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Ovarian Cancer—New Insights into Systemic Therapy

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THE 5-YEAR survival rate of patients with advanced ovarian cancer treated with cisplatin-based chemotherapy is between 20 and 30%, with median survival of 2 years. Current standard therapy involves appropriate surgery followed by either cyclophosphamide (750 mg/m^2) plus cisplatin (75 mg/m^2) every 3 weeks or cyclophosphamide (500 mg/m^2), doxorubicin (50 mg/m^2) and cisplatin (50 mg/m^2) every 3 weeks [1]. Debate continues as to whether carboplatin is as effective as cisplatin in combination schedules. Data from comparative studies have to be analysed with special attention to cross-over, dose delivered, postponement of treatment and follow up. Most trials suggest equivalent results between carboplatin and cisplatin regimens, but with current data European-Canadian investigators recommend that carboplatin should not routinely replace cisplatin in the treatment of patients with potentially curable, low volume disease [2].

The introduction of taxanes into the therapeutic armentarium has stimulated intense discussion about the role of paclitaxel for initial treatment and treatment of relapse. Integration into standard treatment has been criticised because of the inconvenience of the 24-h administration schedule, the side effects of paclitaxel plus cisplatin, and the expense. The Gynecologic Oncology Group (GOG) performed a study in 388 patients with suboptimally debulked stage III and IV disease. The paclitaxel combination resulted in a superior response rate (77% of the cisplatin–paclitaxel patients as opposed to 64% of the cisplatin–cyclophosphamide patients, $P = 0.02$) and more surgically complete responses. More importantly, a statistically significant improvement in progression-free interval was found (median 18 versus 13 months). Median survival was 24 months for cisplatin–cyclophosphamide, and 38 months for the paclitaxel combination [3]. Based on these data obtained in a subgroup with large volume of residual disease, the combination of paclitaxel and cisplatin may be the most effective treatment available today for poor prognosis patients. However, it is felt by some European and Canadian institutions that a confirmatory study is needed before paclitaxel–cisplatin can be recommended as the new standard.

Ozols and co-workers are investigating the combination of paclitaxel with carboplatin as an attractive option in a phase I GOG trial. First reports indicate that it is feasible to combine paclitaxel and carboplatin in an adequate dose of each drug with acceptable toxicity [4].

For the treatment of recurrent disease, the role of paclitaxel appears to be limited. In patients with platinum refractory ovarian cancer, who had at least three prior chemotherapy regimens, the objective response rate was 22% (95% confidence interval 19 to 25% [5]). These results are comparable to results obtained with other drugs in platinum resistant ovarian cancer. For example, etoposide (100 mg) taken orally for 14 days every 21 days resulted in a response rate of 21% among 28 patients who had cancer that progressed while they were receiving a platinum analogue [6].

Efforts to identify new drugs continue. Docetaxel is a semisynthetic compound structurally related to paclitaxel. A more pronounced skin toxicity than with paclitaxel was reported, and in addition, many patients developed oedema after prolonged treatment [7]. The Early Clinical Trial Group of the EORTC reported a response rate of 25% in patients progressing on cisplatin or with progressive disease within 4 months of a cisplatin containing regimen [8].

2′,2′-Difluorodeoxycytidine (Gemcitabine) is a primary antimetabolite with a close structural resemblance to cytosine-arabinoside. In a multicentre phase II study, patients who had received a maximum of two prior treatment regimens received Gemcitabine on a weekly base for 3 consecutive weeks, followed by a fourth week of rest. The majority of patients had bulky disease and all had received prior platinum containing chemotherapy. Eight of 42 evaluable patients (19%; 95% confidence limits 9–34%) achieved a partial response. Treatment with Gemcitabine was very well tolerated [9]. Although encouraging, more studies are needed in ovarian cancer to confirm the results obtained.

Patients who receive retreatment are incurable, and thus toxic side effects must be balanced against possible benefit. Patients who at first relapse after responding to platinum therapy (and not being resistant to cisplatin), are likely to respond again. The chances of second line response depends on a variety of factors. In the European-Canadian paclitaxel study, the maximum diameter of disease, serous histology and normal haemoglobin predicted response [10].

There is little doubt that among the new agents currently explored, important additions to our chemotherapy armentarium will be identified. The results of ongoing phase III trials will most likely change the present standard treatment of ovarian cancer.

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Taxoids

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INTRODUCTION

TAXOIDS REPRESENT an important new class of cytotoxic drugs because they possess a unique mechanism of action. Their target is the cytoplasmic microtubule, and in contrast to the vinca alkaloids, they prevent rather than promote disassembly, thereby disrupting the process of cell division. Development of these drugs has been protracted for over 20 years because of the initial problems of an insufficient drug supply, as well as the concerns over hypersensitivity reactions seen in early clinical trials. Essentially, taxoids are extracts from either the Pacific or the European Yew tree. The initial extraction from the bark was grossly inefficient; more recent semi-synthetic processes using the needles as precursors have solved supply problems, allowing clinical development to accelerate.

PACLITAXEL AND DOCETAXEL

So far, there are two taxoids available for clinical evaluation; doubtless other analogues will shortly emerge. Paclitaxel (Taxol) was the first taxoid to reach the clinic, and it is now marketed in several countries for the treatment of refractory ovarian cancer [1]. Docetaxel (Taxotere) differs from paclitaxel in two separate positions on the taxane ring structure [2]; in preclinical studies, this leads to an increase in its potency over the parent compound and some increase in solubility, although both compounds are insoluble in water and require formulation in lipophilic solvent. The preclinical spectrum of activity and the animal toxicology are similar for the two compounds, although some of the data do suggest some differences in respect of schedule-dependent activity, as well as partial non-cross resistance, and the possibility of an improved therapeutic index with docetaxel [2].

The difference in preclinical potency between the compounds is of the order of 2–3 fold, and this translates fairly closely to the results of clinical Phase I trials. For paclitaxel, the maximum tolerated dose (MTD) without G-CSF support was originally reported as 200 mg/m^2 [3]. This related to a 24 h infusion given 3 weekly, and included the use of premedication comprising steroids, antihistamines and 5-HT$_2$ antagonists, all of which had been developed because of occasional severe hypersensitivity reactions in the initial trial. The dose-limiting toxicity for paclitaxel was neutropenia; alopecia was universal and peripheral neuropathy and mucositis were occasionally seen and were dose-dependent. Recent studies indicate a most interesting difference in toxicity using a shorter (3 h) infusion; myelosuppression is less pronounced, allowing higher doses to be given with no increase in hypersensitivity reactions, but the impact on antitumour efficacy is not yet clear. Indeed, current Phase I trials are exploring both shorter and longer infusion times (1–96 h); it remains to be seen whether significant differences between the schedules causing maximal myelosuppression and those giving optimal efficacy will emerge.

For docetaxel, the MTD is approximately half that of paclitaxel, i.e. 115 mg/m^2 when the drug was given over 1–5 h, and is 90 mg/m^2 when the drug is given over 24 h, in both cases 3 weekly [4, 5]. Again, neutropenia is dose-limiting, and in the early Phase I trials hypersensitivity reactions were rare. Hence, premedication was not given routinely and its toxicity profile was seen to be similar to paclitaxel. As experience with docetaxel extended, a significant difference was noted, namely a trouble-

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