Platinum Based Chemotherapy for Advanced Epithelial Ovarian Cancer (AEOC)

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Abstract : *Between January 1987 to December 1989, thirty-seven patients with advanced epithelial ovarian cancer were treated with various Platinum based chemotherapy according to their financial status. Regimen A consisted of cisplatin, doxorubicin and cyclophosphamide. Regimen B was cisplatin and melphalan. Overall response rates were 80% and 86% for regimen A and B, respectively and median duration of response were 21 and 15 months. The median survival was more than 35 months in both regimens. The proportions of "non responders" was similar in both treatment groups and the proportions in remission at various times following onset of treatment were also similar. When considering the cost effectiveness of treatment of 100 cases of advanced ovarian cancer, the reduction in costs of $ 77,160 would be obtained at the expense of 13 cases failing to survive past 35 months. (Thai J Obstet Gynaecol 1995;7:51-60.)*

Key words : cost effectiveness, advanced epithelial ovarian cancer

Cancer management causes a heavy financial burden to a goverment referral center. Songklanagarind Hospital is a university hospital with complete facilities for treatment of gynecologic cancer. In cases of advanced epithelial ovarian cancer, adjunctive chemotherapy is necessary. Available commercial chemotherapeutic drugs are imported and costly for a developing country like Thailand. Because most of the patients are poor, and have no health insurance, the burden falls largely on the hospital to provide comprehensive treatment. To do so, under the constraint of limited resources, two different postoperative chemotherapy protocols for advanced epithelial ovarian cancer were used. The first was a regimen of cisplatin, doxorubicin and cyclophosphamide (regimen A) and prescribed for affordable patients. The other, regimen B, was the combination of cisplatin and melphalan (phenylanine mustard, L-PAM) and used for indi-

gent patients. This regimen shared comparable activity against ovarian cancer[1-5]. The objective of this study was to compare the results and cost effectiveness of the two treatments.

Materials and methods

From January 1987 to December 1989, patients with advanced epithelial ovarian cancer (stage III or IV, International Federation of Gynecology and Obstetrics classifications) were studied. Histologic confirmation of the disease and the end of disease was required. The end of the study was on 30 April, 1991.

The primary surgery was performed at the Department or elsewhere. In cases where the operation was initially performed at another hospital, a surgical summary indicating the extent of the disease at laparotomy was sought through personal or official contact.

Patients were categorized according to their financial status. Those affordable patients received regimen A. Those indigent patients received regimen B. The chemotherapeutic drugs were started 2-4 weeks after surgery unless delayed by postoperative complications.

The drug doses in regimen A were intravenous 50 mg/m^2 of cisplatin, 50 mg/m^2 of doxorubicin and 200 mg/m^2 of cyclophosphamide on the same day. Prehydration was given before cisplatin infusion with one half normal saline intravenously at a rate of 300-500 ml. per hour for 2-4 hours and 100 ml. 20% mannitol infused in 20 minutes. Another 1000 ml. of one half normal saline was also infused intravenously in 6 hours immediately after cisplatin infusion. The dose of cisplatin and technique of administration in regimen B were the same as in regimen A followed by melphalan given orally 0.2 mg/kg for five days.

Courses of both regimens were repeated every 28 days. provided there was no evidence of toxicity. Six courses of therapy were planned. Patients who received at least 3 courses of therapy were included in the analysis. Although the clinical evaluation which consisted of physical and pelvic examination were performed before the beginning of the next course, the evaluation after receiving three courses of chemotherapy was the first documented response. After 6 courses of therapy, if the patients were clinically free of disease, they would undergo a reevaluation with Chest X-ray and abdominopelvic ultrasonographic studies. If the result of the studies yielded negative findings, a second look would be offered. Patients who refused a second look laparotomy were considered for a 3-6 courses of additional chemotherapy. The schedule of followup was every 4 and 8 weeks in the first and second year, respectively.

Complete response was defined as the disappearance of all evidence of disease as judged by clinical examination and investigation, in particular,

Partial response was defined as more than 50% reduction in the size of the measurable tumor. Duration of response was recorded as the time between the earliest examination at which a response had occurred, and the time at which a reappearance or metastasis of tumor was detected. Patients showing no response (stable or progressive disease) were recorded as having a response duration of zero. During the study period, if the patients received postoperative chemotherapy but they failed to attend follow up programme or never response the questionnaire sent by mail, they were signed as lost to follow up. Patients who were lost to follow up, who had not yet developed recurrence by the end of the study, were considered to be censored. Response curves were constructed by Kaplan and Meier's method[6].

Survival duration was recorded from the date of treatment which was the date of the first operation. Patients who were lost to follow up, or who were still alive at the end of the study, were considered to be censored. Both response and survival curves were constructed by the methods of Kaplan and Meier[6].

Response and survival profiles of the two treatment groups were compared using Chi-square statistic, Fisher-exact test and Log-rank test. Confidence intervals for response and survival propabilities at specified durations were calculated from the values of standard error determined by the method of Peto[7].

For cost effectiveness analysis, only direct costs were identified. Indirect and intangible costs were excluded as it was difficult to allocate a monetary value to these. Direct costs comprise of direct medical costs and non medical direct costs. The former were the cost of hospitalization, drugs, laboratory tests, investigation procedures, pathological examination, and operation fee. The latter were food, transportation, and lodging. It was emphasied that the cost of treatment was calculated under the assumption that no medical or surgical complication occurred and the patients received 6 courses of chemotherapy. The effect in this situation was the number of patients surviving 3 years after treatment.

Results

During the 3 year period, there were 96 patients with epithelial ovarian cancer. Fifty six patients had advanced stages. Of these, 37 were evaluable in that they had received at least 3 courses of the chemotherapy. Patients excluded were those who refused therapy or received less than 3 courses.

The patient characteristics were shown in Table 1. All except one in regimen B were in stage III. The initial operation in more than 60% of patients were total abdominal hysterectomy with bilateral salpingo-oophrorectomy plus omentectomy. The proportion of optimal cytoreduction as well as the post perative

complications in both groups were not different. The common histology of tumor was serous type. Although a second look operation was planned for clinically complete responders, most of the patients refused. Only 3 cases (2 in regimen A and 1 in regimen B) underwent a second look operation and revealed no macroscopic disease. The mean courses of chemotherapy was 7 and 8 in regimen A and B respectively. Although the patients in each group were different in financial status, the follow up times was similar in both regimens ranging from 4 to 39 months in regimen A and 3 to 35 months in regimen B. Median follow up time in both groups were approximately 14 months.

The over all response (complete and partial) were 80% and 86% for regimen A and B, respectively (Table 2.) Response curves and survival curves in the two treatment groups are shown in Figs. 1 and 2, respectively. Median response time were 21 months in regimen A and 15 months in regimen B (non responders included; Table 3.).

Toxicity was tolerable in both regimens. Table 4. listed three major toxic effects and their frequency. Hematological toxicity was more common in regimen B. Almost all patients developed alopecia, anorexia and vomiting. Severe vomiting was more common in regimen A. Electrocardiography of one patient in regimen A showed first degree heart block after receiving 5 courses of chemotherapy. Liver enzymes have definitely increased in 2 patients, of whom had liver scan for suspected liver metastasis but ultrasonography and laparotomy findings yielding negative result. Extravasation rendered skin necrosis occurred only once.

Details of the costs for patients receiving initial surgical treatment were shown in Table 5. The cost of initial surgery was the same in both regimens, $ 160. The costs per patient per course were $ 202 and $ 73.4 in regimen A and B respectively. The laboratory cost of regimen A was expensive than regimen B because of electrocardiography which had to be performed in order to monitor possible cardiotoxicity of doxorubicin. Under the assumption that a patient received surgical treatment plus 6 courses of chemotherapy without complications or serious side effects, the total cost was $ 1372 for regimen A and $ 600 for regimen B. The costs and effects of the treatment of 100 cases of advanced ovarian cancer using two different regimen are shown in Table 7. The effect was defined on the basis of number of patients surviving 35 months after treatment. The saving in cost comparing regimen B with A was $ 77,160, while the effect was 13 cases failing to survive 35 months.

Discussion

The main obstacle in management for advanced ovarian cancer in developing country, such as Thailand, are the high cost of treatment and low

Table 1 *Characteristics of Patient Groups*

Variable	Regimen A(CAP)	Regimen B (PM)
Total number assessed	15	22
Age (yr)		
Range	16-72	23-72
Median	48	53
FIGO stage (no. of patients)		
III	11	21
IV	4	1
Initial operation (no. of patients)		
Biopsy only	1	1
Excision of mass	2	2
TAH/BSO plus omentectomy	10	17
BSO plus omentectomy	1	1
Omentectomy	1	1
Histology of tumor		
Serous	8	10
Mucinous	3	5
Clear cell	1	2
Endometrioid	1	4
Mixed type	-	1
Mixed mullerian	1	-
Undifferentiated	1	-
Mean number of courses of chemotherapy	7	8
Follow up times (months)	4-39	3-35

Note. CAP, cisplatin/doxorubicin/cyclophosphamide; PM, cisplatin/melphalan; TAH/BSO, total abdominal hysterectomy/bilateral salpingo-oophrorectomy.

Table 2 *Results of Therapy*

Results	Regimen A (CAP) (n=15)	Regimen B (PM) (n=22)	ρ value (Fisher Exact)
No. responding:	12 (80%)	19 (86%)	0.67
Complete response	8 (53%)	13 (59%)	0.75
Partial response	4 (27%)	6 (27%)	
No response	3 (20%)	3 (14%)	

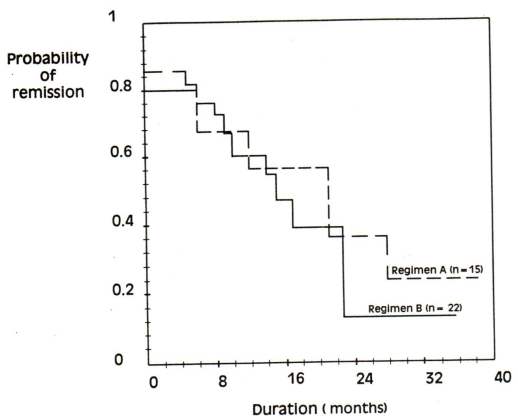

Fig. 1 **Remission curves in the two treatment groups of patients with advanced epithelial ovarian cancer.**
Regimen A = cis-platinum + doxorubicin + cyclophospha-mide.
Regimen B = cis-platinum + melphalan.

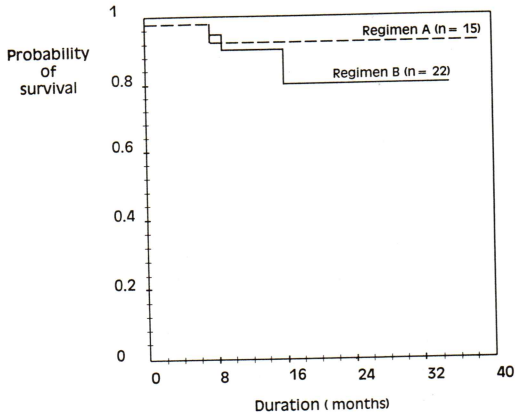

Fig. 2 **Survival curves in the two treatment groups of patients with advanced epithelial ovarian cancer.**
Regimen A = cis-platinum + doxorubicin + cyclophospha-mide.
Regimen B = cis-platinum + melphalan.

Table 3 *Comparison of Treatments*

Parameter	Regimen A (CAP) (n=15)		Regimen B (PM) (n=22)
No. censored	6		9
1-year response, %	57 (30,85)		61 (39, 82)
2-year response, %	34 (11, 57)		12 (0, 25)
35-month response, %	23 (0, 46)		12 (0, 25)
Median duration of response, months	21 (6, 21)		15 (9, 21)
Chi-square for homogeneity		0.152	
ρ value (log rank test)		0.70	
No. censored	14		19
1-year survival, %	92 (76, 100)		88 (72, 100)
2-year survival, %	92 (77, 100)		79 (57, 100)
35-month survival, %	92 (77, 100)		79 (57, 100)
Median survival time, months	>39		>35
Chi-square for homogeneity		0.385	
ρ value (log rank test)		0.53	

Note Non responders were included. Values in parenthesis were 95% confidence limits.

Table 4 *Toxicity from chemotherapy*

	Regimen A (CAP) (n = 15)	Regimen B (PM) (n = 22)
Leukopenia*	-	1
Thrombocytopenia**	1	5
Anemia**	-	7
Vomiting (severe)	5	2
Cardiotoxicity	1	-
Hepatotoxicity	-	2
Skin necrosis	1	-

*1000-2000 leukocytes/mm^3
**<100,000 platelet/mm^3
***hemoglobin<10gm/dL

Table 5 *Cost identification Components of cost with surgery in patient with epithelial ovarian cancer*

Direct costs	U.S $
Direct medical cost	
Hospitalization	9.4
Drugs	
Antibiotic	6.4
Other durgs	1.2
Intravenous line	10.6
Enema & vaginal douche	1.6
Cross match for blood transfusion	14.4
Laboratory test	14.5
X-ray procedure	3.6
Pathological examination	8.0
Operation fee	40.0
Anesthetic fee	28.0
Non-medical direct costs	
Food	10.8
Transportation	8.0
Lodging	1.8
Total	160.0

Note Indirect and intangible cost has been excluded.

Table 6 *Cost identification Component of costs per patient per course of adjuvant chemotherapy*

Direct costs	Regimen A(CAP) U.S. $	Regimen B (PM) U.S. $
Direct medical cost		
Hospitalization	2.1	2.1
Drugs		
Chemotherapy	166.5	41.5
Other drugs	0.8	0.8
Intravenous line	4.8	4.8
Laboratory test	14.6	11.0
X-ray procedures	3.6	3.6
Non-medical costs		
Food	1.2	1.2
Transportation	8.0	8.0
Lodging	0.4	0.4
Total	202.0	73.4

Note Indirect and intangible cost had been excluded.

Table 7 *Cost effectiveness analysis Costs and effects on survival of different regimen for 100 patients with advanced epithelial ovarian cancer*

Strategy	Cost U.S. $	Effects (no. of patients survival at 35 months)
Surgery + CAP	137,200	92
Surgery + PM	60,040	79
Increment cost and effects	77,160	13

Note Surgery plus 6 courses of chemotherapy without complications or serious side effects.

patient compliance. From the research viewpoint, the first obstacle renders a randomized clinical trial which is rather difficult to implement. The latter obstacle was reflected, in this study, by the high rate of refusal or discontinuation of therapy and patients lost to follow up.

Adjuvant chemotherapy in advanced ovarian cancer is necessary since it can improve the median survival time, although the long term survival is still disappointing.[8-11] The combination chemotherpy regimen should minimally consist of a platinum compound and an alkylating agent. The response rate in cisplatin based regimen is expected to be about 60%[12-15]. Although the median duration of response in the current study

are not dissimilar from those in other studies[15-18], the response rate of 80% and the more than 35 months median survival indicate a surprisingly good outcome. A high response rate, however, dose not guarantee a high survival rate. The 5 year survival in other studies is less than 30%.[8,9,11] This study was limited by the small number of patients, the non-randomized allocation to treatment regimens, the high proportion of censored data resulting in wide confidence intervals, and the relatively short follow up times. However, the data are consistent with a duration of partial or complete response to cisplatin plus melphalan similar to the standard regimen. The proportion of "non responders" was similar in both treatment groups, with the proportion in response at various times following onset of treatment.

The most common side effects of cisplatin were nausea and vomiting which occurred in all patients. Fortunately, it was tolerable. Hematological toxicity, including neutropenia and thrombocytopenia was common in patients who received melphalan as it causes a prolonged course interval time.

The total costs for treatment of advanced epithelial ovarian cancer using standard regimen was two times of the alternative regimen. For a cost saving of $ 77,160 per 100 patients, an additional 13 patients may fail to survive beyond 35 months. Evaluating reduced patient survival with savings in treatment cost was very difficult. However, under conditions of limited resources, providing expensive treatment to benefit a few may not be economical appealing. The saving in cost of $ 77,160 in some opinions may not be a large amount of money, but in a developing country whose mean annual income per capita is $ 1,170[19], it represents a relatively large sum. In the management of cancer patients, these aspects should be considered when selecting the treatment protocol. These include efficiency, toxcity, and cost effectiveness. The first is the efficiency, the second is an acceptable toxicity and the third is the cost effectiveness.

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