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Randomized Trial Cisplatinum-Cyclophosphamide with and without Induction Interferon Alpha-2b in Treatment of the Advanced Epithelial Ovarian Cancer

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ABSTRACT

Objective To compare the efficacy of cisplatinum-cyclophosphamide with and without induction interferon-alpha-2b in the treatment of the advanced epithelial ovarian cancer.

Design Randomized trial

Setting Multicenters.

Subjects One hundred and twenty-seven patients of the epithelial ovarian cancer stage III-IV from 5 centers were recruited between August 1992 - November 1995.

Main outcome measure Response rate, drug toxicites, recurrent rate and survival.

Results One hundred and seven evaluable patients included in the study, achieved complete response 51.92% and partial response 19.23% of interferon induction arm (arm-A), compared with 50.90% and 12.72% of without interferon induction (arm-B) respectively ($P > 0.05$). The pathological complete response revealed 47.82% of arm-A and 55.00% of arm-B ($P > 0.05$), the recurrence occured 27.27% of arm-A and 45.45% of arm-B respectively ($P > 0.05$). The median survival time was 17.00 months (95% CI, 4.93 - 29.07) of arm-A and 17.00 months (95 % CI, 11.75 -22.25) of arm-B. The haematologic toxicity and nephrotoxicity showed higher incidence in arm-A ($P < 0.05$)

Key word : induction interferon, cisplatinum, cyclophosphamide, epithelial ovarian cancer

The cisplatinum base regimens are standard chemotherapy for advanced epithelial ovarian cancer, which achieve a pathological complete response (PCR) ranging from 33.3-70.0%[1-6] Even after PCR, the recurrence following first-line chemotherapy occurred in 40.0-60.0% of case.[7] The interferons are glycoproteins showing the inhibition of malignant cell growth and phenotypic transformation in laboratory.[8] There is an antiproliferative effect of epithelial ovarian cancer both in vivo and in vitro,[9-12] and showing efficacy in the epithelial ovarian cancer not only minimal residual cancer but also in the recurrence and refractory cancer for intraperitoneal application and chemotherapy.[12,15] The study was designed to evaluate the efficacy and toxicity of the induction interferon alpha-2b to cisplatinum and cyclophosphamide combination regimen comparing chemotherapy alone in the treatment of advanced ovarian epithelial cancer post surgery, for better PCR with decreased recurrent rate and better survival.

Materials and Methods

Patient selection : Eligible criteria included the histological proof of epithelial ovarian cancer stage III-IV disease after total hysterectomy with bilateral salpingo-oophorectomy and infracolic omentectomy or debulky of the tumour or only biopsy with or without pelvic or para-aortic node sampling, age not more than 65 years and performance status 0-3 ECOG. The patient should have an adequate bone marrow function (a leukocyte count greater than 3,500/Cu.mm., a platelet count greater than 100,000/Cu.mm., haemoglobin level greater than 8 gm/100 ml.), adequate liver function (SGOT, SGPT and alkaline phosphatase level less than or equal to two times of the upper limit), normal renal function (serum creatinine level less than 2 mg/100 ml.) Among those who signed the consent form.

Randomisation : The randomisation was allocated by computer.

Treatment plan and dose modifications : Patients were randomised to receive either induction interferon alpha-2b (intron-A, Schering-Plough) 10×10^6 units in NSS 2-3 ml. subcutaneous injection 6 hours prior to administer cyclophosphamide and cisplatinum (Arm-A), or cyclophosphamide plus cisplatinum (Arm-B). The patient should have oral acetaminophen 500-1,000 mg. before interferon and can be repeated as necessary.

The administration of cyclophosphamide and cisplatinum are following :

- hydration 5% dextrose in half strenght saline 1,000 ml. + KCl 20 mEq. IV in 4-6 hours,

- activan 0.5 mg. oral and repeat every 6 hours as necessary for anti-anxiety, metoclopramide 10 mg. IV and repeat every 4 hours,

- cyclophosphamide 700 mg/m^2 in 5% dextrose in water 100 ml. IV over 15 minutes,

- cisplatinum 70 mg/m^2 in 5% dextrose in half strenght saline 1,000 ml. IV in 4-6 hours,

- hydration post chemotherapy by 5% dextrose in half strenght saline 1,000 ml. + KCL 20 mEq. IV in 4-6 hours.

The treatment would be repeated every 3 weeks for 6 cycles, except in the patients who showed no response or progressive disease, the treatment would be switched off. The non haematologic toxicites were observed such as fever, bone and joint pain, gastro-intestinal, hair loss, cutaneous hyperpigmentation, neurotoxicity, nephrotoxicity, hepatotoxicity and ototoxicity. The complete blood count was performed after treatment at 7-10 days, with repeated blood count and blood chemistry before subsequent courses.

The toxicity was recorded according to WHO classification. For the subsequent cycle of treatment : if the total white count was less than 3,500/Cu.mm., platelets less than 100,000/Cu.mm., or haemoglobin less than 8 gm/100 ml, the treatment would be delayed for one week. If these values were not reached after one week, the supportive treatment was required. The drug was decreased 50% for the haematologic toxicity grade 4. Cisplatinum dose was decreased 50%, if the SGOT level reached 2x normal or creatinine level greater than 2 mg/100 ml, but the cyclophosphamide was given in fixed dose.

Response assessment : Patients were evaluated by physical and gynaecological examination at each cycle of treatment. Chest radiograph, abdomino-pelvic ultrasonogram, tumour marker were used as necessary or according to economic reasons. The clinical response was assessed using stardard criteria of WHO. The second look laparotomy was performed in the patients who achieved the clinical complete response for evaluation of the PCR. Partial response to chemotherapy in previous debulky surgery was treated by radical surgery and second course of chemotherapy. The residual cancer post second look laparotomy may be treated by the first line chemotherapy or external radiation.

Statistical analysis : We expected an increase of pathological complete response from the average 50% to 70-80% after induction of the interferon alpha-2b. Using the normal approximation to the binomial, the required number of the evaluable patients was 48 per group. The difference in patient characteristics, treatment, response rates, toxicities between two arms was determined by Chi-square test. Kaplan and Meier's method were used to estimate and compare survival.

Results

From August 1992 to November 1995, the evaluable 107 out of 127 patients entered this study. Patient characteristics and treatment are summarized in Table 1. There were no significant differences between the two arms of the study in age, performance status, stage of disease, surgical procedure, histological type and grading. The optimal surgery could be performed in minority of cases 23.07% and 25.45% in arm-A and arm-B respectively because of 63.45% and 72.72% fell in stage III c - IV diseases. The majority of cases were serous cystodenocarcinoma 48.07% and 50.90% respectively.

The response of treatment is summarized in Table 2. Arm-A had complete response in

Table 1. Patient characteristic and treatment

	Intron A CDDP + CTX Arm-A	CDDP + CTX Arm-B	P-Value
Eligible for study	n = 52	n = 55	
Age range	31-65	26-65	
median	48	47	
ECOG performance			
0	2 (3.48%)	3 (5.45%)	
1	25 (48.07%)	27 (49.09%)	0.9787
2	23 (44.23%)	23 (41.81%)	
3	2 (3.84%)	2 (3.63%)	
FIGO stage III A	6 (11.53%)	4 (7.27%)	
B	13 (25.00%)	11 (20.00%)	0.7402
C	25 (48.07%)	29 (52.72%)	
IV	8 (15.38%)	11 (20.00%)	
Surgical procedure			
Optimal	12 (23.07%)	14 (25.45%)	
Suboptimal	21 (40.38%)	20 (36.36%)	0.9074
Minimal	19 (36.53%)	21 (38.18%)	
Histological type			
Serous	25 (48.07%)	28 (50.90%)	
Mucinous	7 (13.46%)	3 (5.45%)	
Endometrioid	9 (17.30%)	10 (18.18%)	0.2178
Clear cell	6 (11.53%)	8 (14.54%)	
Mixed	5 (9.01%)	6 (10.90%)	
Histological grade			
1	10 (26.31%)	11 (25.00%)	
2	19 (50.00%)	22 (50.00%)	0.4636
3	9 (23.68%)	11 (25.00%)	
no grading	14	11	

Opitmal surgery = hysterectomy, bilateral salpingo-oophorectomy. Infra colic omentectomy (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)

51.92% and partial response 19.33% of cases, compared with 50.90% and 12.72% respectively in arm-B (P > 0.05). Arm-A achieved the negative second look laparotomy or PCR in 47.82% and 55.00% of cases in arm-B (P > 0.05). The recurrence after negative second look laparotomy were found in 27.27% and 45.45% respectively (P > 0.05). The median survival time was 17.00 months (95% CI, 4.93 - 29.07) in arm-A and 17.00 months (95% CI, 11.75 - 22.25) in arm B. The Kaplan and Meier's survival curve is shown in Figure 1.

Table 2. Response of treatment

	Intron-A CDDP + CTX Arm-A	CDDP + CTX Arm-B	P-Value
Clinical ccmplete response	27 (51.92%)	28 (50.90%)	
Partial response	10 (19.23%)	7 (12.72%)	0.7491
Stable disease	8 (15.38%)	10 (18.18%)	
Progressive disease	7 (13.46%)	10 (18.18%)	
Pathological complete response	11/23 (47.82%)	11/20 (55.00%)	0.6388
Recurrence after negative second-look	3/11 (27.27%)	5/11 (45.45%)	0.6792

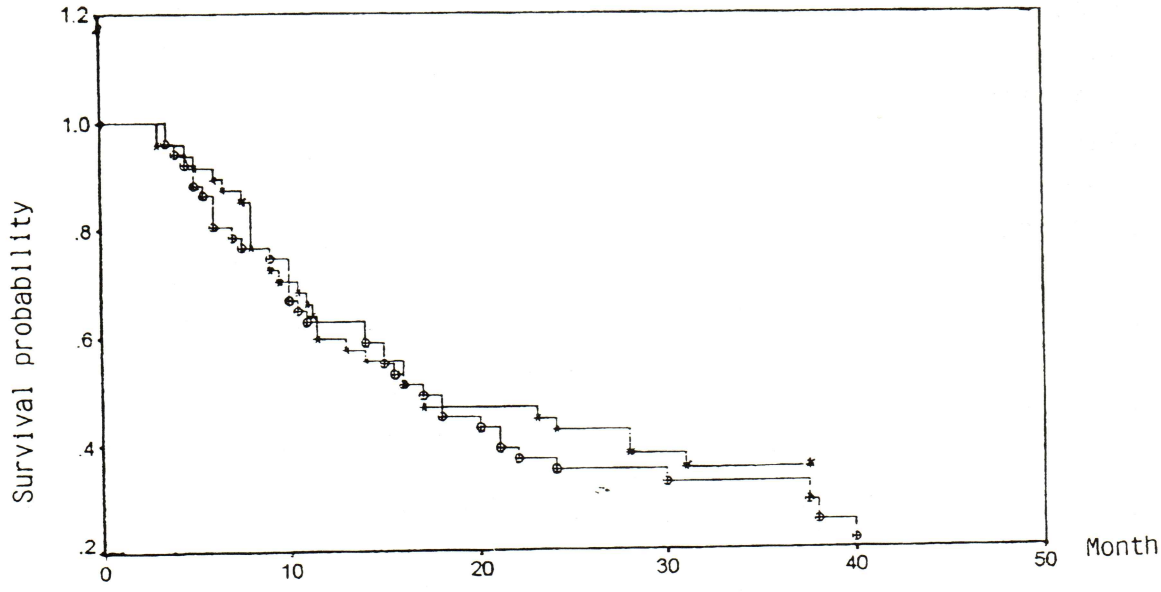

Fig. 1. Survival curve of the patients, *arm-A, ⊕arm - B

Table 3. Toxic effects

	Intron-A CDDP + CTX Arm-A	CDDP + CTX Arm-B	P-Value
1. Haematological			
Haemoglobin grade 3 (< 8 gm/100 ml)	24 (10.27%)	12 (4.31%)	0.0077
Leukocytes grade 3 (< 2,000/mm^3)	19 (8.08%)	9 (3.23%)	0.0176
Platelets grade 4 (< 2,5000/mm^3)	2 (0.85%)	0	-
2. Gastrointestinal			
Nausea/vomiting grade 3	25 (10.63%)	25 (8.99%)	0.7858
Diarrhea grade 1	12 (5.10%)	6 (2.15%)	0.0926
3. Fever grade 1-2	158 (67.23%)	0	-
4. Nephrotoxic			
Creatinine > 2 mg/100 ml	8 (15.38%)	2 (3.63%)	0.0482
5. Hair loss grade 1-2	(100.00%)	(100.00)	-
6. Neurotoxic			
Peripheral neuritis grade 1	15 (28.84%)	12 (21.81%)	0.4029
Constipation grade 1	9 (17.30%)	8 (14.54%)	0.6960
7. Bone and joint pain grade 1	20 (38.46%)	0	-
8. Cutaneous hyperpigmentation	9 (17.30%)	10 (18.18%)	0.9659
Number of cycles in category 1-3	235	278	
Number of patient in category 4-8	52	55	

The toxicities are shown in Table 3. The haemoglobin level grade 3 requiring blood transfusion and leukopenia grade 3 caused delay of treatment and occured more in arm-A ($P < 0.05$). The thrombocytopenia grade 4 requiring platelets transfusion occured in only 0.85% of arm-A. Nausea and vomiting grade 3 were similar of both arms. The fever grade 1-2 was found only in arm-A 67.23%. The nephrotoxic occured in 15.38% of arm - A and in 3.63% of arm-B ($P < 0.05$), one case of arm-A died of renal failure.

Discussion

The induction interferon alpha-2b could not improve the PCR, decreased recurrence or prolonged median survival time, compared with cisplatinum combination in this study. Theoritically interferon has the antiproliferative and immune-modurating activity, these effects did not enhance the chemotherapy and this could be due to the short period of induction. The concomitant and maintenance small dosage interferon 3 times a week for long periods such as 3-6 months after response may succeed but

requires further trial. The higher incidence of haematologic toxicity reflexed the marrow suppression effect of the interferon. High fever in some cases due to interferon and inadequate hydration brought some cases to nephrotoxicity.

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