Thai Journal of Obstetrics and Gynaecology
September 1999, Vol. 11, pp. 173-178

GYNAECOLOGY

Preliminary Report of Ifosfamide plus Epirubicin in Platinum - Resistant Epithelial Ovarian Cancer

Pratag Ouppariputtigul MD,
Chaiyod Thirapakawong MD,
Sumrit Senapad Dr. med, FICS,
Somchaya Neungton MD,
Surintip Piamsombon MD,
Suwanit Therasakvichaya Dr. med,
Chairatana Leelaphatanadit MD.

Division of Gynaecologic Oncology, Department of Obstetrics and Gynaecology, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand

ABSTRACT

Objective To determine the efficacy and toxicity of ifosfamide plus epirubicin in platinum - resistant epithelial ovarian cancer.

Design Prospective phase II study.

Setting Siriraj Hospital.

Patients and Methods Platinum - resistant disease was defined as progressive or persistent disease while receiving a platinum - based regimen or recurrence within 6 months after completing therapy. Eligibility criteria included : age 18 – 70 years; measurable disease; Zubrod – ECOG – WHO performance status 0 – 2; prior chemotherapy regimens, one of which had to contain a platinum agent; adequate hematological, renal and hepatic function and no significant cardiac disease. Patients received intravenous infusion of ifosfamide 1.5 g/m^2 delivered over 3 hours each day for 3 days, intravenous bolus of mesna 300 mg/m^2 delivered every 4 hours for three doses following ifosfamide and intravenous bolus of epirubicin 70 mg/m^2 delivered on the first day. Subsequent cycle was repeated every 21 days.

Results Ten patients were assessable for responses and toxicity. Three patients (30%) had objective responses. One responder continued to respond over 10 months until the time of report. Two patients had partial responses; one died of sepsis after the third cycle and the other loss follow up after the sixth cycle of treatment. For toxicities, grade 3 or grade 4 neutropenia was observed in all patients at the first cycle of chemotherapy (grade 3 40%, grade 4 60%) and grade 4 neutropenia was observed in one patient at the second cycle of chemotherapy. G-CSF prophylaxis was used in 15 treatment cycles (39.5%). Grade 3 alopecia was observed in almost all patients (90%). One treatment – related death occurred from sepsis, originating from skin infection.

Conclusion This regimen is active in platinum – resistant epithelial ovarian cancer at the cost of major toxicities.

Key words: ifosfamide plus epirubicin epilhelial ovarian cancer

Epithelial ovarian cancer is a relatively chemosensitive tumor. Platinum based combination has been the standard chemotherapy regimen for advanced epithelial ovarian cancer following cytoreductive surgery. The overall response rate is 49 – 83.3%, including a complete response rate of 13 – 66.6%.[1-7] However, only about 25% of the patients with advanced disease are alive after 5 years with standard approaches.[8] Therefore, a majority of the patients are candidates for second – line chemotherapy.

Reinduction with platinum – based chemotherapy may still be effective in patients for whom the interval from completion of primary therapy to time of relapse is great.[9,10] But for progressive, persistent or early recurrent disease, at the present time there is no effective treatment which is promising.

Ifosfamide, an isomeric analogue of cyclophosphamide, which lacks cross – resistance with cyclophospamide, had been demonstrated to have activity against ovarian cancer previously treated by platinum compound.[11, 12] The overall response rate is 12 – 20% (CR 2.4 – 7%, PR 9.6 – 13%).

Epirubicin, an anthracycline which belongs to a different class of cytotoxic agents from ifosfamide and platinums, has unequivocal activity against ovarian cancer. An objective response in 34% of untreated patients and in 14% of patients previously treated with chemotherapy.[13,14] Preliminary investigation with epirubicin established less toxicity, thus greater tolerance than observed with the parent compound.

Linasmita et al[15] showed complete response in platinum – resistant epithelial ovarian cancer after using ifosfamide/mesna and adriamycin. Gadducci et al[16] used epirubicin and lonidamine in refractory or recurrent epithelial ovarian cancer. The overall response was 33.3% (CR 8.3%, PR 25.0%).

Casali et al[17] used epirubicin 90 mg/m^2 on day 1, ifosfamide 2,500 mg/m^2/day from day 1 to 3, mesna 500 mg/m^2 every 3 hours for three times and dacarbazine 300 mg/m^2/day from day 1 to 3 in advanced soft tissue sarcoma. The toxicities were tolerable.

Paclitaxel, docetaxel and topotecan had been demonstrated to have activity against platinum-resistant epithelial ovarian cancer.[18,19,20,21] Major disadvantage is cost and toxicities.

On the basis of this data, we decided to test ifofamide and epirubicin in combination in patients with platinum – resistant epithelial ovarian cancer, to determine the efficacy and toxicity.

Patients and Methods

Patient Eligibility Criteria

Patients were required to have a histologically confirmed diagnosis of epithelial ovarian cancer. Platinum – resistant disease was defined as progressive or persistent disease while receiving a platinum – based regimen or recurrence within 6 months after completing therapy.[22] Additional eligibility criteria included age 18 to 70 years; Zubrod – ECOG – WHO performance status 0 to 2; prior chemotherapy regimens, one of which had to contain a platinum agent; presence of at least one bidimensionally measurable lesion. Laboratory criteria for protocol entry included leukocyte count ≥ 4,000 /Cmm; granulocyte count ≥ 2,000 /Cmm; platelet count ≥ 100,000 /Cmm; serum bilirubin, SGOT, SGPT and alkaline phosphatase level less than 1.25 x upper limit of normal (N); serum creatinine concentration less than 1.25 x N (or creatinine clearance > 50 mL/min). Patients with active concomitant malignancy, active systemic infection, significant cardiac disease, or concurrent serious medical illnesses were excluded from protocol entry. All patients were required to sign informed consents.

Treatment protocol

Pretreatment evaluation included assessment of performance status; measurement of the lesion(s); physical examination, which included a pelvic examination; complete blood cell count; microscopic urinalysis; serum electrolytes; bilirubin; SGOT; SGPT; alkaline phosphatase; blood urea nitrogen; creatinine; CA 125; CA 19-9; electrocardiography; chest radiography; and abdominopelvic ultrasonography.

Patients received intravenous infusion of ifosfamide 1.5 g/m^2 delivered over 3 hours each day for 3 days and intravenous bolus of mesna 300 mg/m^2 delivered every 4 hours for 3 doses following ifosfamide.

Microscopic urine examination was required prior to infusion of ifosfamide each day. If RBC in urine was > 10 /HPF, ifosfamide was deferred and mesna was given alone on that day.

Epirubicin 70 mg/m^2 was delivered as a single intravenous bolus on the first day. Subsequent cycle was repeated every 21 days for a maximum of 6 cycles or until progression of disease or serious toxicities were encountered. G – CSF prophylaxis was used if grade 4 neutropenia was observed or subsequent cycle was delayed more than 4 weeks due to neutropenia.

Anti – emetic drugs included intravenous dexamethasone, metoclopramide and diphenhydramine were given on each cycle.

Measurements

Patients were assessed for responses and toxicities using WHO criteria.[23] Response was evaluated every three weeks by clinical examination. Response duration was measured from the date when response (complete or partial) was first noted to the date when progression was documented.

Table 1. Patient Characteristics

Total numbers	10
Ages, (years)	
Range	38 – 61
Median	49
Zubrod – ECOG – WHO performance status	
0	6
1	4
Tumor histology incidence	
Serous adenocarcinoma	4
Endometrioid adenocarcinoma	2
Clear cell carcinoma	1
Serous + Endometrioid	1
Serous + Clear cell	2
Tumor grade incidence	
1	0
2	2
3	6
Unspecified	2
Prior chemotherapy	
Cisplatin + Cyclophosphamide	4
Carboplatin + Cyclophosphamide	1
Carboplatin	1
Carboplatin + Paclitaxel	2
Repeated Cisplatin + Cyclophosphamide	1
Repeated Carboplatin	1
Platinum response	
Progressive disease	2
Persistent disease	6
Recurrence within 6 months	2
Site (s) of disease	
Pelvic	3
Extrapelvic	3
Pelvic + Extrapelvic	4
Tumor markers	
CA – 125 (> 35 U/Cmm)	10
CA 19 – 9 (> 35 U/Cmm)	2

Table 2. Results of treatment

Number of patients				
	Platinum response			
Clinical response	**Total (N=10)**	**Progressive disease (N=2)**	**Persistent disease (N=6)**	**Recurrence within 6 months (N) (%)**
Complete	0	0	0	0
Partial	3	0	2	1
Stable disease	1	0	1	0
Progressive disease	6	2	3	1

Table 3. Response of chemotherapy in platinum – resistant epithelial ovarian cancer

References	Regimen	No.of patients	Response (%)	
			CR	PR
Markman M, et al (12)	Ifosfamide + Mesna	41	2.4	9.6
GOG (11)	Ifosfamide + Mesna	41	7	13
Linasmita V, et al (15)	Ifosfamide + Doxorubicin	14	7.1	0
Gadducci A, et al (16)	Epidoxorubicin + Lonidamine	24	8.3	25
Muggia FM, et al (24)	Liposomal Doxorubicin	35	2.9	22.9
Trimble EL, et al (18)	Paclitaxel	1,000	4	18
Huinink WB, et al (19)	Paclitaxel	59	0	6.8
	Topotecan	60	1.7	11.7
Kudelka AP, et al (21)	Topotecan	28	0	14
Francis P, et al (20)	Docetaxel	23	0	35
Gietema JA, et al (25)	Lobaplatin	21	4.8	0
GOG (26)	Oral Etoposide	41	7.3	19.5
Thirapakawong C, et al (27)	Paclitaxel + Etoposide	27	14.8	18.5
Current study	Ifosfamide + Mesna + Epirubicin	10	0	30

Results

A total of 10 patients were entered onto this trial. Patient characteristics are shown in Table 1.

All 10 patients were considered evaluable for response (Table 2) and toxicity.

Patients received a median of 4 cycles of ifosfamide plus epirubicin with a range of 2 to 6 cycles. No patient achieved a complete response, 3 patients obtained a partial response, one patient had stable disease and 6 patients had progressive disease. The overall response rate was 30% (95% confidence interval, 2 – 58%). One responder (50%) was observed in recurrent diseases that had received carboplatin plus paclitaxel. Two responders (33.33%) were observed in persistent disease: one had received carboplatin plus paclitaxel and the other had received cisplatin plus cyclophosphamide. One responder had 10 months response duration and was still responding at the time of the report. The response duration of two responders could not evalvated the because the first one dead from sepsis after the third cycle of chemotherapy and the other loss follow up after sixth cycle of chemotherapy.

The total treatment cycle was 38. Grade 3 or grade 4 neutropenia was observed in all patients at the first cycle of chemotherapy (grade 3 40%, grade 4 60%) and grade 4 was observed in one patient at the second cycle of chemotherapy. G – CSF prophylaxis was used in 15 treatment cycle (39.5%). One patient died on the 25th day after the third cycle of chemotherapy. She had grade 3 neutropenia in the first and second cycle of chemotherapy during which skin infection was encountered but successfully controlled. Measurable lesion regressed by over 50% after the second cycle of chemotherapy. Unfortunately, the patient developed sepsis, was not recovered and died at another hospital. Clinical signs and symptoms suggested sepsis but no confirmatory laboratory tests. Grade 3 anemia was observed in 2 patients (20%). No thrombocytopenia was observed.

Grade 3 alopecia was observed in 9 patients (90%). Grade 3 nausea/vomiting was observed in one patient (10%). Grade 2 cardiac toxicity was observed in 2 patients. Hematuria and neurotoxicity was not found.

Discussion

The responses of various chemotherapies in platinum-resistant epithelial ovarian cancers are shown in Table 3. Gadducci et al used epirubicin with lonidamine and Muggia et al used liposomal doxorubicin and reported their overall response rates to be 33.3% (CR 8.3, PR 25) and 25.8% (CR 2.9, PR 22.9) respectively

Trimble's study is the largest study of paclitaxel, the overall response 22% (CR 4, PR 18). The median time to progression 7.1 months. Francis et al used docetaxel. The response rate was 35% (CR 0, PR 35). Thirapakawong used paclitaxel and etoposide. The response rate was 33.3% (CR 14.8, PR 18.5). These drugs are expensive. Most patients could not afford the expense. GOG performed the largest study of prolonged oral etoposide. The response rate was 26.8% (CR 7.3, PR 19.5) but the median response duration was only 4.3 months. Three treatment-related death occurred (3%) : two of neutropenic sepsis and one of bleeding secondary to thrombocytopenia. One of 97 patients developed acute myelomonocytic leukemia.

This study achieved the response rate of 30%, only partial response. No response was observed in progressive disease while receiving platinum-based regimen. The response rate in persistent and recurrent disease after receiving platinum-based regimen were 33.33% and 50%, respectively. The difference in response rates in each group prompts further study. Toxicities are rather high especially neutropenia and alopecia.

G-CSF prophylaxis was used in 39% of treatment cycles. It could reduce the severity of neutropenia in all treatment cycles but achieved higher cost per treatment cycle (about 2 times of normal cycle). One treatment-related death occurred from sepsis originating from skin infection. Further study should be adjusted for appropriate dose to reduce hematologic toxicity. However, as the number of patients enrolled in this study was rather small, the result may not be highly reliable. So far the result was getting along well compored with other previous regimens. The author suggests that further study should be carried on.

References

1. Senapad S, Neungton S, and Usavajindawath C. Cyclophosphamide, Adriamycin and Cis-platinum in Treatment of Ovarian Common Epithelial Cancer Stage III – IV. Siriraj Hosp Gaz 1987; 39 : 61 – 65.
2. Sessa C, Bolis G, Colombo N, et al. Hexamethylmelamine, adriamycin, and cyclophosphamide (HAC) versus Cis-dichlorodiamineplatinum, adriamycin and cyclophosphamide (PAC) in advanced ovarian cancer : A randomized clinical trial. Cancer Chemother Pharmacol 1985; 14 : 222 – 228.
3. Gruppo Interregionale Cooperativo Oncologico Ginecologia. Randomised comparison of cisplatin with cyclophosphamide/cisplatin and with cyclophosphamide/doxorubicin/cisplatin in advanced ovarian cancer. Lancet 1987; 2 : 353 – 359.
4. Omura GA, Bundy BN, Berek JS, et al. Randomized Trial of Cyclophosphamide Plus Cisplatin With or Without Doxorubicin in Ovarian Carcinoma : A Gynecologic Oncology Group Study. J Clin Oncol 1989; 7 : 457 – 465.
5. Alberts DS, Green S, Hannigan EV, et al. Improved Therapeutic Index of Carboplatin Plus Cyclophosphamide Versus Cisplatin Plus Cyclophosphamide : Final Report by the Southwest Oncology Group of a Phase III

Randomized Trial in Stages III and IV Ovarian Cancer. J Clin Oncol 1992; 10 : 706 – 717.
6. Swenerton K, Jeffrey J, Stuat G, et al. Cisplatin – Cyclophosphamide Versus Carboplatin – Cyclophosphamide in Advanced Ovarian Cancer : A Randomized Phase III Study of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1992; 10 : 718 – 726.
7. Hoskins WJ, McGuire WP, Brady MF, et al. Combination paclitaxel (Taxol®)-cisplatin Vs cyclophosphamide – cisplatin as primany therapy in patients with suboptimally debulked advanced ovarian cancer. Int J Gynecol Cancer 1997; 7(suppl 1) : 9 – 13.
8. Thiqpen JT, Bertelsen IC, Eisenhauer E, et al. Long – term follow-up of patients with advanced ovarian carcinoma treated with chemotherapy. Ann Oncol 1993; 4(suppl 4) : 35 – 40.
9. Seltzer V, Vogl S, and Kaplan B. Recurrent Ovarian Carcinoma : Retreatment Utilizing Combination Chemotherapy Including Cis-Diamminedic Chloroplatinum in Patients Previously Responding to This Agent. Gynecol Oncol 1985; 21 : 167 – 176.
10. Markman M, Rothman R, Hakes T, et al. Second-Line Platinum Therapy in Patients With Ovarian Cancer Previously Treated With Cisplatin. J Clin Oncol 1991; 9 : 389 – 393.
11. Sutton GP, Blessing JA, Homesley HD, et al. Phase II Trial of Ifosfamide and Mesna in Advanced Ovarian Carcinoma : A Gynecologic Oncology Group Study. J Clin Oncol 1989; 7 : 1672 – 1676.
12. Markman M, Hakes T, Reichman B, et al. Ifosfamide and Mesna in Previously Treated Advanced Epithelial Ovarian Cancer : Activity in Platinum – Resistant disease. J Clin Oncol 1992; 10 : 243 – 248.
13. Hurteloup P, Cappellaere P, Armand JP, et al. Phase II clinical evaluation of 4' epi-doxorubicin in refractory epithelial ovarian cancer. Cancer Treat Rep 1983; 67 : 337 – 341.
14. Simonsen E, Bengtsson C, Hogbhert T, et al. A phase II stady of the effect of 4-epidoxorubicin, administered in high dose 150 mg/m^2 in 24 hours intravenous infusion, in advanced ovarian carcinoma. Proc. 4th Eur. Congress Clin. Oncol. and Cancer Nursing, Madrid, 1987, abstract 863.
15. Linasmita V, Wilailak S, Srisupundit S, et al. Ifosfamide/ mesna plus adriamycin as salvage therapy of advanced epithelial ovarian cancer. Int J Gynecol Cancer 1997; 7 : 388 – 391.
16. Gadducci A, Brunetti I, Muttini MP, et al. Epidoxorubicin and Lonidamine in Refractory or Recurrent Epithelial Ovarian Cancer. Eur J Cancer 1994; 30A : 1432 – 1435.
17. Casali P, Pastorino U, Zucchinelli P, et al. Epirubicin plus ifosfamide and dacarbazine (EID) in advanced soft tissue sarcomas. Ann Oncol 1992; 3(Suppl.2) : S 125 – S 126.
18. Trimble EL, Adams JD, Vena D, et al. Paclitaxel for Platinum – Refractory Ovarian Cancer : Results From the First 1,000 Patients Registered to National Cancer Institute Treatment Referral Center 9103. J Clin Oncol 1993; 11 : 2405 – 2410.
19. Huinink WB, Gore M, Carmichael J, et al. Topotecan versus Paclitaxel for the Treatment of Recurrent Epithelial Ovarian Cancer. J Clin Oncol 1997; 15 : 2183 – 2193.
20. Francis P, Schneider J, Hann L, et al. Phase II Trial of Docetaxel in Patient With Platinum – Reflactory Advanced Ovarian Cancer. J Clin Oncol 1994; 12 : 2301 – 2308.
21. Kudelka AP, Tresukoso LD, Edwards CL, et al. Phase II Study of Intravenous Topotecan as a 5 – Day Infusion for Refractory Epithelial Ovarian Carcinoma. J Clin Oncol 1996; 14 : 1552 – 1557.
22. Thigpen JT, Vance RB, and Khansur T. Second-Line Chemotherapy for Recurrent Carcinoma of the Ovary. Cancer (suppl) 1993; 71 : 1559 – 1564.
23. WHO Handbook for Reporting Results of Cancer Treatment. WHO offset – publication No. 48, World Health Organization, Geneva, 1979.
24. Muggia FM, Hainsworth JD, Jeffers S, et al. Phase II Stady of Liposomal Doxorubicin in Refractory Ovarian Cancer : Antitumor Activity and Toxicity Modification by Liposomal Encapsulation. J Clin Oncol 1997; 15 : 987 – 993.
25. Gietema JA, Veldhuis G-J, Guchelaar H-J, et al. Phase II and pharmacokinetic study of lobaplatin in patients with relapsed ovarian cancer. Br J Cancer 1995; 71 : 1302 – 1307.
26. Rose PG, Blessing JA, Mayer AR, and Homesley HD. Prolonged Oral Etoposide as Second-Line Therapy for Platinum-Resistant and Platinum-Sensitive Ovarian Carcinoma : A Gynecologic Oncology Group Study. J Clin Oncol 1998; 16 : 405 – 410.
27. Thirapakawong C, Senapad S, Neungton S, et al. Paclitaxel and Etoposide in Platinum Refractory Epithelial Ovarian Cancer. Thai J Obstet Gynaecol 1997; 9 : 293 – 298.