

Single Agent Paclitaxel in Resistant and Relapsed Epithelial Ovarian Cancer After First-line Platinum-based Chemotherapy—Experience in an Asian Population

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Abstract

The efficacy and toxicity profile of paclitaxel (Taxol®) was studied in 33 Singaporean women with epithelial ovarian carcinoma who had either failed to respond or relapsed after an initial response to first-line chemotherapy with combined platinum and cyclophosphamide. Paclitaxel was given intravenously as a single agent at a dose of 200 mg/m² over 3 hours, with standard pre-medication, at 4 weekly intervals. A total of 102 cycles were administered. The median number of cycles was 3 (range 1 to 8) per patient. Twenty-six patients were eligible for response evaluation. Six (23.2%) patients showed a complete response and 4 (15.4%) showed a partial response. Two (7.7%) patients had stable disease and 14 (53.8%) patients had progressive disease. The response rate was 22.2% (2 of 9 patients) for patients with progressive disease while on the first-line platinum-based chemotherapy, 37.5% (3 of 8 patients) for patients with response-relapse interval of less than 6 months, 40.0% (2 of 5 patients) for patients with response-relapse interval of 6 to 12 months, and 75% (3 of 4 patients) for patients with response-relapse interval of more than 12 months. The median duration of survival was 10 months for the entire cohort of patients, but all complete responders and 75% of partial responders survived the duration of the study period of 24 months, compared to 50% of patients with stable disease and 7% of patients with progressive disease. Toxicity of paclitaxel treatment was evaluated in 102 cycles. Grade 3 or 4 alopecia, grade 1 or 2 sensory peripheral neuropathy and mild facial flush occurred in all patients. Haematological toxicity was mild, with 9.8% of the cycles complicated by grade 3 or 4 neutropenia. Bone marrow suppression was of short duration. No treatment delay or dose modification was needed.

It is concluded that the effectiveness of paclitaxel for salvage treatment of patients with resistant or relapsed epithelial ovarian carcinoma after first-line platinum-based chemotherapy among Asian patients is comparable to that reported in Western populations. The treatment was well tolerated by our patients. It should be considered the chemotherapy of choice for patients with relapsed ovarian cancer after prior platinum-based chemotherapy.

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Introduction

Ovarian carcinoma ranks fourth among causes of death in women and is the leading cause of death from gynaecological malignancies in Western countries. In Singapore, the incidence of this cancer has been rising for the last 25 years.¹ Most cases of ovarian carcinoma are diagnosed late at FIGO stage III or IV. Despite radical cyto-reductive surgery and chemotherapy, the overall 5-year survival remains poor, approximately 10% to 20%.²

The most significant prognostic factors for survival are volume of residual tumour after cyto-reductive surgery and response to chemotherapy.^{3,4} Since the 1970s, the most effective chemotherapy has been cisplatin or its analogue carboplatin. A combination of cisplatin or carboplatin and cyclophosphamide is one of the most

widely adopted first-line regimens.⁵ Initial response rates to both single agent cisplatin and combination cisplatin chemotherapy are good, but majority of patients relapse within 2 years.⁶ Repeat treatment with cisplatin may be successful in patients who have a disease-free interval of 6 months or more.⁷ However, some patients develop intolerable toxicity and others exhibit multiple drug resistance. The overall outcome of these patients is dismal.

The introduction of paclitaxel in the late 1980s and early 1990s for clinical trials offered a hope of salvage therapy for these patients. The early phase II trials reported a tumour response rate of between 20% and 50% to single agent paclitaxel treatment in patients with platinum resistant epithelial ovarian carcinoma.⁸⁻¹² The duration of response ranged from 3 to 15 months. In

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these studies, grade 4 neutropenia which occurred in more than half of the patients was the dose limiting toxicity for paclitaxel treatment. Severe acute hypersensitivity reactions were prevented by pre-medication with anti-histamines, cortico-steroids and H_2 -receptor blockers.

Reports on the efficacy and adverse reactions of paclitaxel have been based on studies in Caucasian patients. There are no reported data on Asian patients. We therefore report our experience of paclitaxel single agent therapy in Singapore patients with cisplatin resistant or relapsed ovarian epithelial carcinomas. The aim of the study was to determine the tumour response rate, response interval and patient survival rate with this treatment.

Patients and Methods

Patients

All patients had staging laparotomy and cyto-reductive surgery with histologically confirmed ovarian epithelial carcinoma. They received at least one regimen of platinum-based chemotherapy. The tumour either progressed during the chemotherapy or recurred after a disease-free interval. All patients had measurable disease. Other eligibility criteria included good performance status, adequate haematological reserve (total white cell $\geq 2 \times 10^6$ /ml, haemoglobin ≥ 10 g/dl, platelet $\geq 100\ 000$ /ul), and normal liver and renal functions. Patients with significant ischaemic heart disease were excluded.

Regimen

Pre-medication with 20 mg dexamethasone orally 12 and 6 hours before chemotherapy and cimetidine 300 mg and Benadryl® 50 mg both intravenously immediately before chemotherapy were given to all patients. Paclitaxel (Taxol®) 200 mg / m² was administered via a 3-hour intravenous infusion. The treatment was repeated at 4 weekly intervals for a maximum of 8 cycles. Patients with progressive disease after 3 cycles were withdrawn from further treatment.

Follow-up

Patients were reviewed 1 week after chemotherapy for assessment of toxicity and symptomatology. Clinical examination was performed and haematological and biochemical parameters measured. Toxicities were graded according to the WHO classification.

After completion of chemotherapy, patients were followed up 3 monthly.

Assessment of Response

The classification of complete response and partial response, stable disease and progressive disease was carried out objectively by clinical, radiological (CT scan) and biochemical investigations. Serum CA 125 levels

were determined before and after each cycle of paclitaxel. Tumour response was first evaluated after 2 or 3 cycles, and again after completion of 6 cycles of treatment.

Definition of Response Groups

Response groups as defined by the WHO criteria are as follows:

1) *Complete response*: Defined as complete disappearance of all clinical evidence of tumour including normalisation of serum CA 125 level as determined by two observations not less than four weeks apart.

2) *Partial response*: Defined as more than or equal to 50% decrease in the sum of the products of measured lesions determined by two different observations not less than 4 weeks apart. No simultaneous increase in the size of any lesion or the appearance of new lesions may occur. Non-measurable lesions must remain stable or regress for this category.

3) *Stable disease*: Defined as a steady state of response less than partial response or progression less than that of progressive disease of at least 4 weeks duration. There may be no appearance of new lesions.

4) *Progressive disease*: Defined as the unequivocal increase of at least 25% in the sum of the product of measured lesions. Appearance of significant new lesions also constitute progressive disease.

5) *Duration of response*: Defined from the date when partial or complete response criteria were met until clinical or radiological progression of the disease.

6) *Survival*: Defined as the time from initiation of treatment with paclitaxel until death or until 31 July 1996 when the data analysis was completed.

Results

A total of 33 patients were treated with paclitaxel. The mean age at diagnosis was 54 years (range 27 to 79 years). Their characteristics are summarised in Table I. All patients received a dose of 200 mg / m² of paclitaxel per cycle. The median number of cycles administered per patient was 3 (range 1 to 8). Complete follow-up data were available in all the patients. Only those patients who received two or more cycles of paclitaxel were evaluable for response.

Response

Of the 33 patients, 7 were not evaluable for response. Three patients declined further chemotherapy with paclitaxel after one cycle. Four patients died before the second cycle. In no patient was paclitaxel chemotherapy withheld because of toxicity.

Of the 26 evaluable patients, 6 (23.1%) had a complete response after 3 to 4 cycles of paclitaxel over a period of 7 to 13 weeks. Four (15.4%) patients had partial response after 3 to 5 cycles of paclitaxel over 8 to 16 weeks and 2

patients had stable disease at the time of evaluation. Fourteen patients (53.8%) had progressive disease while on chemotherapy. Thus, the overall response rate was 38.5% with 23.1% of patients showing complete response (Table II). The median duration of response was 10 months (range 1 to 27 months). The response rates increased with the increased interval between initial platinum-based chemotherapy and relapse (Table III).

Survival

During the study period, none of the patients who relapsed received any other third-line chemotherapy. The median duration of follow-up for the entire cohort of patients was 24 months (range 4 to 69 months). The overall survival rate was 42.3% and the disease-free survival was 15.4%. Among responders, 90% of the patients survived while only 12.5% of non-responders

survived the study period ($P < 0.001$). The median duration of survival was 6.3 months (range 0.5 to 34.3 months). The survival for different response groups is shown in Table IV.

Toxicity

A total of 102 cycles among the 33 patients were eligible for analysis of toxicity. The most common toxicities encountered were gastro-intestinal disturbances, haematological and neurological toxicities (Table V).

Grade 3 or 4 neutropenia was reported in 9.8% of patients treated with paclitaxel. Generally, the duration of neutropenia was short and not associated with serious complications. Complete haematologic recovery occurred before the next cycle and there were no treatment delays or deaths due to toxicity. Fifteen patients experienced grade 3 neutropenia after one cycle and 1 patient had grade 4. Two patients required G-CSF rescue and 1

TABLE I: PATIENT CHARACTERISTICS

FIGO stage	n	%
I	4	12.1
II	3	9.1
III	23	69.7
IV	3	9.1
Histology		
Serous papillary	19	57.7
Mucinous	5	15.1
Endometrial	45	15.1
Clear cell	3	9.1
Others	1	3.0
Previous platinum-based regimen		
1 regimen	27	81.8
2 regimens	6	18.2
Initial surgery		
Optimal	20	60.6
Suboptimal	10	30.3
Biopsy only	3	9.1

Optimal surgery — Residual tumour ≤ 2 cm in diameter

Suboptimal surgery — Residual tumour > 2 cm in diameter

TABLE II: OVERALL INITIAL CLINICAL RESPONSE IN 26 ASSESSABLE PATIENTS

Response	Patients (n)	Response (%)
Complete response	6	23.1
Partial response	4	15.4
Progressive disease	14	53.8
Stable disease	2	7.7

TABLE IV: SURVIVAL OF PATIENTS IN DIFFERENT CLINICAL RESPONSE GROUPS

Response group	n	Alive/ NOD	Alive/ D	Died	Survival (%)
Complete response	6	4	2	0	100
Partial response	4	0	3	1	75
Stable disease	2	0	1	1	50
Progressive disease	14	0	1	13	7

Alive/NOD: Alive with no disease

Alive/D: Alive with disease

TABLE III: RESPONSE TO PACLITAXEL SALVAGE THERAPY ACCORDING TO INTERVAL-TO-RELAPSE AFTER PLATINUM-BASED CHEMOTHERAPY

Interval-to-relapse (m)	Response (no. of patients)					
	n	CR	PR	Stable	Progressive	Overall response
0	9	1	1	1	6	2 (22.2)
<6	8	2	1	0	5	3 (37.5)
6-12	5	1	1	1	2	2 (40.0)
>12	4	2	1	0	1	3 (75.0)
Total	26	6	4	2	14	10 (38.5)

CR: complete response; PR: partial response

TABLE V: TOXICITY ENCOUNTERED IN 102 CYCLES OF PACLITAXEL SALVAGE THERAPY

Toxicity	WHO Grade					
	0	1	2	3	4	3 or 4
Anaemia	1	70	27	3	1	4 (3.9)
Neutropenia	40	25	27	9	1	10 (9.8)
Thrombocytopenia	10	86	4	2	0	2 (2.0)
Neuropathy	35	41	23	3	0	3 (2.9)
Myalgia / Arthralgia	76	24	2	0	0	0 (0)
Diarrhoea	96	6	0	0	0	0 (0)
Sepsis	98	1	1	1	1	2 (2.0)

patient required hospitalisation and treatment with antibiotics for grade 4 sepsis.

No significant hyper-sensitivity reactions were reported. Minor reactions such as facial flush was the most commonly noted event. Grade 1 or 2 sensory neuropathy was encountered in a large number of patients after 1 or 2 cycles of paclitaxel, but they were not severe enough to compromise further treatment. Motor neuropathy was not encountered in any patient.

Alopecia was universal and was commonly of grade 3 or grade 4 severity. Nausea and vomiting of mild degree (grade 1 and grade 2) was reported by almost all the patients which was easily controlled by 5HT₃ antagonists. Grade 3 or 4 myalgia or arthralgia was not encountered, though most patients complained of less severe myalgia. Diarrhoea or loose stools was reported by 13 patients. One patient developed thrombophlebitis and was treated with antibiotics. There were no deaths reported due to toxicity.

Discussion

The overall response rate of 38.5% to paclitaxel single agent chemotherapy in our patients with recurrent ovarian cancer is similar to those reported in other phase II studies.⁸⁻¹² The median duration of response of 10 months compares favourably with that reported by McGuire et al⁸ and Thigpen et al.¹¹ The proportion with complete response (23.1%) observed in this study is higher than that reported by others.^{8,10,11} This may partly be due to the higher dose (200 mg/m²) of paclitaxel used in our patients as compared to the other studies.⁸⁻¹²

We observed that the tumour response rate to paclitaxel was low in patients with a short interval to relapse following platinum-based chemotherapy. However response rate to paclitaxel salvage therapy was higher in 3 out of 4 patients in whom this interval exceeded 12 months. Tumour biology may be the determining factor for failure of some tumours to respond to platinum as well as paclitaxel, despite differences in cytotoxic mechanisms between these drugs.

It is noteworthy that all 6 patients showing complete response survived the 24-month duration of the study

period, compared to 3 out of 4 patients with partial response and only 2 out of 16 patients with stable or progressive disease. These results highlight the survival impact in responders to paclitaxel therapy.

Treatment in patients with relapsed epithelial ovarian cancer is essentially palliative in nature and therefore treatment related adverse reactions are of major importance. In this study, the most common toxicity was grade 3 or 4 alopecia, grade 1 nausea, myalgia and mild hyper-sensitivity reaction in the form of facial flush. These reactions are similar to those reported in other reports.^{13,14}

Sensory neuropathy occurred in all patients, however, no grade 3 or 4 neuropathy was encountered. Neurotoxicity of paclitaxel was dose limiting at higher doses and was more severe in patients with pre-existing neuropathy.^{15,16}

Haematological complications were mild. Less than 10% of the treatment cycles induced grade 3 or 4 neutropenia while in 2% of cycles grade 3 or 4 thrombocytopenia occurred. Both neutropenia and thrombocytopenia recovered quickly with expectant treatment. Only 2 patients required G-CSF rescue in 2 cycles and were the only 4 cycles of treatment complicated by sepsis which responded to antibiotic therapy. No treatment-related mortality was encountered in this study.

In conclusion, this study has shown that paclitaxel is an active chemotherapeutic agent for relapsed epithelial ovarian carcinoma in Asian women. The response rate was high, with a survival advantage in responders. The mild toxicity profile of the drug has significant clinical implication for its use. Patients with relapsed epithelial ovarian cancer should be offered paclitaxel for salvage therapy.

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