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Paclitaxel and Etoposide in Platinum Refractory Epithelial Ovarian Cancer

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ABSTRACT

Objective To evaluate the efficacy of combined paclitaxel and etoposide in the treatment of platinum-refractory epithelial ovarian cancer.

Design Open.

Setting Siriraj Hospital.

Subjects Platinum-refractory epithelial ovarian cancer patients between April 1994-December 1996.

Main outcome measure Response rate, duration of response, survival, and drug toxicities.

Results The evaluable patients included 27 cases, achieved the response rate of 33.33% with complete response of 14.8%, median duration of response 5.0 (3-28 months), median survival of responders 16.0 months (95% CI, 1.4-30.6) and 6.5 months (95% CI, 2.7-10.3) for non-responders. More than 55.0% showed anemia and leukopenia grade 3, with 11.0% thrombocytopenia grade 4.

Conclusion Combined low dose paclitaxel and short period etoposide administration for platinum-refractory epithelial ovarian cancer showed similar results of response rate and median duration of response, comparing with previous trial of high dose paclitaxel. The toxicities were manageble.

Key word : paclitaxel, etoposide, refractory epithelial ovarian cancer

The standard chemotherapy regimen for advanced epithelial ovarian cancer should be platinum-based combination, which achieved the pathological complete response 33.0-83.3%.[1-8] Even after pathological complete response, the recurrence following first-line chemotherapy occured 20.0-60.0%.[8-9] The persistent, progressive, or recurrent disease should have the efficient drug for prolonged life or a chance of survival. Paclitaxel showed high efficacy in the treatment of advanced epithelial cancer, with complete response 51.0% and pathological response 26.0%.[10] The previous trial of paclitaxel in platinum-refractory epithelial ovarian cancer showed response rate 13.1-36.0% and complete response 2.6-12.0%,[9,11,12] with median duration of response 4.9 months.[11] Etoposide has potential additive of even synergistic activity to paclitaxel,[13,14] then we use these combination in trial.

Materials and Methods

Patient eligibity : Patients must have (1) histologically proven epithelial ovarian cancer, (2) resisted to either cisplatinum or carboplatin base regimen, (3) measurable disease, (4) Zubrod performance status grade 0-2, (5) expected survival more than 3 months, (6) adequate bone marrow function leukocyte count greater than 4000/Cu.mm., a platelet count greater than 100,000/Cu.mm., haemoglobin level greater than 8 gm/100 ml., (7) adequate renal function, serum creatinine level less than 2 mg/100 ml., (8) verbal or signed the consent form.

Treatment plan : Etoposide 80 mg/m^2/day was administrated orally or intravenously for 5 days, start on the day of admission before paclitaxel. The patients received premedication before paclitaxel as following, dexamethasone 20 mg intravenous 12 and 6 hours with cimetidine 300 mg intravenous half a hour before paclitaxel for prevention of hypersensitivity, and ondansetron (zofran) 8 mg. intravenous before paclitaxel 150 mg/m^2 day 2. The cycle of therapy will be repeated very 3 weeks.

The non haematologic toxicities was observed such as nausea-vomitting, hair loss, cardiovascular disorder, neurotoxicity. The complete blood count was performed after treatment 7-10 days. Subsequent courses of treatment, the patient should have the adequate bone marrow and renal function. If those was inadequate, the treatment should be delayed and was given supportive treatment.

Response assessment : Patients were evaluated by physical and gynaecological examination before each cycle of treatment. Chest radiography, abdomino-pelvic ultrasound scan and computer tomogram was used as necessary. Serum CA-125 and CA 19-9 were detected specially in the case of partial or complete response. The clinical response was assessed using standard criteria of WHO.

Statistical analysis : The difference of responders and non-responders in the median survival were determined by Log Rank test. The others difference used Fisher's Exact test. Kaplan and Meier's method were used to estimate and compare survival.

Results

From April 1994 - December 1996, 27 patients entered this trial, patients characteristics were summarized in Table 1. Fourteen patients were treated by cyclophosphamide-cisplatinum or cyclophosphamide-paraplatin, or cyclophosphamide-adriamycin (or epirubicin)-cisplatinum as first line drug and paraplatinifosphamide as second-line drug, 2 cases recieved cyclophosphamide-epirulicin-paraplatin and external pelvic

Table 1. Characteristics of patients

Total number		27
Age- Range (years)		26-65
Median		48
Initial stage : Ic		2
III A		1
B		8
C		10
IV		6
Initial surgery : Optimal		6
Suboptimal		13
Minimal		8
Pathology : Serous cystadenocarcinoma		12
Endometriold adenocarcinoma		7
Clear cell adenocarcinoma		5
Mucinous cystadenocarcinoma		3
Status of diseases after previous treatment :		
Recurrence after-clinical		
- complete response		6
- pathological complete response		8
Partial response		2
Progressive disease		11
Size of tumour : Mass in pelvic cavity diameter 5-11 cm., no ascites		20
3-5 cm, with ascites		3
5 cm, with liver metastasis		1
4 cm, with supraclav. metastasis		1
Ascites		1
Para-aortic node diameter 5 cm.		1

Table 2. Results of treatment

	Responders n = 9	**Non-responders n = 18**	**P-value**
*Median cycle of treatment	6 (6-10)	4 (3-11)	NS
Response			
Complete	4 (14.81%)	-	-
Partial	5 (18.51%)	-	-
Stable	-	4 (14.81%)	-
Progressive	-	14 (51.85%)	-
Median duration of response (months)	5 (3-28)	-	-
**Median survival (months)	16 (95% CI, 1.4-30.6)	6.5 (95% CI, 2.7-10.3)	0.0082

* Fisher's Exact test

** Log Rank test

Table 3. Toxic effects

Toxic effects	Responders (%) n = 9	Non-responders (%) n = 18	P-value Fisher' Exact test
1. Haematology			
Haemoglobin grade 3 (< 8 gm/dl)	5 (55.55)	10 (55.55)	NS
Leukocytes grade 3 (2,000/mm^3)	6 (66.66)	13 (72.22)	NS
Platelets grade 4 (2,500/mm^3)	0	2 (11.11)	-
2. Nausea-vomiting grade 1-2	9 (100.00)	18 (100.00)	NS
3. Hair loss grade 1-2	9 (100.00)	18 (100.00)	NS
4. Cardiovascular			
Peripheral vasodilate (facial flushing)	4 (44.44)	9 (50.00)	NS
Bradycardia	3 (33.33)	8 (44.44)	NS
Trachycardia	0	2 (11.11)	-
5. Neurotoxicity			
Peripheral paresthesia	6 (66.66)	11 (61.11)	NS
Pain (arthralgia, myalgia) grade 1	6 (66.66)	13 (72.22)	NS

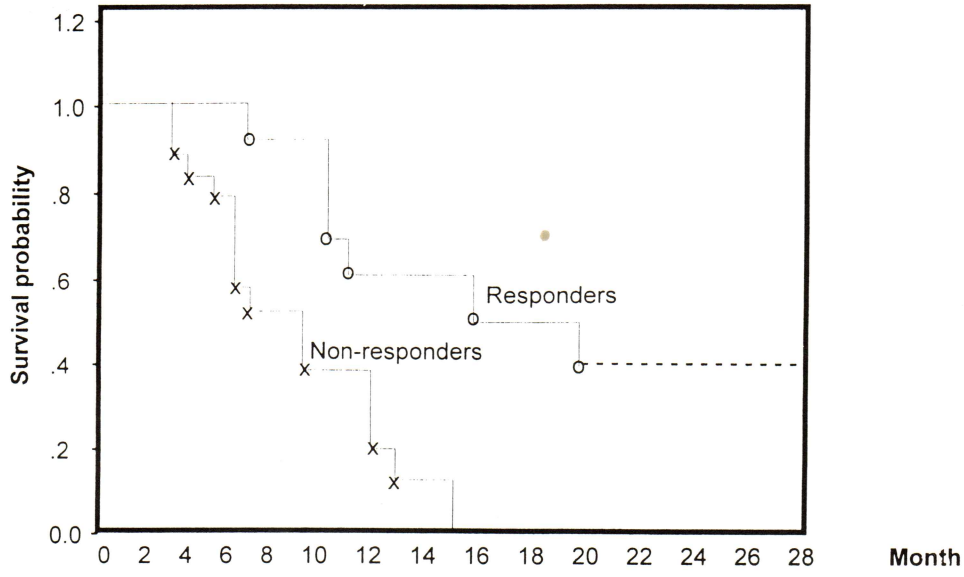

Fig. 1 Survival curve of the patients.

radiation.

The results were summarized in Table 2, achieved complete response 14.81%, partial response 18.51%, with median duration of response 5.0 months. The median survival time was 16.0 months (95% CI, 1.4-30.6) for responders and 6.5 months (95% CI, 2.7-10.3) for non-responders (P = 0.0082). The Kaplan and Meier's survival curve were constructed in Figure 1. One patients of clinical complete response alives without disease, survival time 24.0 months. Two patients of the same group alive with disease, disease free survival 6.0 and 25.0 months respectively.

The toxicities were shown in Table 3. The haemoglobin levels grade 3, requiring blood tranfusion was found 55.55%. The leukocytes count grade 3 caused delay of treatment, occurred in responders group 66.66% and 72.22 % of non-responders, 2 patients required granulocyte colony-stimulation factor (GCSF). Nausea and vomiting grade 1-2, hair loss grade 1-2, were found 100.0%. The facial flushing occurred in responders 44.44% and 50.0% of non-responders. Bradycardia were found in responders 33.33% and 44.44% for non-responders. Trachycardia occurred only in non-responders 11.11%. Peripheral paresthesia occurred 66.66% and 61.11% respectively. Arthralgia or myalgia grade 1 were found 66.66% and 72.22%, requiring supportive treatment in some cases.

Discussion

Etoposide was administrated prior to paclitaxel because, the cytotoxic effects of etoposide were maximal in G2 phase.[15] There was also some activity against cells in late S-phase, the drug could halt cell cycle traverse at the S-G2 interphase and cound not progress to the M-phase.[16] Whereas paclitaxel adversely affected microtubule function during G2 interphase and M-phase.[17] Oral etoposide in the first day of admission is practical during premedication of paclitaxel, with short duration in hospital. Thus few patients were treated by intravenous etoposide. This trial achieved the response rate of 33.33%, complete response 14.8%, median duration of response 5.0 months. The results were not better than previous study of high dose paclitaxel should be slightly low dose of paclitaxel and short period of etoposide administration. Of course the higher dose paclitaxel and longer period etoposide must required GCSF or GMCSF prophylaxis, which achieved higher cost. Our trial without prophylaxis, only 2 patients required supportive GCSF. The other toxicities were tolerable.

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