Paclitaxel Based Chemotherapy in Recurrent Epithelial Ovarian Carcinoma (EOC)

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Summary

Prognosis of patients with recurrent epithelial ovarian carcinoma (EOC) is poor. Among the newer drugs tested, paclitaxel has been found to be most active. Between May, 1994 and December, 1997, 22 patients (median age, 45 years) with recurrent EOC received paclitaxel based chemotherapy (CT). All 22 patients had received earlier platinum based CT but were paclitaxel naïve. Thirteen patients received paclitaxel and cisplatin, 7 paclitaxel alone and 2 patients received paclitaxel and adriamycin. Paclitaxel was administered intravenously over 3 hours as saline infusion in the dose of 135 mg/m2 every 3 weeks to a total of 6 cycles. All patients were evaluated for response and toxicity. Ten of 22 patients (45.4%) responded; complete 8(36.4%) and partial (PR) in 2 (9%) patients. Four patients had minimal response and 8 progressed while on CT. Response rates were higher for patients with good performance status (p=.01), and those with platinum sensitive disease (p=.23). The overall median survival for all patients was 23.5 months (range, 5 to 52 months). CT responders had a significantly higher survival compared to non responders, 18.5 vs 8 months, p<.001. Currently, 8 of 10 responders are alive, 7 with disease and one disease free at a median interval of 18.5 months (range, 13-52 months) after CT.

Introduction

Epithelial ovarian cancer (EOC) is the second commonest gynaecological cancer among women in India (ICMR, 1989). Debulking surgery followed by cisplatin based chemotherapy (CT) is the standard treatment approach. Relapse after initial response to CT is the major cause of treatment failure. Salvage CT is invariably used response to salvage chemotherapy is dependent upon treatment free interval. Patient who relapse within 6 months of completion of treatment, typically have low response rates with short survival. Paclitaxel and platinum based (cisplatin or carboplatinum) CT is promising salvage CT. Though a number of studies are available from west, Indian data is rather scanty (Advani et al, 1994). We here report our preliminary experience.

Patients and Methods

Between May 1994 and December, 1997, 22 patients with recurrent or refractory EOC received paclitaxel based CT. All patients had earlier received platinum based CT. Patients characteristics are shown in table-1. The median age was 45 years (range, 36-82 years). 10 patients had received one CT regimen, 9 had received 2 and 3 patients received 3 CT regimens before receiving paclitaxel based CT. Median time to relapse was 7 months (0 to 33 months). A total of 206 CT cycles were delivered (mean 9.3). Paclitaxel was administered either as single agent (n=7) in combination with cisplatin (n=13) or adriamycin (n=2). The latter patients had developed renal insufficiency earlier following cisplatin based CT and had decreased creatinine clearance at the time of relapse, therefore platinum was avoided in these

patients. Paclitaxel was administered as IV infusion over 3-4 hours in the dose of 135 mg/m2, all patients had received premedication using diphenhydramine, dexamethasone and ranitidine. A minimum of two courses of CT were planned, with a maximum of six courses in responders. Response to CT was defined as per the WHO criteria (Miller, et al 1981). Patients were categorised as having platinum sensitive disease if they had received prior cisplatin and had achieved at least partial response of 6 months duration. Patients with progressive or persistent disease or relapse within 6 months after a prior platinum based treatment were categorized as having platinum resistant disease (Markman and Hoskins, 1992).

Table I
Patients Characteristics

No. of patients	:	22
Age range	:	36-82
Median	:	45
Initial stage		
I	:	1 (4.6%)
II	:	1(4.6%)
III	:	14 (63.6%)
IV	:	6 (22.2%)
Histology		
Serous	:	15 (61.2%)
Mucinous	:	4(18.2)
Endometrial	:	2 (9%)
Undifferentiated	:	1(4.6%)
Response to primary treatment, n = 22		
CR	:	15 (68.2%)
PR	:	5(22.6%)
NR	:	1 (4.6%)
PD	:	1 (4.6%)
Previous CDDP chemotherapy		
Total cycles	:	206
Mean	:	9.3
No. of previous Chemotherapy regimens		
1	:	10
2	:	9
3	:	3
Platinum Sensitive Disease	:	12
Platinum Resistant disease	:	10
Sites of Relapse		
Pelvic	:	7 (31.8%)
Abdominal	:	13 (59.1%)
Distal	:	12 (54.5%)
CA-125 positive alone	:	1(4.6%)

Results

All 22 patients were evaluated for response and toxicity to CT. 10 of 22 (45%) patients responded; CR-8(36.4%) and PR-in 9% of patients. Four patients had minimal response and 8 progressed while on CT. Patients with good performance status (ECOG, 0-2) had a significantly higher response to CT: 10/16 vs 0/6, p<.01. Patients who received paclitaxel and cisplatin had a better response compared to either paclitaxel alone or paclitaxel and adriamycin; 8/13 vs 2/9, p=.1. CR+PR rates were higher for patients with platinum sensitive disease compared to those with platinum resistant disease, 58% vs 30%, p=0.30. Patients receiving CT for the first relapse event had a higher response rate than those who received CT for 2nd and 3rd relapse, 61.5% vs 22.2%, p=1. All 8 complete responses occurred in patients receiving CT for 1st relapse event.

The median overall survival for all patients was 17.5 +/-5.16 (range, 5-52 months). The median progression –free survival was 11.5 months (range, 6 to 21 months). The median overall survival was significantly better for responders (CR+PR) compared to non-responders; 23.6 +/- 7.22 (13-52) vs 8+-2.37 (5-23) months, p<.001 (Fig. 1).

Currently, 7 of 8 complete responders are alive, 6 with disese and one disease-free. Of two partial responders, one patient is alive with disease at 15 months and another had died of progressive disease 14 months after CT. Remaining 12 patients with minimal response or progressive disease have died at a median interval of 8 months (range, 5-23 months) due to progressive disease.

Chemotherapy Toxicity

A total of 108 CT cycles were given (mean, 4.8). The main side effects to CT included nausea/vomiting and myelosuppression. Three patients had severe myalgia and paraesthesia. None of side effects were severe enough to necessitate dose reduction or hyperalimentation. No patient had hypersensitivity or cardiotoxicity to paclitaxel. One patient had hypokalemia and atrial ectopics which improved following correction of hypokalemia.

Discussion

Management of recurrent/refractory epithelial ovarian cancer is a therapeutic challenge. Patients with platinum sensitive disease respond to platinum based CT with a response rate of 30-60% depending upon treatment-free interval. For patients with platinum

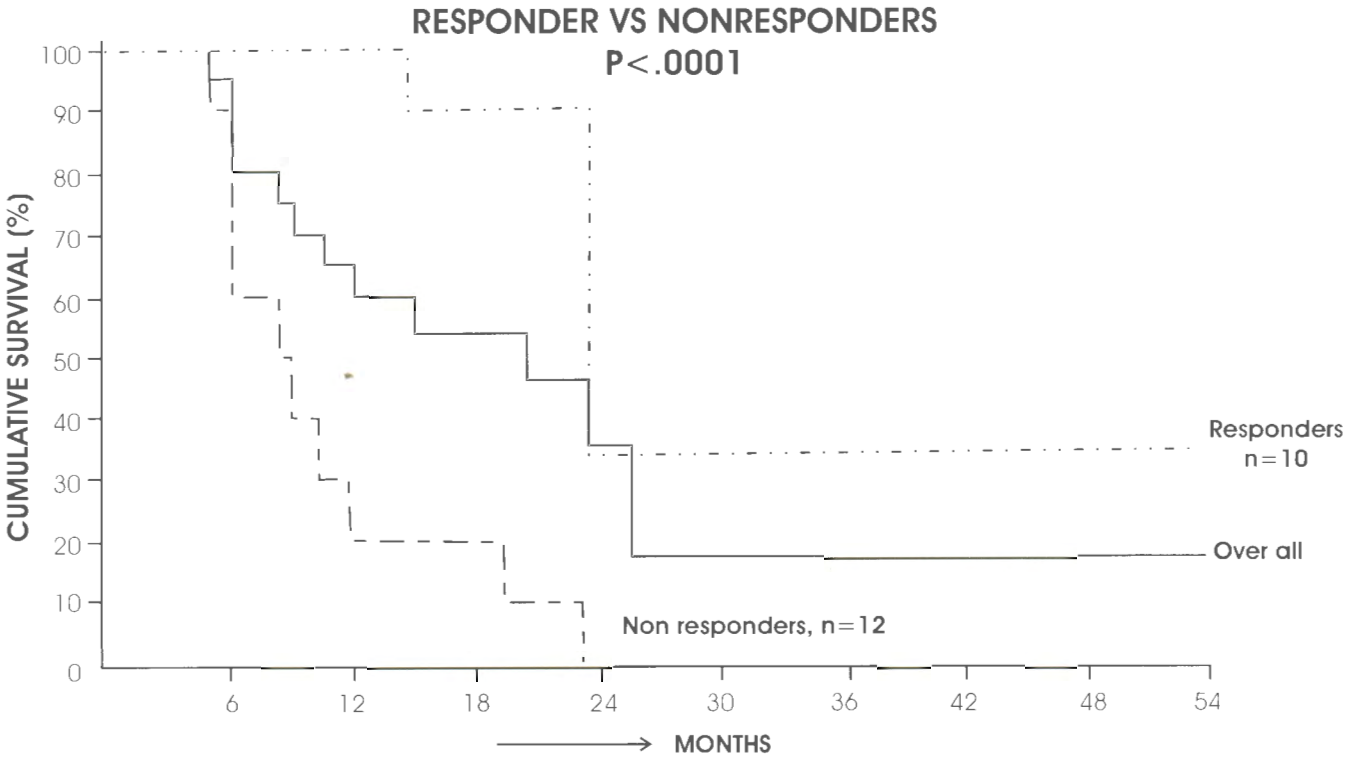

Fig 1

resistant disease other CT drugs are required as response rate to platinum based CT is low with short survival. (Kumar 1995). In past decade a member of newer drugs have undergone phase II, III trials. These include- paclitaxel, docetaxel, gemcitabine, oral etoposide, liposomal doxorubicin, topotecan etc. Paclitaxel has been studied most extensively (Rowinsky et al 1992) either alone (Trimble et al 1993, Trope et al 1998) or in combination with cisplatin or carboplatin (Goldberg, et al 1996, Rose, et al 1998). The response rates obtained in our study is similar to those reported in previous studies (Advani et al 1994, Goldberg et al 1996, Rose et al 1998). The combinattion of paclitaxel + cisplatin or carboplatin is now standard therapy in the primary management of advanced EOC (Piccart, et al 2000, Nejit, et al 2000) In the present study, paclitaxel was administered over 3 hours. The results obtained are similar to those obtained in the European-Canadian study (Fisenhauer, et al 1994). In the later study, patients were randomized to receive paclitaxel in the dose of 135 mg / m2 vs 175 mg / m2 and infusion over 3 vs 24 hours. The response rate in both arms were not significantly different. The toxicity was higher in 24 hour infusion arm. Thus, presently paclitaxel is administered as 3 hours infusion as practiced in our study.

In the present study, patients in good performance status responded significantly. Response rate was higher for patients with platinum sensitive disease, however, it was significantly different possibly due to small number of patients (table II). These results are similar to those observed in earlier studies. All complete responses were observed in patients who received paclitaxel during the first relapse. However these results are different to those obtained by Goldberg, et al who did not find such difference. CT was tolerated well. Grade II-III hematological toxicity was seen in only 11% of CT cycles. Higher frequency of myelosuppression in earlier studies (Eisenhauer, et al 1994) could have been related to the higher dose of paclitaxel, 175 mg / m2 and longer duration of infusion (over 24 hours) compared to 135 mg / m2 given over 3 hours in our study.

Thus, paclitaxel and cisplatin combination is a reasonable option in patient with recurrent EOC. It should be considered in patients with good performance status and those with platinum sensitive disease.

Conclusion : Treatment with paclitaxel based chemotherapy is a reasonable option in patients with recurrent EOC and should be considered in patients with good performance status.

Table II
Analysis of Prognostic Factors

Factor	No of Pts	CR	PR	CR + PR (%)	MR	NR/PD
Performance Status						
0-2	16	8	2	10(62.5)	2	4
3-4	6	0	0	0(9)	2	4
						p=.01
cDDP sensitive dis.	12	5	2	7(58.3)	1	4
cDDP resistant dis.	10	3	0	3(30.0)	3	4
						p=.23
CT Regimen						
Paclitaxel + Paclitaxel + Adr	9	2	0	2(22.2)	2	5
Paclitaxel + cDDP	13	6	2	8(61.5)	2	3
						P=.1
Relapse Event						
First	13	8	0	8(61.5)	2	3
Second	6	1	0	1(16.6)	1	4
Third	3	0	1	1(33.3)	1	1
						P=.4

CR-complete response, PR-partial response, MR-minimal response, NR-no response, PD-progressive disease, cDDP cisplatin, Adr-adriamycin, CT-chemotherapy, p=p value

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