase II Trials of Docetaxel (Taxotere®) in Advanced Ovarian Cancer—an Updated Overview

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Docetaxel (Taxotere®) has been studied at a dose of 100 mg/m² i.v. as a one hour infusion every 3 weeks, in four phase II trials in patients with extensively pretreated ovarian cancer. A total of 340 patients were treated, including 256 patients in two separate EORTC (European Organization for Research and Treatment of Cancer) trials and 84 patients in two trials in the U.S.A. All patients had received prior cisplatin or carboplatin therapy and the treatment-free interval was less than 4 months in 155 patients. The overall response rate using conventional UICC criteria was 30% among 315 evaluable cases (95% confidence interval: 24–36%). Among 155 patients whose disease was most refractory (i.e. treatment-free interval was less than 4 months), the overall response rate was 28% (95% confidence interval: 19–36%). Response duration ranged from 4 to 17 months. Grade IV neutropenia was a common finding and fluid retention was observed. The incidence of febrile neutropenia ranged from 8 to 44% of patients with two deaths (i.e. 0.6% of the total treated) related to neutropenic sepsis. Docetaxel and paclitaxel (Taxol®) have comparable activities in ovarian cancer. Ongoing studies with docetaxel include its use in patients as part of first-line therapy, as well as in patients refractory to paclitaxel. To prevent the development of fluid retention, these now involve the routine use of steroid prophylaxis. It is expected that docetaxel will prove to be an important addition to the drugs available for the treatment of ovarian cancer. © **1997 Elsevier Science Ltd.**

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INTRODUCTION

TAXOIDS HAVE been identified as an important new class of cytotoxic agents for the treatment of epithelial ovarian cancer. Their efficacy in this indication has been confirmed in the context of first-line therapy in a randomised GOG (Gynaecology and Oncology Group) phase III study in which patients with suboptimally debulked Stage III/IV ovarian cancer received treatment with cisplatin, 75 mg/m² and either paclitaxel, 135 mg/m² over 24 h, or cyclophosphamide, 750 mg/m². A total of 410 (386 eligible) patients were randomised and the results showed a significant improvement, particularly in median survival, for the paclitaxel–cisplatin combination (38 months versus 24 months with cyclophosphamide–cisplatin, $P < 0.001$) [13].

Docetaxel offers an alternative taxoid treatment to paclitaxel of intriguing potential. It is more potent *in vitro* than paclitaxel and preclinical studies suggest a superior therapeutic index [3]. Potential clinical advantages include ease of administration (a one hour infusion versus longer treatment times) and a different side-effect profile, providing an alternative for those paclitaxel combination regimes where synergistic toxicity, e.g. neurotoxicity, has been noted. We have previously reported a preliminary phase II experience with docetaxel in advanced ovarian cancer [9], and this report now represents updated and extended results in over 300 patients. Reports of individual trials involving most of these patients have recently been published [1, 7, 8, 15].

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PATIENTS AND TREATMENT

All the patients in the studies reviewed here were previously treated with platinum compounds and had recurrent or progressive disease. Patients had received a maximum of two prior chemotherapy regimens. The four studies included 256 patients in two multicentre trials in Europe and 84 patients in two single-institution trials in the U.S.A. All patients were treated (without routine premedication) with an initial dose of docetaxel, 100 mg/m^2 i.v. every 3 weeks; dose modifications were generally as described previously [9]. In one study (from the MD Anderson Cancer Center) an alternative policy was pursued, i.e. the use of supplemental G-CSF to maintain full doses of docetaxel if the initial neutrophil nadir fell below 1.0×10^9/l. Response assessment was conducted by standard UICC criteria and involved external review (by independent radiologists). The two European studies [1, 15] both involved EORTC groups (i.e. the Early Clinical Trials Group [ECTG] and the Clinical Screening Group [CSG]. The U.S.A. studies [7, 8] were performed at the Memorial Sloan Kettering Cancer Center (MSKCC) and the MD Anderson Cancer Center (MDACC). The numbers of patients, median age and interval since prior platinum exposure in the four studies are shown in Table 1.

RESPONSE RATES

The results from the four docetaxel studies are shown in Table 2. In the ECTG study, patients were described as non-evaluable if they did not have evidence of disease as shown by a bidimensionally measurable CT scan. In the most refractory patients (treatment-free interval 0–4 months) there was a response rate of 20%. The response rate was higher in patients who had the longer treatment-free interval (35%), but this was not statistically significant ($P = 0.093$). The CSG trial showed similar results to those seen in the ECTG study in that the response rate differed according to interval since prior therapy. The two U.S. studies showed slightly higher response rates than the European studies. This may relate to the fact that the U.S. studies were conducted in single institutions, whereas the EORTC studies were conducted on a multicentre basis; other prognostic factors are discussed below.

Response duration (measured from the time response was confirmed) and survival were similar in all these studies (Table 3). When the four phase II trials were analysed together, the overall response rate in 315 evaluable patients was 30% (93/315) (95% confidence interval: 24–36%). For the patients with a treatment-free interval of less than 4 months, the response rate was 28% (44/155) (95% confidence interval: 19–36%). For the other patients with more than 4 months treatment-free interval, the response rate was 31% (49/160).

CA125

Because of the acknowledged difficulties in accurately determining the response of intraperitoneal disease using established radiological techniques, the ECTG have examined serial measurements of CA125, the cancer-associated antigen, as a tool for measuring tumour response [16]. The CA125 criterion for response was defined as a minimum of 50% reduction on at least three serial samples confirmed at 4 weeks [17]. This compares with standard clinical (WHO) criteria which require CT scan measurability. Of the total 132 eligible patients, CA125 evaluation was possible in 109 and of these 45 (41%) responded. Of the 116 who were evaluable clinically, 32 (28%) had an objective response using standard criteria. A total of 23 patients were found to have responded using both methods of assessment; a further 14 patients showed a CA125 but not a clinical response, compared with an additional 7 patients who showed a clinical but not a CA125 response.

Table 1. Patient characteristics in the four phase II docetaxel trials in ovarian cancer

	ECTG	CSG	MDACC	MSKCC	Total
No. of patients	132	124	59	25	340
Median age (range)	54 (30–75)	57 (35–76)	58 (26–70)	59 (36–73)	—
No. of evaluable patients	116	121	55	23	315
Interval since prior platinum (no. of evaluable patients in each group)					
0–4 months	35	46	55	19	155
4–12 months	41	75	—	4	120
> 12 months	40	—	—	—	40

Table 2. Results of the four docetaxel trials

	ECTG			CSG		MSKCC	MDACC
	0–4*	4–12*	> 12*	0–4* (I)	> 4* (II–III)		
No. eligible patients	42	48	42	48	76	25	59
No. evaluable patients	35†	41†	40†	46	75	23	55
Complete response	0	2	1	1	7	0	3
Partial response	7	9	13	7	16	8§	19
No change	15	18	14	20	23	10	21
Progressive disease	9	11	11	18	29	5	12
Overall response rate‡	20%	27%	35%	17%	31%	35%	40%

*Treatment-free interval in months. †Non-evaluable chiefly on response assessment. ‡Response rate in evaluable patients. §7 of 8 had a treatment-free interval of 0–4 months.

Table 3. Response duration and survival in the ECTG, MDACC and MSKCC studies

	ECTG	MDACC	MSKCC	CSG
Median response duration (months) (range)	6.7 (4.1–17.4)	4.5 (1–12)	5.0 (3–9)	5.8 (1.4–13.5)
Median survival (months)	8.4	10	8	10.4

Table 4. Main toxicities associated with docetaxel administration in ovarian cancer

Grade 3–4 toxicity	Percentage of patients
Neutropenia	90–96*
Stomatitis	0–5
Diarrhoea	6–10
Dermatitis	4–8
Acute hypersensitivity reactions	7–12
Fluid retention (severe)	8–12

*Febrile neutropenia 8–44%, includes two neutropenic deaths.

As regards other studies, all eight responders in the MSKCC study showed a more than 80% decline in CA125 levels [7]. In this and other trials, however, patients demonstrated symptomatic benefit with a fall in CA125 without a clearly documentable clinical response. Thus, serious consideration is currently being given to the proposition that CA125 measurements be incorporated into standard response criteria.

TOXICITY

The profile of toxicity was similar in each of the four trials, and the range of incidence of significant (grade 3/4) side-effects is shown in Table 4. Fluid retention of any degree was seen in 44–71% of patients, but was described as severe, i.e. leading to treatment withdrawal, in only 8–12% patients. These trials did not incorporate steroid premedication. Data from other studies suggest that the use of routine prophylaxis (with steroids) significantly reduces the degree of fluid retention [18] and this procedure is incorporated in all current docetaxel studies.

DISCUSSION

Docetaxel clearly demonstrates activity in patients with previously treated ovarian cancer. The overall response in 315 evaluable patients in four phase II trials with docetaxel, 100 mg/m^2 i.v. every 3 weeks, was 30%. Interestingly, this level of activity is maintained even in those patients with a treatment-free interval of < 4 months; the response rate was 28% in the 155 most refractory patients. The data suggest that docetaxel is at least as active as paclitaxel, particularly in very refractory patients. Response rates for paclitaxel in relapsed ovarian cancer range from 21 to 48% depending on dose and prior exposure [5, 12, 19]; a large population-based study of 1000 patients with platinum-refractory disease gave a response rate of 22% [20]. The overall response rate was somewhat lower, at 17%, in 382 evaluable patients treated in a European–Canadian trial which randomised for two doses of paclitaxel in platinum pretreated patients [6]. Survival rates following paclitaxel are also comparable to those achieved with docetaxel [12]. Detailed comparisons, however, are not possible because equitoxic doses of the two taxoids have not generally been used and in due course, randomised comparative trials (probably as first-line therapy) will be appropriate. At present it is clear that the two drugs have rather different spectrums of toxicity. They also differ in respect of cellular pharmacology, for example, paclitaxel cellular efflux is significantly (3-fold) faster than that for docetaxel in tumour cell lines [10]. This may partly explain the differences seen in schedule dependency, whereby paclitaxel activity evidently relates to duration of exposure [11], a feature not seen with docetaxel. Interestingly, longer exposure to docetaxel reveals toxicities (e.g. mucositis) which are rarely observed with a 1-h infusion [4].

An important issue is whether there are specific factors predicting response to docetaxel, including the dose received. In fact, part of the data from this review (the EORTC studies) has been included in a larger examination of this particular issue, which included data on 704 patients treated in phase II trials in ovarian cancer with 6 drugs, including 237 patients treated with docetaxel [22]. A total of 10 factors (excluding dose received) were examined by stepwise logistic regression and the two independent factors predicting response were found to be tumour burden (size and number of sites) and histology (serous). Interestingly, time from last chemotherapy was not an independent predictive factor, but it correlated significantly with tumour size ($P = 0.0005$).

It is not possible to assess the impact of dose received in this analysis since most patients received at least two cycles at full dose (100 mg/m^2). The majority of dose reductions were actually made after two cycles in patients who were continuing treatment because of evidence of response (with the exception of one study in which GCSF was used). A proper assessment of the impact of dose on response would therefore require prospective studies at different dose levels.

In summary, further clinical trials are now indicated with docetaxel to be used as part of a first-line therapy, perhaps in combination with cisplatin, carboplatin and/or anthracyclines. Preliminary information from one feasibility study indicates that a regime of docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 (with steroid prophylaxis) would be suitable as first-line chemotherapy [21]. It will also be important to assess the activity of docetaxel after paclitaxel failure particularly as increasing numbers of patients receive this drug as part of front-line treatment. In view of its ease of administration, it is expected that docetaxel will prove to be an important addition to the drugs available for the treatment of ovarian cancer.

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