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Progress in the treatment of ovarian cancer

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With an overall response rate (ORR) of 30% in 315 evaluable patients in phase II trials, single-agent docetaxel has a level of activity in extensively pretreated ovarian cancer which is at least equivalent to and possibly superior to that of other new agents such as paclitaxel. In an initial series of 100 patients treated with the combination of docetaxel 75–85 mg/m² plus cisplatin 75 mg/m², the ORR was 66%. However, the combination was associated with a range of toxicities and only two-thirds of the patients were able to complete all six prescribed cycles. The combination of docetaxel with carboplatin has proved to be better tolerated while maintaining activity (ORR 67%). Based on these results, a randomized trial comparing docetaxel (75 mg/m²) in combination with carboplatin (AUC 5) versus paclitaxel (175 mg/m²) plus carboplatin (AUC 5) is underway. These results will provide important information on the role of docetaxel in the treatment of ovarian cancer. [© 1999 Lippincott Williams & Wilkins.]

Key words: Carboplatin, combination, docetaxel, ovarian cancer, paclitaxel.

Introduction

Whilst the outlook for the management of ovarian cancer has improved, the majority of patients still die from this disease, with a 5-year survival rate of 30%.[1,2]

New treatment options are needed and the taxoids have become increasingly important in this setting. Two randomized trials have confirmed the activity of paclitaxel in the first-line therapy of ovarian cancer.[3,4] This development, along with the widespread use of carboplatin, means that the overall outlook for treatment in 1998 was undoubtedly brighter than in the past. Currently, the optimal therapy for ovarian cancer involves the combination of the taxoid paclitaxel with a platinum compound. However, improvements in survival for patients with ovarian cancer are still clearly needed.

Docetaxel in advanced ovarian cancer

In vivo, docetaxel is 2–3 times more potent than paclitaxel and, perhaps more importantly, has demonstrated a superior therapeutic index.[5] Intracellularly, the two taxoids bind to different tubulin polymers and different cellular pharmacokinetics lead to longer intracellular retention of docetaxel.[5] There is incomplete cross-resistance between docetaxel and paclitaxel in a range of pre-clinical models.[5,6]

Phase I clinical trials of docetaxel identified 1 h infusion as the optimal means of administering the drug.[7–12] Additionally, antitumor activity was observed in patients with ovarian cancer in phase I studies. Neutropenia was dose limiting. The edema which emerged as an unexpected toxicity is now preventable with the use of steroids.[13]

In ovarian cancer, four separate phase II trials [conducted by the Early Clinical Trials Group (ECTG), Clinical Screening Group (CSG), MD Anderson Cancer Center (MDACC) and the Memorial Sloan Kettering Cancer Center (MSKCC)] have shown docetaxel to be active when administered at a dose of 100 mg/m² , as a 1 h i.v. infusion, every 3 weeks.[14–20] In total, an overall response rate (ORR) of 30% was observed in the 315 evaluable patients (all of whom had previously received platinum) (Table 1). These results are at least equivalent and possibly superior to that seen with paclitaxel. Among the 155 patients defined as having refractory disease (with a treatment-free

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Table 1. Overview of the initial phase II studies with single-agent docetaxel in ovarian cancer[14–20]

	ECTG	CSG	MDACC	MSKCC
No. of evaluable patients	116	121	55	23
Median age (years)	54	57	58	59
Interval since prior platinum				
(a) 0–4 months	35	46	55	19
(b) 4–12 months	41	75	–	4
(c) >12 months	40	–	–	–
Complete/partial response (overall response rate) according to interval (a), (b), (c)	(a) 0/7 (20%) (b) 2/9 (27%) (c) 1/13 (35%)	1/7 (17%) 7/16 (31%)	3/9 (40%)	0/7 (37%) 0/1 (25%)

ECTG, Early Clinical Trials Group; CSG, Clinical Screening Group; MDACC, MD Anderson Cancer Center; MSKCC, Memorial Sloan Kettering Cancer Center. Adapted with permission from Kaye *et al.*[15]

interval of less than 4 months), the response rate was 28% and the median response duration 7 months.

It would appear that docetaxel 100 mg/m^2 might produce more grade III/IV neutropenia and skin/nail toxicity but less peripheral neuropathy and myalgia than 175 mg/m^2 paclitaxel. Further, the administration of the 1 h docetaxel infusion is more convenient.

Docetaxel in combination with platinum

Based on these considerations and on the phase II evidence of activity, the Scottish Gynaecological Cancer Trials Group have conducted a series of studies of docetaxel/platinum combinations as first-line therapy in advanced ovarian cancer.

Docetaxel in combination with cisplatin

In an initial series, 100 patients received 75 mg/m^2 cisplatin plus either 75 or 85 mg/m^2 docetaxel every 3 weeks, together with 5 days' prophylactic 8 mg b.d. dexamethasone.[21]

Sixty-six out of the 100 patients (66%) were able to complete six cycles of therapy. The major reason for discontinuation was cisplatin-induced toxicity, with no patients withdrawing because of edema. The ORR was 66%. Grade III/IV neutropenia occurred in 70% of patients and there were three neutropenic deaths, all among women who had received 85 mg/m^2 docetaxel.

Docetaxel in combination with carboplatin

Given accumulating evidence that carboplatin is equivalent in activity to cisplatin with decreased toxicities,[22,23] it was decided to investigate the combination of docetaxel with the less toxic platinum compound. There had been initial concern at the dose reductions which seemed necessary when carboplatin was used in combinations. However, this was largely dispelled by evidence showing that carboplatin could be given in full dose when combined with paclitaxel.[24]

In a phase I feasibility study, 141 patients were treated at five dose levels ranging from 60 to 85 mg/m^2 docetaxel plus carboplatin administered to achieve an EDTA-measured AUC of 5–7 mg/ml per min.[25] Treatment was administered every 3 weeks until the intended six cycles had been completed or toxicity supervened.

The combination of docetaxel with carboplatin proved less problematic than the combination with cisplatin. Ninety-one percent of patients were able to complete the scheduled six cycles. Although 86% experienced grade III/IV neutropenia, the neutropenia was prolonged in only 18% and there were no neutropenic deaths. Given the intensity of carboplatin treatment, unusually few patients (14%) developed grade III/IV thrombocytopenia and no patient required platelet transfusion. This suggests that the platelet sparing effect seen with the combination of paclitaxel and carboplatin extends to docetaxel and is a class effect of the taxoids.

As expected, alopecia was common, developing in 64% of patients. However, the incidence of edema (following use of a 3-day regimen of steriod prophylaxis), myalgia/arthralgia (6%) and sensory neuropathy (5%) was low. The latter is of particular interest, because the incidence reported for paclitxel–carboplatin incidence of sensory neuropathy is considerably higher (over 30%).

Two of the first six patients treated with docetaxel 85 mg/m^2 plus carboplatin at an AUC of 6 mg/ml per min developed dose-limiting toxicity (myelosuppression + diarrhea), as did two of six patients treated with 75 mg/m^2 docetaxel and carboplatin at an AUC of 7 mg/ml per min. These doses were thereafter defined as the maximum tolerated doses (MTD).

The ORR observed in the first 83 patients was 67%, with a 40% rate of complete response, and the median progression-free survival is 16 months (12.7–19.1 months).[25]

The doses recommended for further phase II studies were docetaxel 75 mg/m^2 and carboplatin AUC 5 mg/ml per min, given 3-weekly for three courses.

Randomized trials versus paclitaxel

There are suggestions that docetaxel in combination with carboplatin may have the advantages over paclitaxel of greater convenience of administration as an outpatient therapy, less neurotoxicity and (if the experience in ovarian cancer parallels that in breast cancer) potentially greater activity. However, confirmation of any relevant clinical differences can come only from a randomized controlled trial.

One such trial is now underway ('SCOTROC') in stage Ic–IV epithelial ovarian cancer. Patients are randomized to either docetaxel 75 mg/m^2 or paclitaxel 175 mg/m^2 (over 3 h), each administered with carboplatin to achieve an AUC of 5 mg/ml per min. Treatment will be continued every 3 weeks for six cycles. The aims of the study are to detect a relatively small difference in progression-free survival between the two arms of 25% (or to establish clinical equivalence within the same limit) and to compare toxicities (particularly neurotoxicity). It is intended that 1050 patients will be recruited from 75 centers in Europe, Australia and North America within 2 years.

However, there is still concern in some quarters that the combination of paclitaxel with carboplatin may not provide the appropriate control arm (instead of paclitaxel/cisplatin). In this context, it is relevant to note that three randomized trials comparing paclitaxel plus cisplatin with paclitaxel/carboplatin have been conducted. Preliminary data from two of these show no difference in progression-free survival between these two treatment options, although mature survival data are not yet available.[26,27]

In addition to answering questions relevant to choice of therapy, large studies such as that of carboplatin plus docetaxel or paclitaxel also offer the opportunity of answering more fundamental questions about factors determining response, i.e. underlying clinical drug resistance.

Mismatch repair deficiency, which determines how tumor cells react to DNA damage, may be relevant to mechanisms of drug resistance. It is now possible to investigate this property of tumor cells not only by biopsy (difficult in the case of ovarian cancer) but also by looking at tumor DNA in blood. An equally important question is whether variation in surgical practice influences outcome and the SCOTROC trial will also involve international audit of the initial operative procedure.

Discussion

Although the results of treatment for ovarian cancer have improved over the past 20 years, in the majority of cases the disease is still fatal.[2,28] For most cases initial chemotherapy is essential and two randomized trials have confirmed the superiority of paclitaxel-containing regimens over earlier 'standard' regimes.[3,4] However this combination is not without side-effects, including neurotoxicity.

Docetaxel is an alternative taxoid, with increased potency, a better therapeutic index and partial non-cross-resistance compared to paclitaxel in pre-clinical models.[5,6] Additionally, activity has been observed with docetaxel in patients with ovarian cancer who had failed prior paclitaxel-containing chemotherapy.[29] Phase II trials confirmed at least equivalent activity in patients with platinum-refractory ovarian cancer (response rate of 28% in pooled total of 155 patients from four studies) and an overall response of 30% in 315 evaluable platinum pretreated patients.[14–20] Toxicity includes myelosuppression and alopecia, but earlier problems with edema have been abrogated by the use of prophylactic steroids.

The incorporation of docetaxel into first-line regimes for ovarian cancer, together with cisplatin, and subsequently carboplatin, in two successive feasibility trials run by the Scottish Gynaecological Cancer Trials Group was successful with ORRs of 66 and 67%, respectively.[21,25] The docetaxel/carboplatin combination proved to be better tolerated than the docetaxel/cisplatin combination. Complicated neutropenia was rare. Interestingly, grade III/IV thrombocytopenia was also unusual, occurring in 14% of cases and this is similar to the

experience with paclitaxel combined with carboplatin. A major difference, however, is that significant neurotoxicity is rare, occurring in only 5% of cases, in comparison to reports of 30–70% incidence with paclitaxel (3 h) in combination with carboplatin.

The randomized trial which is now underway, comparing six cycles of paclitaxel (175 mg/m^2 in 3 h) and carboplatin (AUC 5) with six cycles of docetaxel (75 mg/m^2) and carboplatin (AUC 5), will be important in determine any significant difference in progression free survival between the two arms, and importantly should be able to demonstrate any differences in side-effects, particularly neurotoxicity.

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