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REVIEW

Paclitaxel and Docetaxel in Advanced Ovarian Cancer

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The taxoids, paclitaxel and docetaxel, represent a novel class of antineoplastic drugs. They share similar mechanisms of action, i.e., the promotion of microtubule assembly and the inhibition of microtuble disassembly.[1-3] Paclitaxel (Taxol) is a taxane analog extracted from the bark of the Pacific yew, Taxus brevifolia. Docetexel (Taxotere) is a semisynthetic taxoid derived from the needles of the European yew, Taxus baccata. An efficient semisynthetic process using a renewable drug source led to extensive preclinical testing. Although the molecular structures are similar, the toxicity are different. Docetaxel causes cumulative edema but less neuropathy.[4] Premedication to prevent anaphylactoid reaction is necessary with both taxoids. For paclitaxel, premedication consists of oral steroids and parenteral diphenhydramine plus cimetidine before drug administration. With docetaxel, oral steroids are started 24 hours before treatment and continued for a total of 5 days. Docetaxel should be administered through tubes not lined with polyvinyl chloride. Both compounds have a significant clinical activity in platinum-resistant ovarian cancer (Table 1, 2).[5-17]

Paclitaxel as a single agent in previously treated patients

In platinum refractory ovarian cancer, paclitaxel has a consistent activity, with response rates ranging from 20 to 48%.[9] The activity of paclitaxel seems to be dose dependent. The dose commonly reported in trials range from 135 to 250 mg/m^2 with infusion duration of 3 to 24 hours. Three phase II trials included 111 patients with prior platinum-based combination chemotherapy.[5-7] The paclitaxel dose ranged from 110 to 250 mg/m^2 infused over 24 hours every 3 weeks. Overall, 20 to 37% partial response with 7 patients achieved complete response. Responses

Table 1. Studies of Paclitaxel in refractory and advanced ovarian cancer

Institution	No. of Patients	Dose, mg/m^2	Overall response (%)	CR % (No.) (Months)	Median Survival
Single Agent					
JHOC[5]	40	135 (110-170)	30	2.5 (1)	8.2
GOG[6]	41	170	37	12 (5)	15.9
Einstein[7]	30	180-250	20	3 (1)	6.5
NCI-TRC[8]	619	135	22	3	9
European-Canadian[9]	195	135	15	1 (2)	11.0
High Dose (with G-CSF)					
NCI[10,11]	44	250	48	14	11.5
M.D. Anderson[12]	48	250	48	4	12.0
UK[13]	155	135 - 175	16	1.3 (2)	8.1

CR = complete response, G-CSF = granulocyte colony - stimulating factor, GOG = Gynecology Oncology Group, JHOC = Johns Hopkins Oncology Centre, NCI = National Cancer Institute, TRC = Treatment Referral Centre.

Table 2. Docetaxel phase II trials in advanced ovarian cancer

Study	No. of patients	CR No. (%)	Total Response (CR + PR)
EORTC[14]	97	4 (4)	23 (24)
EORTC[15]	76	6 (4)	26 (34)
MSKCC[16]	23	-	8 (35)
MDACC[17]	55	3 (6)	22 (40)

CR-Complete remission ; PR-Partial remission ; MDACC-M.D. Anderson Cancer Centre ; MSKCC-Memorial Sloan-Kettering Cancer Centre

were 40 to 50% in platinum-sensitive tumours and 24 to 30% in platinum-resistant tumours. The median duration of response was 6 months. The overall median survival was 11 months (17 months in patients with platinum-sensitive tumours and 9 months in those with platinum-resistant tumours).[10] The NCI designated Comprehensive Cancer Care provided paclitaxel 135 mg/m^2 in a

24-hour infusion to patients with platinum-refractory ovarian cancer and demonstrated 22% response rate (4% complete response, 18% partial response).[8] The median survival was 9 months.

The effect of dose intensification of paclitaxel on outcome is suggestive in ovarian cancer. Nonrandomized studies have been made to better define dose intensification with paclitaxel in this disease.[11,12] Paclitaxel was given as a single agent at 250 mg/m^2 over 24 hours to patients with platinum-resistant ovarian cancer. Granulocyte colony-stimulating factor (G-CSF) also was administered starting 24 hours after completion of paclitaxel infusion. Objective tumour response was seen in 48% of patients. The duration of response was 6 months and the median survival was 12 months.

In an attempt to define the optimal dose and duration of paclitaxel infusion, a joint European- Canadian trial coordinated by the National Cancer Institute of Canada prospectively randomized patients to two dose levels of paclitaxel(135 or 175 mg/m^2) and two different infusion schedules (3 or 24 hours).[9] Responses were more frequent at larger doses (20% vs. 15%) and with longer infusion (19% vs. 16%). Though neither of these differences in response was statistically significant, paclitaxel at 175 mg/m^2 given over 3 hours was recommended in that study. The recommendation was based on the greater response rate and the lesser haematopoietic toxicity with more convenience and lesser cost of the 3-hour infusion. A recent study from Gynecologic Oncology Group / Southwest Oncology Group/ North Central Cancer Treatment Group / Eastern Cooperative Oncology Group (protocol 134) which compared paclitaxel at dose 175 mg/m^2 with 250 mg/m^2 infused over 24 hours with G-CSF support administered every 3 weeks.[18] They concluded that there is a dose-response effect but more toxicity and no survival benefit for the dose 250 mg/m^2 versus 175 mg/m^2 as a second line therapy (overall response 27.5% in 175 mg/m^2 vs. 36% in 250 mg/m^2 group ; survival 12.5 vs. 11.9 months respectively). Kudelka et al reported similar results as the median survival is comparable in two dose group despite the difference in response rates (overall response 21% in 135 mg/m^2 vs. 48% in 250 mg/m^2).[19] The role of high dose paclitaxel remains to be proven.

Interestingly, patients with at least a six-month paclitaxel-free interval and previously low dose paclitaxel (135 mg/m^2), or a complete response with high dose paclitaxel (250 mg/m^2) may respond to high dose paclitaxel retreatment.[20,21]

Paclitaxel based regimens in newly diagnosed patients

Paclitaxel plus cisplatin

McGuire et al reported the final result of Gynecologic Oncology Group 111 study in 1996, compared cisplatin plus cyclophosphamide and paclitaxel plus cisplatin as first-line therapy in suboptimally debulked (> 1 cm diameter of residual mass) refractory ovarian cancer patients.[22] Patients were randomized to receive either 750 mg/m^2 cyclophosphamide and 75 mg/m^2 cisplatin or 135 mg/m^2 of paclitaxel and 75 mg/m^2 of cisplatin. They reported an overall response (OR) 73% and median survival (MS) 38 months in paclitaxel plus cisplatin arm and an OR 60% and MS 24 months in cisplatin plus cyclophosphamide arm, respectively. The progression-free survival on each arm was 18 and 13 months, respectively. The toxicity of the paclitaxel cisplatin was considered to be clinically manageable. However, some doubts exist about

the reproducibility of this result.[23-26] The overall survival data of this subgroup has not been reported. The use of salvage paclitaxel may result in an overall survival which is comparable to its use with platinum as primary therapy. The dose-schedule of paclitaxel used on this study may not have been optimal as that remains to be defined. This promising result of one phase III study should be confirmed before cisplatin with paclitaxel in this dose schedule can supplant a platinum compound combined with alkylating agent as standard initial therapy. Moreover, the quality of life and cost-utility should be studied prospectively.

Paclitaxel plus carboplatin

The rationale for substitution of cisplatin to carboplatin in this combination is that carboplatin is as effective as cisplatin with less toxicity. Based on early clinical data, carboplatin (like cisplatin) should be given after the paclitaxel administration.[27] However, studies showed that paclitaxel has no effect on the pharmacokinetics of carboplatin. Currently, carboplatin is infused after the completion of paclitaxel infusion. Interestingly, thrombocytopenia appears to be less severe than expected leading to the suggestion that paclitaxel provides some protection against carboplatin induced thrombocytopenia.[28] A phase I study of the Gynecologic Oncology Group in this combination was reported with an overall response rate of 75% (complete response 67%) and a median progression-free survival of 15 onths.[29] Accordingly, the combination of paclitaxel 175 mg/m^2 over 3 hours followed by carboplatin dosed with a target area under the curve of 7.5 mg/ml (min every 3 weeks was recommended for a phase III Gynecologic Oncology Group trial.[30] Meerpohl et al recommended dose for phase III trial is paclitaxel dose 185 mg/m^2 and carboplatin AUC 6 mg/ml (min.[31]

Paclitaxel based regimens in pretreated patients

Guastalla et al performed a study of paclitaxel 175 mg/m^2 infusion over 3 hours with carboplatin area under the curve of 5 mg/ml (min infusion over 30 minutes administered every 3 weeks in pretreated advanced ovarian cancer patients.[32] They reported an overall response rate of 41% (complete response 12%) with a median duration of response of 8 months. They concluded that this regimen is effective, safe and convenient for outpatient administration.

Docetaxel

Docetaxel has significant activity in the treatment of many type of malignancies such as breast, lung, gastric, and pancreatic cancer. For ovarian cancer, it provides a response rate of 17-37%.[33,34] From European Organization for Research and Treatment Centre study, Kaye et al reported an overall response rate of 31.5% with docetaxel in 200 previously platinum treated patients at dose of 100 mg/m^2 as 1- hour intravenous infusion every 3 weeks.[35] Similarly, Piccart et al reported the result of their study using docetaxel at the same dose and schedule in 97 patients with platinum-refractory ovarian cancer and they reported an overall response rate of 23.5% with a median overall survival of 8.4 months.[14] A study from M.D. Anderson Cancer Centre demonstrated the result of docetaxel 100 mg/m^2 1 hour infusion every 3 weeks in 55 platinum-refractory patients. A response rate of 40% and median overall survival of 10 months were noted.[17] Premedication to prevent anaphylactoid reaction was used with this drug. The main problem associated with docetaxel use is the development of fluid retention, including

pleural effusions and ascites. The frequency and severity increase with increasing total dose of this drug. This side effect becomes problematic as the cumulative dose exceeds 400 mg/m^2. It has been ameliorated with systemic steroids and with early diuretic use on evidence of fluid retention.

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