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Paclitaxel Chemotherapy in Refractory Epithelial Ovarian Cancer : A 32 Cycle Experience

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ABSTRACT

Objective To report our experience in using 200 mg/m^2 paclitaxel every three weeks in platinum resistant epithelial ovarian cancer patients between September 1994-August 1995.

Design Cross-sectional study.

Setting Ramathibodi Hospital.

Subjects Platinum-resistant epithelial ovarian cancer recruited for Taxol Chemotherapy between September 1994-August 1995.

Main outcome measures Response of tumour to chemotherapy according to WHO criteria.

Results The patients tolerated this regimen fairly well, acheiving one complete response, two stable disease and one progressive disease.

Conclusion Paclitaxel may be considered for refractory epithelial ovarian cancer patients with tolerable toxicity.

Key words : paclitaxel, refractory epithelial ovarian cancer

Ovarian cancer is the leading cause of gynaecologic cancer death.[1] Despite the introduction of platinum-based chemotherapy, epithelial ovarian cancer death rate remains high.[2] Seventy percent of patients with epithelial ovarian cancer will initially have a response to platinum-based chemotherapy, but resistance and progression will ultimately develop in 60% - 80%.[2,3] The

problem of treating this group of patients confronts the physicians.

Paclitaxel is a novel antineoplastic agent that is isolated from the bark of the western Yew tree, Texas brevifolia. Paclitaxel promotes microtubule assembly by preferentially binding to polymerized tubulin[4] and has documented activity against a number of solid tumours including ovarian cancer.[5]

We report our experience in using paclitaxel in platinum resistant ovarian cancer.

Materials and Methods

Patient eligibility : Patients must have (1) histologically proven epithelial ovarian cancer, (2) platinum resistance, (3) measurable disease, (4) Zubrod performance status grade 0-2, (5) expected survival of > 3 months, (6) absolute granulocyte count > 1,500/ul, platelet count > 100,000/ul, Hb > 8.5 gm/dL, (7) > 4 weeks from the last chemo/radiation therapy, (8) adequate financial support.

Treatment plan : Paclitaxel 200 mg/m^2 was administered as a 24-hour continuous infusion that was delivered in 1 L of 5% dextrose solution. All patients received standard premedication of cimetidine 300 mg and diphenhydramine 50 mg, which were given intravenously 60 minutes before paclitaxel, and dexamethasone 20 mg, which was given 14 and 7 hours before paclitaxel to prevent acute hypersensitivity reactions. Granulocyte colony-stimulation factor (Filgastim 10 ug/kg per day or Lenogastim 5 ug/kg per day) subcutaneously was initiated

Table 1. Patient and disease characteristics

Characteristic	PT. 1	PT. 2	PT. 3	PT. 4
Age (year)	36	49	41	63
Zubrod performance score	1	2	1	2
Histology	clear cell	Serous cystadeno CA	Papillary serous cystadeno CA	Serous cystadeno CA
Tumour Grade	3	2	2	3
FIGO Stage	IA	IIIC	IIIC	IIIC
Year of diagnosis	1991	1994	1992	1993
Prior chemo. regimen	- CDDP + CTX - CARBO + CTX - CARBO + CTX	- CARBO + CTX	- CDDP + CTX - CARBO + CTX	- CARBO + CTX - CARBO + CTX
Site of tumour	Pelvis	Pelvis	Pelvis	Pelvis
Tumour diameter (cm)	8	7	7.5	8
No. of paclitaxel cycles	17	3	6	6
Response	SD	PD	CR	SD
Days of G - CSF use (mean)	7.5	7.7	8.3	8.5
Mean hospital stay (day)	11.2	11.0	11.3	11.6

PT = patient, CDDP = cis - diamminedichloroplatinum, CARBO = carboplatin, CTX = cytoxan, SD = stable disease, PD = progressive disease, CR = complete response

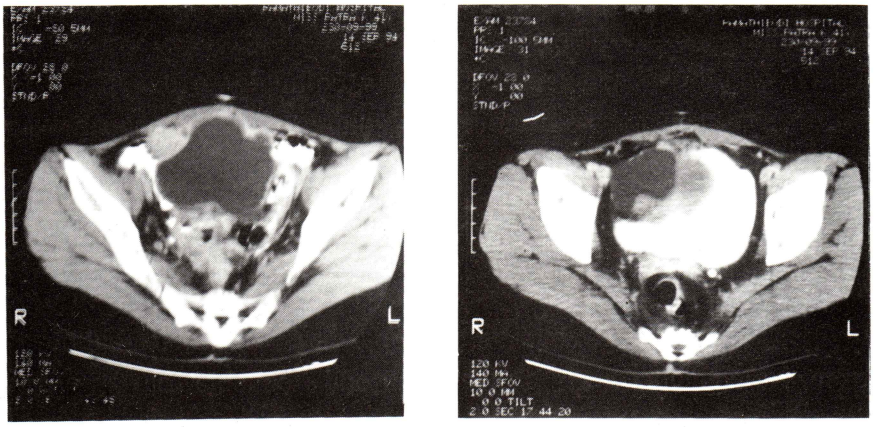
Table 2. Haematologic toxicity

Grade	PT. 1 (cycle) n = 17	PT. 2 (cycle) n = 3	PT. 3 (cycle) n = 6	PT. 4 (cycle) n = 6
WBC (x 10^3/uL)				
0 (≥ 4.0)	10	-	-	-
1 (3.0 - 3.9)	2	-	-	-
2 (2.0 -2.9)	2 (1*)	-	-	1
3 (1.0 - 1.4)	2 (2*)	3 (1*)	3	3
4 (< 1.0)	1 (1*)	-	3 (1*)	2 (1*)
Platelets (x 10^3 /uL)				
0 (≥ 100)	17	3	5	4
1 (75 - 99)	-	-	1	1
2 (50 - 74)	-	-	-	1
3 (25 - 49)	-	-	-	-
4 (< 25)	-	-	-	-
Anaemia (Hb)				
0 (≤ 11.0)	3	2	3	-
1 (9.5 - 10.5)	12	1	3	4
2 (8.0 - 9.4)	2	-	-	2
3 (6.5 - 7.9)	-	-	-	-
4 (< 6.5)	-	-	-	-

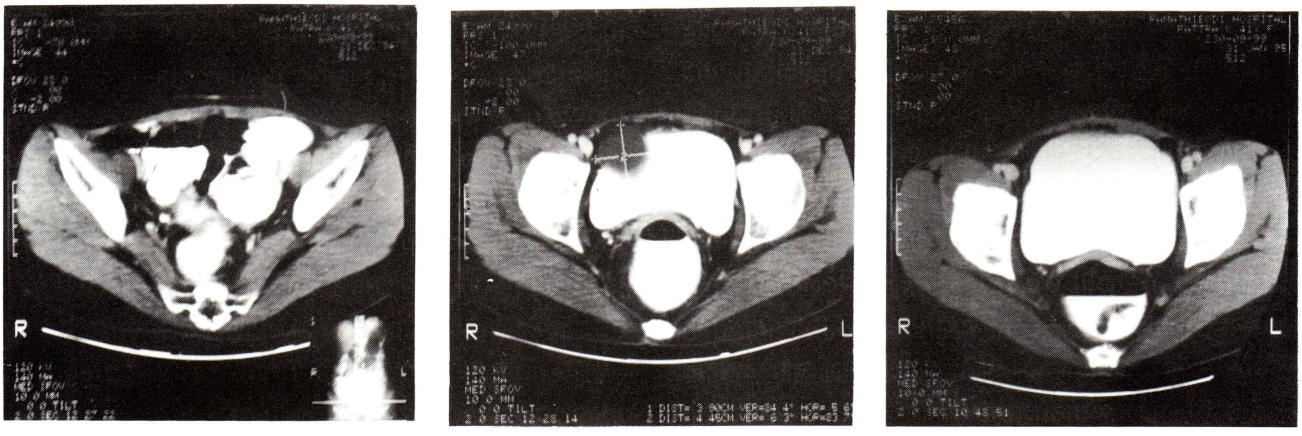
* Fever > 38°C

Table 3. Nonhaematologic toxicity

Type of toxicity	Maximum grade[9] PT. 1	PT. 2	PT. 3	PT. 4
Allergic	0	0	0	0
Gastrointestinal				
- Nausea/vomiting	1	1	1	1
- Diarrhea	0	0	0	0
Neurologic				
- Peripheral neuropathy	1	1	1	1
Cardiac	0	0	0	0
Alopecia	3	3	3	3



A, B. Before paclitaxel treatment.



C, D. After 3 cycles of paclitaxel.

E. After 4 cycles of paclitaxel.

Fig. 1. Computerized tomography of the disease in patient no. 3.

24 hours after the completion of paclitaxel until total WBC count > 3,000/ul.[6] Then the patient was discharged from the hospital. Paclitaxel administration will be repeated every 3 weeks.

Definitions : Complete response was defined as the complete resolution of disease by physical examination and radiographic examination and normalization of CA-125 lasting at least 4 weeks.

Partial response was defined as an 50% or greater reduction in the sum of the products of bidimensional measurements of all sites of disease (determined by physical examination and radiographic analysis) lasting at least 4 weeks and without the development of new lesions.

Stable disease was defined as any condition other than objective response or progressive disease.

Progressive disease was defined as a 25% or greater increase in the sum of the products of the perpendicular diameters of all measurable lesions and/or the development of new lesions.[7]

Platinum resistance was defined as disease progression during or within 6 months of the most recent platinum treatment.[8,9]

Results

During the period of September 1994 -

August 1995, there were 4 assessable patients. One case was clear cell carcinoma and 3 cases were serous cystadenocarcinoma. Patient and disease characteristics are summarized in Table 1. All had tumour recurrence/persistence in the pelvis. Patient no. 1 had stable disease after receiving 17 cycles of paclitaxel with mean G-CSF use of 7.5 days and mean hospital stay 11.2 days. Patient no. 2 had progressive disease after receiving 3 cycles of paclitaxel with mean G-CSF use of 7.7 days and mean hospital stay 11.0 days. Patient no. 3 had complete response after receiving 4 cycles of paclitaxel (after 3 cycles, tumour decreased in diameter from 7.5 cm to 3 cm and was undetectable after the 4th cycle-Fig. 1), so paclitaxel was continued for 2 cycles more. The mean G-CSF use was 8.3 days and mean hospital stay 11.3 days. Patients no. 4 had stable disease after receiving 6 cycles of paclitaxel with mean G-CSF use of 8.5 days and mean hospital stay 11.6 days.

Haematologic toxicity collected from nadir count of each series in each cycle. Haematologic toxicity was moderate and affected granulocytes more than platelets or red blood cells. Table 2 summarizes haematologic toxicity data. Febrile complication occurred in the cycles that had WBC < 3,000/uL (toxicity grade ≥ 2). Patients had fever in 7 out of 32 cycles of paclitaxel. All febrile episodes recovered after increased WBC count. Patient no. 1 and 2 had no episode of platelet < 100,000/uL. Patient no. 3 and 4 had 3 episodes of platelet < 100,000/uL. No platelet transfusion was required. No bleeding complication occurred. Mild anaemia (Hb 8-11 gm/dL) was observed in all patients.

Concerning nonhaematologic toxicity (Table 3), none had allergic reaction to paclitaxel, diarrhea or cardiac toxicity. Three patients had some nausea, patient no. 4 had some vomitting. All patients had mild peripheral neuropathy. All had complete alopecia. All treatment cycles could be restarted 21-25 days after previous cycles.

Discussion

This is our preliminary report of using paclitaxel in refractory epithelial ovarian cancer. In other reports using paclitaxel 135-175 mg/m^2, the overall response rate has ranged between 13 and 36%.[7,10-13] Using higher dose (200-250 mg/m^2), in 24 hour infusion the response rate was reported to be 48%.[6,14] So we choose paclitaxel in the dose of 200 mg/m^2 in 24 hr continuous infusion with G-CSF support with our patients. In our 4 patients with 32 cycles of paclitaxel, we obtained 1 complete response, 2 stable disease and 1 progressive disease. Report of percentage of response requires more patient number.

The patients had acceptable and managable haematologic toxicity with G-CSF support. Nonhaematologic toxicity were tolerable. The cumulative toxicity of paclitaxel was not appeared. So from our preliminary experience, paclitaxel may be considered for refractory epithelial ovarian cancer.

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