Efficacy of Platinum Plus Cyclophosphamide in Patients with Epithelial Ovarian Cancer

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Objectives: *To determine the response rate (RR), 5-year progression-free survival (PFS), and the 5-year survival rate (SVR) of epithelial ovarian cancer patients who received platinum plus cyclophosphamide as adjuvant postoperative chemotherapy.*
Material and Method: *Epithelial ovarian cancer patients who underwent tumor debulking surgery and received platinum plus cyclophosphamide as adjuvant chemotherapy at Vajira Hospital from January 1995 to December 2003 were identified. All clinical and pathological data were reviewed.*
Results: *Among 114 patients included in the present study, 101 patients were evaluable for response. Overall response rate was 79.2%. The 5-year PFS and 5-year SVR were 60.3% (95% confidence interval [95% CI]; 50.5, 70.1%) and 60.7% (95% CI; 50.9, 70.5%) respectively. Subgroup analysis showed better RR, PFS, and SVR in early stage than advanced stage disease.*
Conclusion: *The overall RR, 5-year PFS, and 5-year SVR of patients of the whole group were modest. These outcomes were significantly better in the early stage than the advanced stage.*

Keywords: *Epithelial ovarian cancer, Response rate, Survival rate, Platinum, Cyclophosphamide.*

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Ovarian cancer is the second most common gynecological cancer in Thailand[1]. Regarding treatment, surgery is universally accepted as the cornerstone in management of ovarian cancer. The goals of primary surgery are to confirm the diagnosis, to precisely evaluate the extent of disease, and to reduce the bulk of the tumor[2]. Surgery is considered as adequate treatment when the tumor is low grade and the disease limits to ovary. Beyond these circumstances, adjuvant chemotherapy is mandatory to decrease the risk of recurrence in early stage diseases or to irradicate the microscopic or gross residual cancer in advanced stage.

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Chemotherapy for ovarian cancer, for which many new drugs have been rapidly emerging in recent years, has a long history of evolution. In earlier years, alkylating agents such as melphalan[3] and subsequently platinum drugs, particularly cisplatin and carboplatin, are the standard chemotherapy for epithelial ovarian cancer (EOC)[4,5]. The most common chemotherapy regimen used is platinum plus cyclophosphamide[4-6]. In 1996, the Gynecologic Oncology Group by McGuire et al[7] reported the better efficacy of cisplatin and paclitaxel combination over cisplatin and cyclophosphamide; this finding has initiated a new era of chemotherapy regimen in the treatment of EOC. The superiority of paclitaxel in combination with cisplatin or carboplatin were supported by the unanimous results from other subsequent studies[8,9]. Carboplatin, which has comparable efficacy to cisplatin, is more favorable than cisplatin in combination with paclitaxel[9] because it has no neurologic toxicity as cisplatin or paclitaxel,

and is more convenient to administer. At present, carboplatin-paclitaxel is considered as a standard treatment for EOC, especially in developed countries. However, in developing countries including Thailand where financial resource is a major limitation, the routine use carboplatin-paclitaxel administration in all EOC patients is impractical because of the high cost of paclitaxel[10,11]. Thus, platinum-cyclophosphamide is still currently and mostly used as the primary adjuvant chemotherapeutic regimen after surgery in Thailand. The objective of the present study was to evaluate the efficacy of platinum-cyclophosphamide as adjuvant chemotherapy in epithelial ovarian cancer patients after primary surgery.

Material and Method

Patients

The present study included ovarian cancer patients who were treated at the Gynecologic Oncology Unit, Department of Obstetrics and Gynecology, Bangkok Metropolitan Administration Medical College and Vajira Hospital. The eligibility criteria were patients who had histologically confirmed EOC, had primary tumor debulking surgery, and received adjuvant chemotherapy as cisplatin or carboplatin, plus cyclophosphamide. The patients who had a low malignant tumor or had neoadjuvant chemotherapy prior to surgery were excluded.

Methods

The present study was conducted after the approval of the Ethics Committee of Vajira Hospital. Between January 1995 and December 2003, patients with EOC who received cisplatin or carboplatin plus cyclophosphamide as adjuvant chemotherapeutic treatment were identified. The patients who met the eligibility criteria were included in the study. Patient's clinical and pathological data were collected from the in-patient and out-patient charts. Data were collected on: age; International Federation of Gynecology and Obstetrics (FIGO) stage[12]; tumor histologic cell type and grade; the type and outcome of surgery; the particular type of platinum drug; and number of cycles of chemotherapeutic treatments. The main outcomes to evaluate drugs efficacy were response rate (RR), 5-year progression-free survival (PFS) and 5-year survival rate (SVR). The clinical response was determined from the physical examinations, CA125, or radiologic imaging[11]. Complete response was defined when there was no clinical evidence of tumor after chemotherapy treatment. A partial response was defined when tumor reduction was > 50%. Stable disease was defined as a tumor that was unchanged in size or that was decreased $\leq$ 50% or increased $\leq$ 25%. Progressive disease was defined as an increase in tumor size > 25% or development of new lesion. PFS was defined as the interval from the date of chemotherapy started to the date of documented disease progression. For patients who were lost to follow-up, PFS data were right-censored at the time of the last evaluation or contact when the patient was known to be progression-free. Overall survival was defined as the interval when the date of chemotherapy started to the date of death or last follow-up visit. For patients who were alive at the end of the presentstudy, overall survival data were right-censored at the time of the last evaluation or contact.

Data were analyzed using SPSS version 11.5 (SPSS, Chicago, IL). Descriptive statistics were used for demographic data and summarized as mean with standard deviation or frequency with percentage. Progression-free survival, and 5-year survival were analyzed with the Kaplan-Meier method. Survival data between groups were compared with the Log-rank test. The outcomes were statistically significant only if $p < 0.05$.

Results

Between January 1995 and December 2004, 114 patients with EOC who received cisplatin or carboplatin plus cyclophosphamide as adjuvant chemotherapy and met all other eligibility criteria were identified. The mean age of the patients was 51.36 $\pm$ 11.86 years (range 24-72 years). The age interval between 40-49 years was the most common age range, at 29.8%.

The number of patients of early stage (stage I-II) and advanced stage (stage III-IV) were 61 patients (53.5%) and 53 patients (46.5%) respectively. Stage I disease comprised nearly half of the total (53 cases or 46.5%) and the second was stage III disease (44 cases or 38.6%) (Table 1).

The histologic cell types were mainly serous, mucinous and clear cell adenocarcinonomas. Approximately half of tumors were grade 3. The clinical features of disease, the type of surgery, and the surgical outcome are shown in Table 1.

After primary surgery, cyclophosphamide was given together with cisplatin in 78 patients (68.4%) and with carboplatin in 24 patients (21.1%). The number of adjuvant chemotherapy treatment ranged from 1-10 cycles (mean 6 cycles). The detail of chemotherapy treatment are shown in Table 2.

Table 1. Clinical and histologic features of the patients (n = 114)

Tumor characteristics and detail of surgery	Number	Percent
Stage		
I	53	46.5
II	8	7.0
III	44	38.6
IV	9	7.9
Histology		
Serous cystadenocarcinoma	28	24.6
Mucinous cystadenocarcinoma	25	21.8
Clear cell carcinonoma	24	21.1
Endometrioid adenocarcinoma	19	16.7
Adenocarcinoma, not otherwise specified	13	11.4
Adenosquamous	1	0.9
Mixed epithelial tumor	4	3.5
Tumor grade		
I	10	8.8
II	28	24.6
III	59	51.8
Unknown	17	14.8
Type of surgery		
Complete surgical staging	80*	70.2
Incomplete surgical staging	34	29.8
Result of surgery		
Optimal surgery	80*	70.2
Suboptimal surgery	23	20.1
Unknown	11	9.7

* The two subgroups were composed of different individual patient

Table 2. Specific type of chemotherapy and numbers of chemotherapeutic treatment (n = 114)

Chemotherapy	Number	Percent
Type of chemotherapeutic drugs		
Cisplatin plus cyclophosphamide	78	68.4
Carboplatin plus cyclophosphamide	24	21.1
Platinum, not otherwise specified, plus cyclophosphamide	12	10.5
Number of chemotherapeutic treatment (cycle)		
1	11	9.6
2	8	7.0
3	16	14.1
4	16	14.1
5	3	2.6
6	56	49.1
> 6	4	3.5

Of the 114 patients, 101 patients were evaluable for response. Clinical complete response and partial clinical response were found in 75 patients (74.3%) and five patients (4.9%) respectively. Stable disease was noted in six patients (5.9%) while 15 patients (14.9%) had progressive disease. Twelve patients could not be evaluated for response because they received only one cycle of chemotherapy (including one patient who died from neutropenic sepsis) or were lost to follow up.

The authors also studied the RR according to the extent of primary disease as early (stage I-II) or advanced stages (stage III-IV). From 57 patients who

were in early stage disease and evaluable for response, 56 patients showed complete or partial responses (98.2%) while only 24 out of 44 patients (54.5%) in the advanced stage had tumor response ($p < 0.0001$).

From 114 patients who received platinum plus cyclophosphamide as first-line adjuvant chemotherapy, 36 patients (28.1%) subsequently received second-line chemotherapy. These comprised five patients with partial response from the first-line chemotherapy, six with stable disease, 13 with progressive disease, and 12 patients who had recurrences. Thirty patients received chemotherapy in our institution and the other six had treatment elsewhere.

The 5-year PFS rate of 114 patients was 60.3% (95% confidence interval [95%CI]; 50.5, 70.1%); 84.9% (95%CI; 74.1, 95.7%) in patients with early stage disease and 28.9% (95% CI; 14.6, 43.2%) in the advanced stage ($p < 0.0001$) (Table 3). The median PFS of all patients as a whole and of the patients with early stage disease were not reached, while the median PFS of the patients in the advanced stage was 10 months (95%CI; 8,11 months). The PFS of patients in early and advanced stage are shown in Fig. 1.

The overall 5-year SVR of the whole group was 60.7% (95%CI; 50.9, 70.5%) and were 78.8% (95%CI; 67.0, 90.6%) and 39.0%(95%CI; 23.3, 54.7%) in early and advanced stage respectively ($p < 0.0001$) (Table 3). The median survival duration of the whole group and of early stage patients were not reached, while the median survival duration of patients in the advanced stage was 21.1 months (95%CI 10.3, 31.8 months). The survival of patients in early and advanced stage is shown in Fig. 2.

The authors also studied the result of platinum and cyclophosphamide treatment according to the result of surgery. From 103 patients whose result of surgery was clearly recorded, 80 patients (77.7%) had optimal surgery and 23 (22.3%) had suboptimal surgery. The overall RR, 5-year PFS, and 5-year SVR of the patients in whom optimal surgery was achieved were statistically significantly higher than those patients who had suboptimal surgery (Table 3). The PFS and SVR of patients who had optimal and suboptimal surgery are shown in Fig. 3 and 4 respectively.

Discussion

The benefit of platinum as a single agent or as combination chemotherapy for the treatment of EOC has long been recognized for decades. The Advanced Ovarian Cancer Trialists' Group by Aabo et al reported a meta-analysis study regarding the role of platinum in the treatment of advanced ovarian cancer[14]. The quantitative review using individual data of 5,667 patients from 37 available randomized trials was performed. The authors made three conclusions. First of all, the results suggested that platinum based treatment was better than non-platinum regimens in terms of survival. Secondly, platinum in combination with other chemotherapeutic drug was better than single agent platinum when used at the same dose. Finally, cisplatin and carboplatin were equally effective. The combination of platinum and cyclophosphamide is one of the most common chemotherapy regimens used for EOC. Its efficacy is reported to be better than melphalan or intraperitoneal P-32 in terms of 5-year disease-free survival (DFS) and 5-year SVR[3] or single agent cyclo-

Table 3. Result of platinum and cyclophosphamide chemotherapy in epithelial ovarian cancer (n = 114)

Characteristics	N (n)	Overall RR (%)	p value*	5-year PFS (%)	p value#	5-year SVR (%)	p value#
Stage IC-IV	114 (101)	79.2		60.3		60.7	
Early stage (I-II)	61 (57)	98.2	<0.0001	84.9	<0.0001	78.8	<0.0001
Advanced stage (III-IV)	53 (44)	54.5		28.9		39.0	
Result of surgery							
Optimal surgery	80 (73)	89.0	<0.0001	68.2	<0.0001	71.2	<0.0001
Suboptimal surgery	23 (19)	36.8		26.7		29.9	

Abbreviations: N, number of all patients in each category; n, number of patients who were evaluable for response in each category; PFS, progression-free survival; RR, response rate; SVR, survival rate

* p value comparing response rate of early versus advanced stages and optimal versus suboptimal surgery were obtained by Chi-square test

\# p value comparing 5-year progression-free survival and 5-year survival of early versus advanced stages and optimal versus suboptimal surgery were obtained by log rank method

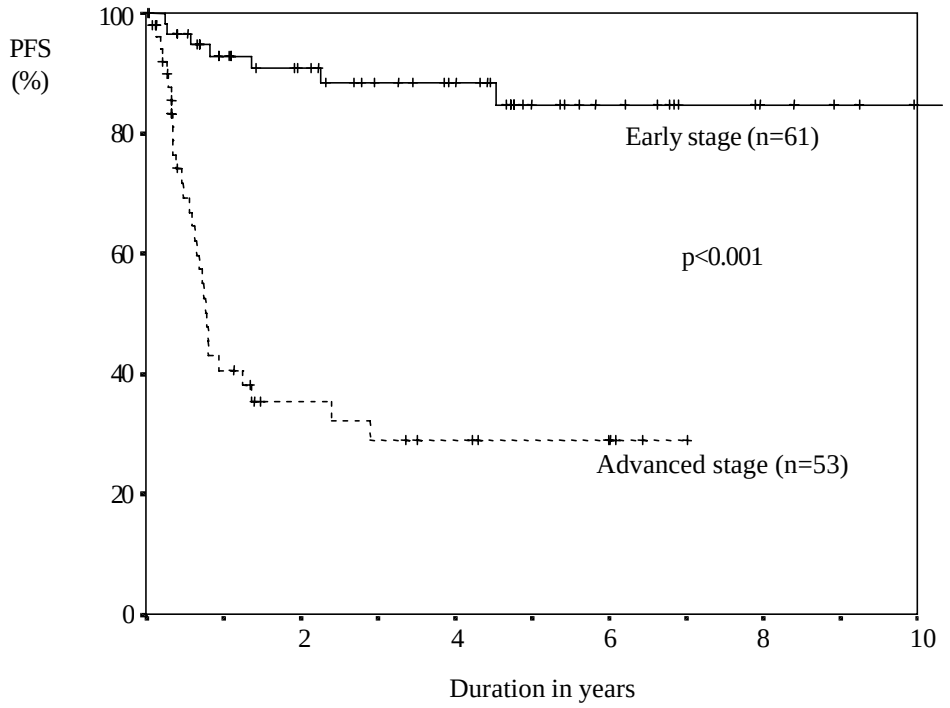

Fig. 1 Progression–free survival of ovarian cancer patients by stage group (n = 114)

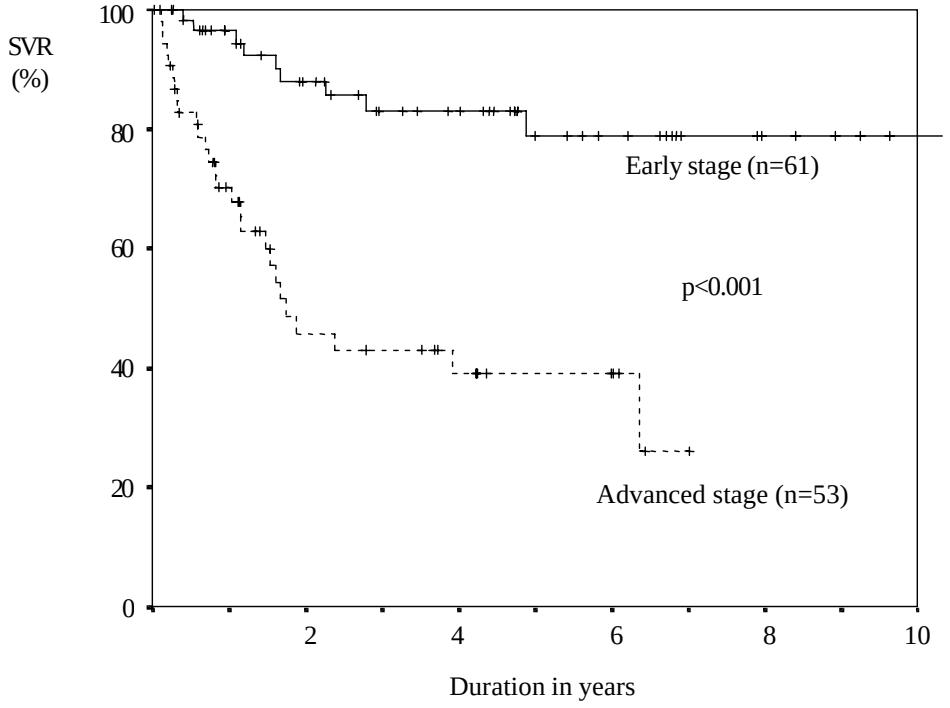

Fig. 2 Survival rates of ovarian cancer patients by stage group (n = 114)

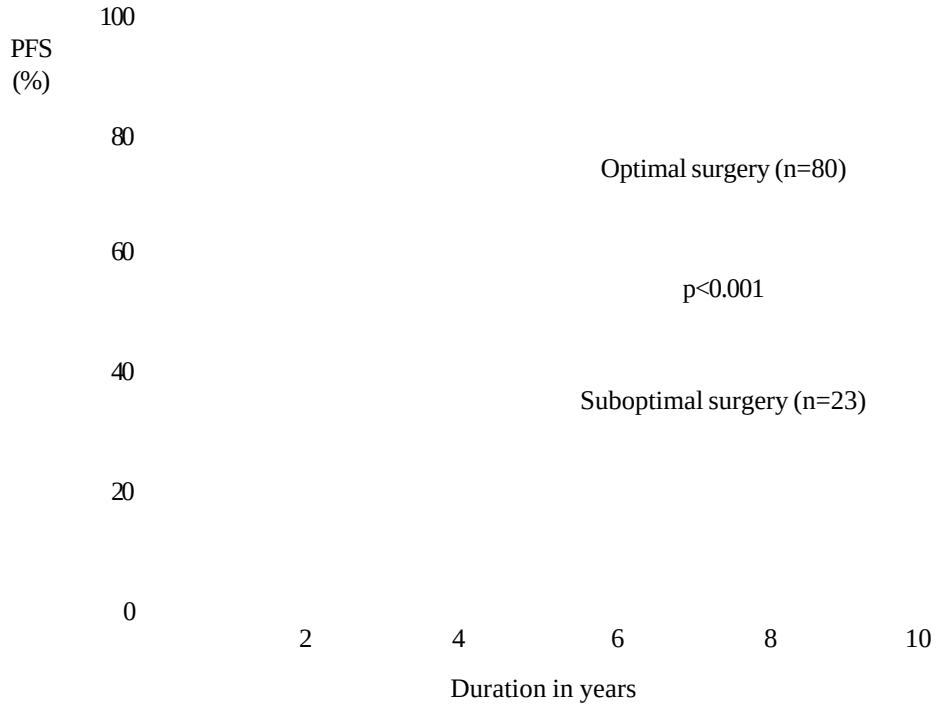

Fig. 3 Progression–free survival of ovarian cancer patients by result of surgery (n = 103)

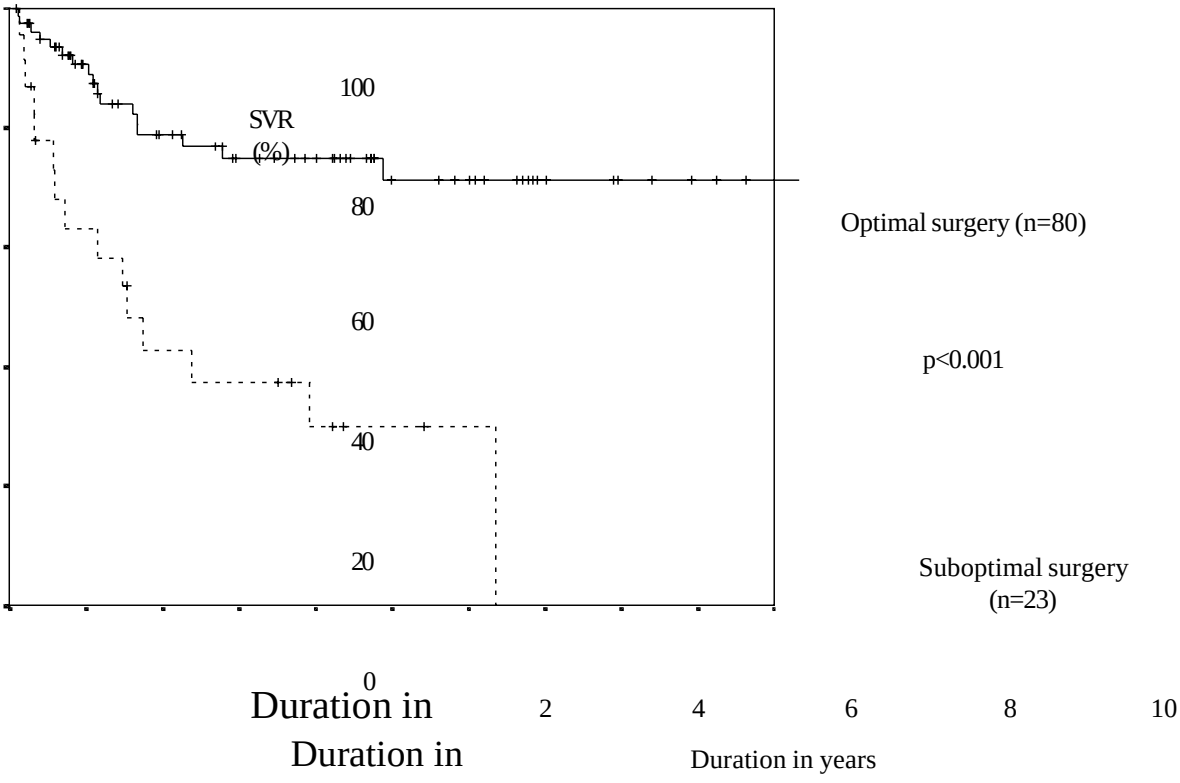

Fig. 4 Survival rates of ovarian cancer patients by result of surgery (n = 103)

phosphamide in terms of DFS and 2-year SVR[5]

This retrospective descriptive study was to evaluate the efficacy of cisplatin or carboplatin plus cyclophosphamide as adjuvant chemotherapy in the EOC patients treated in our institution. The authors included the patients who received either cisplatin or carboplatin (with cyclophosphamide) together as the same group because many studies showed similar efficacy of these two drugs in treatment for EOC[14-16].

The authors found that the overall RR, 5-year PFS, and 5-year SVR of the patients in the present study were 79.2%, 60.3%, and 60.7% respectively. From the literature review, most studies of chemotherapy treatment in EOC focused on the patients who were in the advanced stage. Only a few studies included all stages of disease[4,6,17]. In 1982, Conte et al[4] reported RR of 48% from 125 stage IC-IV EOC (22 patients in stage I-II and 103 patients in stage III-IV) who received cisplatin and cyclophosphamide. This figure was similar to that reported by Piccart et al[6] who compared the efficacy of cisplatin-paclitaxel or cisplatin-cyclophosphamide in EOC patients. The RR of 338 patients (23 patients in stage II and 315 in stage III-IV) treated with cisplatin-cyclophosphamide was 44.7%. The overall RR 79.2%, in the present study was much higher than those from the two studies. The difference might lie in the distinctive proportion of patients in early stage disease (stage I-II) of each study; more than half of the present patients were in the early stage (53.5%) compared to only 17.6% and 6.8% in the studies of Conte[4] and Piccart[6] respectively. One study in Thailand by Linasmita et al also reported their experience of platinum and cyclophosphamide in all stages EOC patients[17]. However, the authors could not compare the present result in terms of RR with their study because the authors did not include the RR in the study result.

The result of chemotherapy for ovarian cancer patients depends on many prognostic factors; one of the most important is the stage of disease. Hence, the authors studied the result of the treatment outcomes according to the stage of diseases as early (stageI-II) or advanced stages (stgae III-IV). The authors found that the RR, 5-year PFS, and 5-year SVR were significantly higher in patients with the early stage disease than the advanced stage (Table 3). The better SVR of patients with early stage disease in the present study was similar to the study of Linasmita et al who reported their experience of platinum and cyclophosphamide in 77 EOC patients in terms of progression-free interval and the 3-year SVR. The median progression-free interval of the whole group was 16 months with the 3-year SVR of 64%. Their 32 patients (41.6%) who were in early stage had significantly longer survival compared to 45 patients (58.4%) in advanced stage with the 3-year SVR of 84% and 45% respectively.

In advanced stage, the author's RR was 54.5%. The 5-year PFS and 5-year SVR were 28.9% and 39% respectively. The median PFS and the median survival were 10 months and 21 months respectively. The presented RR, PFS and survival duration were comparable to other trials using the combination of cisplatin or carboplatin plus cyclophosphamide in advanced stage ovarian cancer. The other studies reported the RRs ranging from 32-75%, median PFSs of 11-26 months, and median survivals of 22-35 months[4,7,8,18]. Gershenson et al in 1987[4] retrospectively studied the efficacy of cisplatin and cyclophosphamide in 50 advanced stage EOC patients. The authors reported the RR of 32%, median PFS and overall survival of approximately 20 and 27 months respectively. The lower RR in the study of Gershenson[3] was probably due to a slightly higher proportion of their patients being in stage IV compared to the present study, 11/50 patients (22%) versus 9/53 patients (17%). Lower dose of cisplatin at 50 mg/m^2 used in their study compared to the routine dose of 75 mg/m^2 used in the authors' institution might be the other explanation for this finding. Regarding the better PFS of Gershenson[3] compared to the present study, 20 months versus 10 months, the procedure of interval debulking, rating at 22%, in their study might account for this difference.

The result from the present study was very similar to the study of McGuire et al[7], who reported better efficacy of paclitaxel and cisplatin in comparison to cyclophosphamide and cisplatin in advanced stage EOC. Their patients who received cyclophosphamide and cisplatin had RR of 60%, median PFS and overall survival of approximately 13 months and 24 months respectively. These figures were comparable to the present results; RR 60.7%, PFS and survival of 10 months and 21 months respectively.

Thirapakawong et al[19] conducted a comparative study in Thailand between the efficacy of paraplatin® (carboplatin) and paclitaxel or paraplatin and cyclophosphamide in advanced stage EOC. From 48 patients who received paraplatin plus cyclophosphamide, the median PFS at 11 months was close to 10 months from the present study. However, their RR was higher than the authors' RR, 75% versus 54.5%; this difference might be due to the fact that more percentages of their patients had optimal surgery, 91.3% versus 43.4% (data not shown). This factor might also

Table 4. Result of platinum and cyclophosphamide chemotherapy treatment in epithelial ovarian cancer from our study in comparison with other studies

Authors (year)[Ref]	Stage	N (n)	Overall RR (%)	PFS (median) (mos)	Overall survival (median) (mos)
Conte (1986)[6]	IC-IV	125 (125)	48	12.5	22.3
Gershenson (1987)[4]	III-IV	50 (50)	32	19.8	27
Neijt (1987)[18]	III-IV	191 (191)	74	26	-
McGuire (1996)[7]	III-IV	202 (116)	60	13	24
Piccart (2000)[8]	IIB-IV	161 (126)	44.7	11.5	25.8
Thirapakawong(2000)[19]	III-IV	48 (36)	75	11	35.2*
Our study (2004)	IC-IV	114 (101)	78	80*	80.7*
	III-IV	53 (44)	54.5	10	21.1

Abbreviations: N, number of all patients in each category; n, number of patients who were evaluable for response in each category; PFS, progression-free survival; RR, response rate

* Progression-free survival or overall survival were presented as mean values because the median values were not reached

account for their better survival, which had not been reached, compared to the present median survival of 21 months. The result of treatment with platinum and cyclophosphamide in the present study and other studies are summarized and shown in Table 4.

Although the authors recognized the influence of many other prognostic factors to the result of treatment aside from the stage of disease, such as histologic cell type, grade of tumor, and result of surgery, the authors further studied only the factor of surgical outcome - due to the limited number of patients. From 103 patients whose result of surgery were documented, the patients who had optimal surgery had significantly better treatment outcome in all aspects of RR, PFS, and overall survival (Table 3). The present results were in accordance with other studies which demonstrated FIGO stage and result of surgery as important prognostic factors in the survival of EOC patients[6,18,19]. Neijt et al[18] reported that the residual tumor size of less than 1 cm was associated with improved survival independently from the other factors. Thirapakawong et al [19] also concluded that patients who experienced optimal surgery had a longer survival than those with suboptimal surgery, 38 months versus 18 months.

Based on the findings of many comparative studies showing superior efficacy of paclitaxel and platinum over platinum and cyclophosphamide in advanced stage EOC[7-9,19], together with the unsatisfactory result from platinum plus cyclophosphamide in the present study (Table 3) and others (Table 4), the replacement of chemotherapy regimen with platinum and paclitaxel is very appealing for this particular group of patients. However, in the low financial resource settings as in Thailand, the decision for the drug regimen must be derived from the careful clinical appraisal based on these academic data and other administrative factors. The authors hope that the findings in the present study would be the basic data in selecting the most appropriate treatment for the patients.

In conclusion, the overall 5-year SVR of EOC patients who received platinum and cyclophosphamide as adjuvant chemotherapy after primary surgery in the present study was 60.7%. The SVR of the patients who were in early stage or had optimal surgery were higher than the patients in advanced stage or suboptimal disease. The RR and PFS of these two groups of patients were also in the same direction as the survival rates.

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ประสิทธิภาพของยาเคมีบำบัดกลุ่ม platinum ร่วมกับ cyclophosphamide ในผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิว

ศิริวรรณ ตั้งจิตกมล, สุมนมาลย์ มนัสศิริวิทยา, สุรวุฒิ ลีฬหกร, เถาวลัย ถาวรามร, กมล ภัทราดุลย์, พาชื่น ศึกวัฒนา, เกรียงไกร สิทธิดิลกรัตน์

วัตถุประสงค์: *ศึกษาอัตราการตอบสนอง อัตราที่โรคไม่ดำเนินต่อที่ 5 ปี และ อัตราการอยู่รอดที่ 5 ปี ของผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิวที่ได้รับยาเคมีบำบัดกลุ่ม platinum ร่วมกับ cyclophosphamide หลังการรักษาด้วยการผ่าตัด*

วัสดุและวิธีการ: *ผู้วิจัยรวบรวมรายชื่อและข้อมูลทางคลินิกและทางพยาธิวิทยาจากเวชระเบียนของผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิวที่ได้รับการรักษาด้วยการผ่าตัดและได้รับยาเคมีบำบัดกลุ่ม platinum ร่วมกับ cyclophosphamide ที่วิทยาลัยแพทยศาสตร์กรุงเทพมหานครและวชิรพยาบาล ระหว่างเดือนมกราคม พ.ศ. 2538 ถึง เดือนธันวาคม พ.ศ. 2543*

ผลการศึกษา: *จากผู้ป่วยทั้งหมดที่ศึกษา จำนวน 114 ราย มีผู้ป่วยที่สามารถประเมินการตอบสนองได้ 101 ราย พบว่ามีการตอบสนองโดยรวม ร้อยละ 79.2 อัตราที่โรคไม่ดำเนินต่อและ อัตราการอยู่รอดของผู้ป่วยที่ 5 ปี ของผู้ป่วยทั้งหมดเท่ากับ ร้อยละ 60.3 (ค่าความเชื่อมั่นที่ร้อยละ 95 เท่ากับ ร้อยละ 50.5, 70.1) และ ร้อยละ 60.7 (ค่าความเชื่อมั่นที่ร้อยละ 95 เท่ากับ 50.9, 70.5) ตามลำดับ ผู้ป่วยในระยะแรกมีผลการตอบสนอง อัตราที่โรคไม่ดำเนินต่อ และอัตราการอยู่รอดของผู้ป่วยที่ 5 ปี ดีกว่าผู้ป่วยในระยะลุกลาม*

สรุป: *ผลการรักษาผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิวด้วยยาเคมีบำบัดกลุ่ม platinum ร่วมกับ cyclophosphamide หลังการผ่าตัดดีพอควร โดยผู้ป่วยในระยะแรกมีผลการรักษาดีกว่าผู้ป่วยในระยะลุกลาม*