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Randomized Trial of Paclitaxel Plus Paraplatin Versus Cyclophosphamide Plus Paraplatin in the Treatment of Advanced Epithelial Ovarian Cancer

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ABSTRACT

Objective To compare the efficacy and toxicity of paclitaxel plus paraplatin with paraplatin plus cyclophosphamide in the treatment of the advanced epithelial ovarian cancer.

Design Randomized trial.

Setting Multicenters.

Subjects The valuable 95 patients of the stage III-IV epithelial ovarian cancer from 3 centers were recruited between December 1995-April 1998.

Main outcome measure Response rate, drug toxicity, recurrent rate and survival

Results The paclitaxel 150 mg./m^2 plus paraplatin AUC 6 and cyclophosphamide 700 mg./m^2 plus paraplatin AUC 6 achieved similar results in clinical complete response 63.8% and 66.7%, pathological complete response 76.0% and 75.0%, recurrence after pathological complete response 36.8% and 55.5% respectively (P>0.05). The median disease free survival in the pathological complete response group of paclitaxel plus paraplatin cannot be estimated, whereas 11.0 months of paraplatin plus cyclophosphamide. The mean disease free survival of two groups fell in 39.8 and 27.1 months (p=0.07). The overall mean survival achieved 36.1 and 35.2 months (p>0.05). The toxicity was similar in both arms, except myalgia/arthralgia and skin rash occurrence in paclitaxel plus paraplatin arm.

Conclusion Paclitaxel plus paraplatin comparing with cyclophosphamide plus paraplatin in the treatment of advanced epithelial ovarian cancer showed no significant difference in complete response, recurrence, disease free survival and median survival with the acceptable toxicity.

Key word: paclitaxel plus paraplatin, cyclophosphamide plus paraplatin, epithelial ovarian cancer

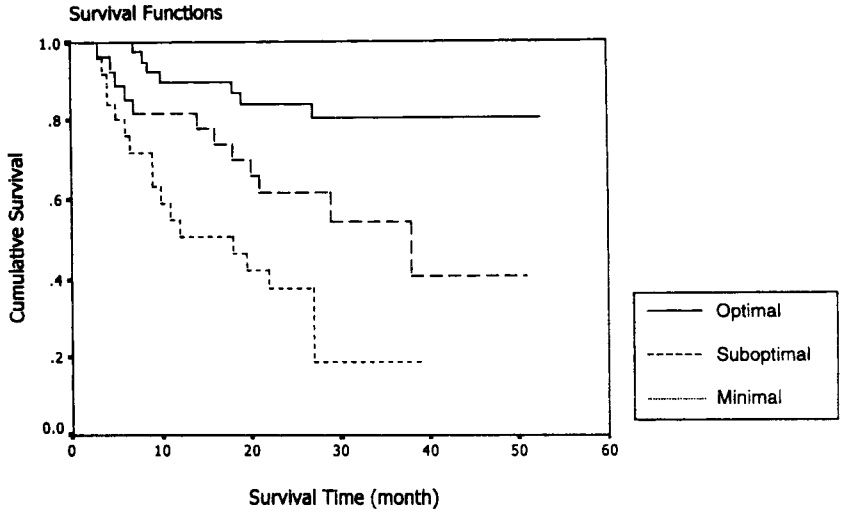

Fig. 2. Survival curves of the patients comparing operability.

Median survival (time to death)
- Optimal: cannot be estimated
- Suboptimal: 38 months
- Minimal: 18 months

Mean survival (time to death)
- Optimal: 45.1 months
- Suboptimal: 32.5 months
- Minimal: 18.5 months

Log rank comparison of 3 survival curves: p = <0.001

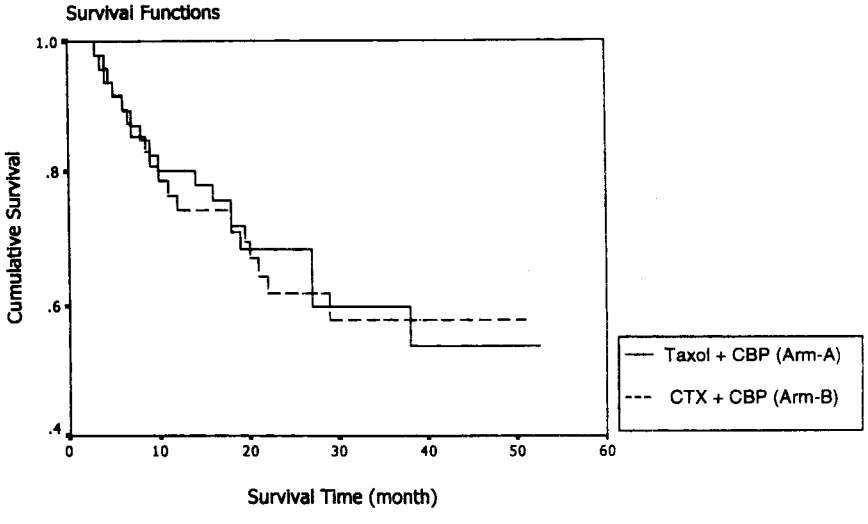

Fig. 3. Survival curves of the patients in both arms.

Median survival (time to death)
- Taxol + CBP: cannot be estimated
- CTX + CBP: cannot be estimated

Mean survival (time to death)
- Taxol + CBP: 36.1 months
- CTX + CBP: 35.2 months

Log rank comparison of 2 survival curves: p = 0.88

Table 1. Patient characteristic and treatment

		Arm-A TAXOL+CBP	Arm-B CTX+CBP	P-value
Eligible for Study		47	48	
Age - range		27-65	25-68	
- mean ± SD		48.6 ± 9.2	48.7 ± 8.5	0.97
ECOG performance	0	5 (10.63%)	4 (8.33%)	
	1	24 (51.06%)	23 (47.9%)	0.84
	2	18 (38.29%)	21 (43.75%)	
FIGO stage	III A	5 (10.63%)	6 (12.50%)	
	B	8 (17.02%)	11 (22.92%)	0.87
	C	25 (53.19%)	23 (47.92%)	
	IV	9 (19.14%)	8 (16.67%)	
Surgical procedure	- optimal	19 (40.42%)	23 (47.92%)	
	suboptimal	14 (29.78%)	13 (27.08%)	0.75
	minimal	14 (29.78%)	12 (25.00%)	
Histological type	- serous	21 (44.68%)	24 (50.00%)	
	endometrioid	9 (19.14%)	11 (22.92%)	
	mucinous	7 (14.87%)	4 (8.33%)	0.79
	clear cell	4 (8.51%)	5 (10.42%)	
	mixed	6 (12.76%)	4 (8.33%)	
Histological grade	1	13 (27.65%)	14 (29.17%)	
	2	13 (27.65%)	15 (31.25%)	0.87
	3	21 (44.68%)	19 (39.58%)	

TAXOL = paclitaxel, CBP = paraplatin, CTX= cyclophosphamide

Optimal surgery = hysterectomy, bilateral salpingo-oophorectomy, infra colic omentectomy, with may be pelvic and para-aortic node sampling (residual cancer ≤ 1 cm.)

Suboptimal surgery = as optimal surgery but residual cancer > 1 cm.

Minimal surgery = partial resection of cancer or only biopsy (bulky residual cancer)

Table 2. Response of treatment

	Arm-A TAXOL+CBP		Arm-B CTX+CBP		P-value
	Optimal surgery	Suboptimal+ minimal surgery	Optimal surgery	Suboptimal+ minimal surgery	
Clinical complete response	16 (88.88%)	14 (47.27%) p=0.01	21 (91.30%)	11 (44.00%) p=0.002	
	63.82%		66.66%		0.94
Partial response	1 (5.55%)	4 (13.79%) p=0.64	-	4 (16.00%) p=0.11	
	10.63%		8.33%		0.74

Table 2. Response of treatment

	Arm-A TAXOL+CBP		Arm-B CTX+CBP		P-value
	Optimal surgery	Suboptimal+ minimal surgery	Optimal surgery	Suboptimal+ minimal surgery	
Stable disease	-	5 (17.24%)	-	5 (20.00%)	
		10.63%		10.41%	1.00
Progressive disease	1 (5.55%)	6 (20.68%)	2 (8.69%)	5 (20.00%)	
		14.89%		14.58%	0.80
Pathological complete response	10/11(90.90%)	9/14 (64.28%)	12/14(85.71%)	6/10 (60.00%)	
		76.00%		75.00%	0.80
Recurrence after PCR		7/19 (36.84%)		10/18 (55.55%)	0.73

Table 3. Toxic effects

	Arm-A TAXOL+CBP n = 47	Arm-B CTX+CBP n = 48	P-value
1. Haematologic			
Haemoglobin grade 3 (< 8 gm/100 ml)	10 (21.27%)	10 (20.83%)	
Leukocytes grade 3 (< 2,000/mm^3)	13 (27.65%)	14 (29.16%)	0.91
Platelets grade 4 (< 25,000/mm^3)	4 (8.51%)	3 (6.25%)	
2. Gastrointestinal			
Vomiting grade 2 (transient)	15 (31.91%)	8 (16.66%)	
Diarrhea	3	0	0.29
SGOT/SGPT grade 3	2	0	
3. Hair loss grade 1-2	44 (93.61%)	47 (97.91%)	0.36
4. Peripheral neuritis grade 1	26 (53.31%)	18 (37.50%)	0.12
5. Myalgia/arthralgia grade 1	38 (80.85%)	0	<0.001
6. Cutaneous			
Hyperpigmentation	6 (12.76%)	4 (8.33%)	0.52
Rash	4 (8.51%)	0	0.06

Results

From December 1995 to April 1998, the evaluable 95 out of 102 patients from three centers entered in this study. Patient characteristics and treatment are summarized in Table 1. There were no significant difference between two arms of the study in age, performance status, stage of disease, surgical procedure, histological cell type and grade. The patients fell in stage IIIc disease of arm-A and B 53.2% and 47.9% respectively. The optimal surgery could be performed in arm-A and B 40.4% and 47.9%. The majority of cases were serous cystadenocarcinoma and endometrioid adenocarcinoma of two arms 63.8% and 72.9% respectively.

The response of treatment are summarized in Table 2. Arm-A achieved complete and partial response in 63.8% and 10.6% comparing with 66.7% and 8.3% of arm-B (P>0.05). The optimal surgery showed higher complete response comparing with suboptimal and minimal surgery of both arms (P=0.01 arm-A, and 0.002 arm-B). The pathological complete response or negative second look laparotomy demonstrated 76.0% and 75.0% in arm-A and B (P>0.05). The recurrence rate after pathological complete response occurred 36.8% and 55.5% in arm-A and B respectively (P>0.05). The disease free survival of pathological complete response group ranged from10.0-52.5 months of arm-A, and 3.0-51.0 months of arm-B. The median time of disease free survival in this group of arm-A could not be estimated, where as 11.0 months of arm-B (Fig. 1.). The mean time of disease free survival was 39.8 and 27.1 months in arm-A and B respectively (P=0.07).

The overall patients showed longer survival in optimal surgery comparing with suboptimal and minimal surgery. The median survival of the optimal surgery could not be estimated, whereas 38.0 months of suboptimal surgery and 18.0 months of minimal surgery. The mean survival was 45.1, 32.5 and 18.5 months of the optimal, suboptimal, and minimal surgery (P<0.001, Fig. 2.). The overall survival of both arms showed in Fig. 3., the median survival could not estimated, but the mean survival has 36.1 and 35.2 months of arm-A and B (P>0.05).

The toxicity of both arms were shown in Table 3. The hematological toxicity such as grade 3 hemoglobin level (21.3% vs 20.8%), grade 3 leukocytes level (27.6% vs 29.2%), and grade 4 platelet (8.5% vs 6.2%) were similar of both arms. Of those required only delay of treatment. The non-hematological toxicities were similar in both arms, excepted mild myalgia/ arthralgia occurrence 80.8% and skin rash 8.5% of arm-A.

Discussion

Our trial either paclitaxel plus paraplatin of cyclophosphamide plus paraplatin showed similar in complete response, recurrence, and overall survival. The median disease free survival of pathological complete response group could not be estimated of arm-A, because 12 out of 19 cases are alive without recurrence after follow-up at least 2 years, the longer period may be clarify, where as 11.0 months of arm-B. The mean disease free survival was 39.8 and 27.1 months in arm-A and B (P=0.07). Of those should be due to low dosage of paclitaxel. In 1995 we had no experience in administration of paclitaxel, then use only 150 mg./m^2 with 6 hours infusion, the higher dose may produce better results. The paclitaxel 175 mg./m^2 plus paraplatin AUC 7.5 every 3 weeks for 6 cycles showed response rate 75.0% with clinical complete response 66.66% in measurable disease, and median progression free survival 15.0 months without initial G-CSF.[13] With the same dosage achieved the clinical complete response 67.0% in measurable disease.[14] The paclitaxel 185 mg./m^2 plus paraplatin AUC 6 for advanced measurable disease revealed overall response rate 70.5% and progression free survival 17.2 months.[15] Our trial achieved the clinical complete response 47.3% of paclitaxel plus paraplatin and 44.0% of cyclophosphamide plus paraplatin for the suboptimal and minimal surgery. The standard dose of paclitaxel 175 mg/m^2 plus paraplatin AUC 6-7 should be administrated for better result of this arm.[13-18] We expected the average clinical response of paraplatin plus cyclophosphamide only 30.0%, was lower than

the result in this trial. The increase of the average complete response from 55.0% of paraplatin plus cyclophosphamide to 80.0% of paclitaxel plus paraplatin should be applied for calculation of the sample size, which require the 55 patients of each arm for the further evaluation of the difference.

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