Epithelial Ovarian Cancer Treated by Platinum or Platinum Analogue with Cyclophosphamide : Experience in Ramathibodi Hospital

VASANT LINASMITA, M.D., F.A.C.O.G.*, SARIKAPAN WILAILAK, M.D.*,
SOMKEART SRISUPUNDIT, M.D.*, SOMSAK TANGTRAKUL, M.D.*,
SUNCHAI BULLANGPOTI, M.D.*, NATHAPONG ISRANGURA, M.D.*

Abstract

This study presented the outcome of 92 EOC patients treated by platinum or platinum analogue with cyclophosphamide from January 1, 1993 to December 31, 1995. There were 77 evaluable patients. The follow-up ranged from 4 - 42 months (median 14 months). The over all 3-year survival was 64 per cent and the median progression-free interval was 16 months for the whole group. There was no significant difference in survival between patients who received cisplatin and those who received carboplatin (P=0.093). Patients who underwent optimal debulking surgery had significantly longer progression-free interval (P=0.001) than those who had suboptimal surgery. Fifty four per cent of patients with clear cell carcinoma died of the disease. Patients who received cisplatin had a drop out rate while on therapy more often (24% *vs* 5.3%) than that of carboplatin. Toxicities from chemotherapy were moderate but manageable.

In Thailand, ovarian cancer ranks sixth among the leading cancers found in women. It is the second most common gynecological cancer, behind cervical cancer. Epithelial ovarian cancer (EOC) is the most common histological type[1]. The platinum-based combination with cyclophosphamide has been the standard treatment for patients with EOC. It is not certain, however, how many cycles of chemotherapy should be administered postoperatively to obtain an optimal effect. At the beginning, our protocol called for up to 12 courses in patients with advanced diseases[2]. Until recently, we limited the number of cycles to six among patients with advanced EOC who achieve clinically complete remission and four among patients with early diseases. This report presents our latest experience with the platinum-based chemotherapy in treatment of patients with EOC.

* Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

Table 1. Treatment protocol of epithelial ovarian cancer in Ramathibodi Hospital.

Stage and grade	Treatment
IA, IB - grade 1, 2	Surgery only
IA, IB - grade 3 IC - all grades IA, IB, IC with clear cell carcinoma IIA, IIB, IIC - all grades with no residual disease	Surgery + PC* 4 cycles
IIA, IIB, IIC - all grades with residual disease III IV	Surgery + PC* 6 cycles

*PC = Cisplatin 75 mg/m^2 IV + Cyclophosphamide 600 mg/m^2 IV repeat cycle every 3 weeks or Carboplatin 300 mg/m^2 IV + Cyclophosphamide 600 mg/m^2 IV repeat cycle every 4 weeks.

MATERIAL AND METHOD

During January 1, 1993 and December 31, 1995, all previously untreated patients who had histologically confirmed ovarian adenocarcinoma were recruited for postoperative chemotherapy. Usually, surgery includes peritoneal cytology, complete abdominal exploration, total abdominal hysterectomy with bilateral salpingo-oophorectomy, infracolic omentectomy ± random biopsies and lymph node sampling. The dosage and schedules of administration of the chemotherapeutic agents consisted of cisplatin 75 mg/m^2/day IV over 60 min. for 1 day with vigorous hydration before and after therapy, and cyclophosphamide 600 mg/m^2/day IV over 15 min. for 1 day, repeat cycle every 3 weeks. Or carboplatin 300 mg/m^2/day IV over 60 min. for 1 day plus cyclophosphamide 600 mg/m^2/day IV over 15 min. for 1 day, repeat cycle every 4 weeks. Four cycles were given in patients with early diseases, and six cycles in patients with advanced diseases. The treatment protocol was shown in Table 1. Serum CA-125 levels were measured in all patients. Prior to chemotherapy, their performance status should be 0-2 (WHO)[3]. They must have adequate bone marrow and renal function. Dexamethasone, metroclopramide or ondansetron were used as the antiemetic agents.

The hematopoietic growth factors was not routinely used in patients with myelosuppression. The patients were assessed for toxicities and response by WHO criteria[3]. Survival analysis was determined by Kaplan and Meier's method, and using log rank test to assess their differences.

RESULTS

During the studied period, there were 92 patients with EOC (borderline tumors were not included) treated by chemotherapy after surgery. However, fifteen (15.2%) patients were lost to follow-up during chemotherapy, thus, there were 77 evaluable patients. As shown in Table 2, 32 cases were in early stage (FIGO stages I, II) and 45 cases were in advanced stage (FIGO stages III, IV). According to histologic type, mucinous cystadenocarcinoma was the most common, followed by serous, clear cell, and endometrioid carcinoma.

Table 2. Patients characteristics.

	No. patients
Entered	92
No. of evaluable patients	77
Age in years - median 49	
- range 24-72	
Initial FIGO staging	
I	25
II	7
III	36
IV	9
Histologic type	
Mucinous	26
Serous	19
Clear cell	13
Endometrioid	10
Adeno (unspecified)	6
Brenner	2
Adenosquamous	1
Chemotherapy	
Cisplatin + Cyclophosphamide	41
Carboplatin + Cyclophosphamide	36

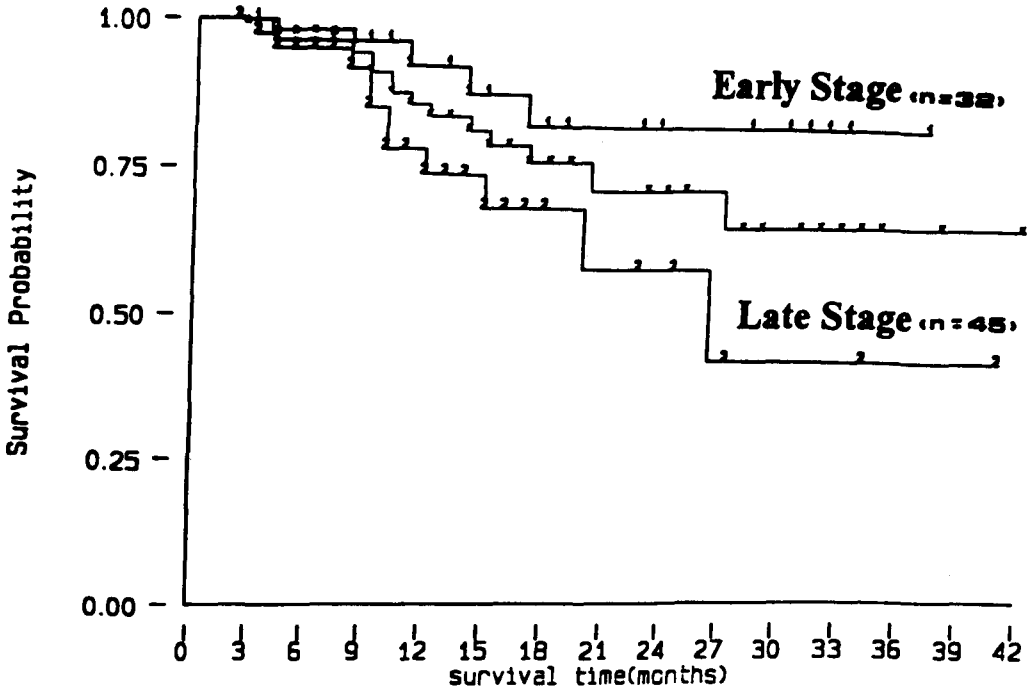

Fig. 1. Overall survival curves of all patients and according to stage.

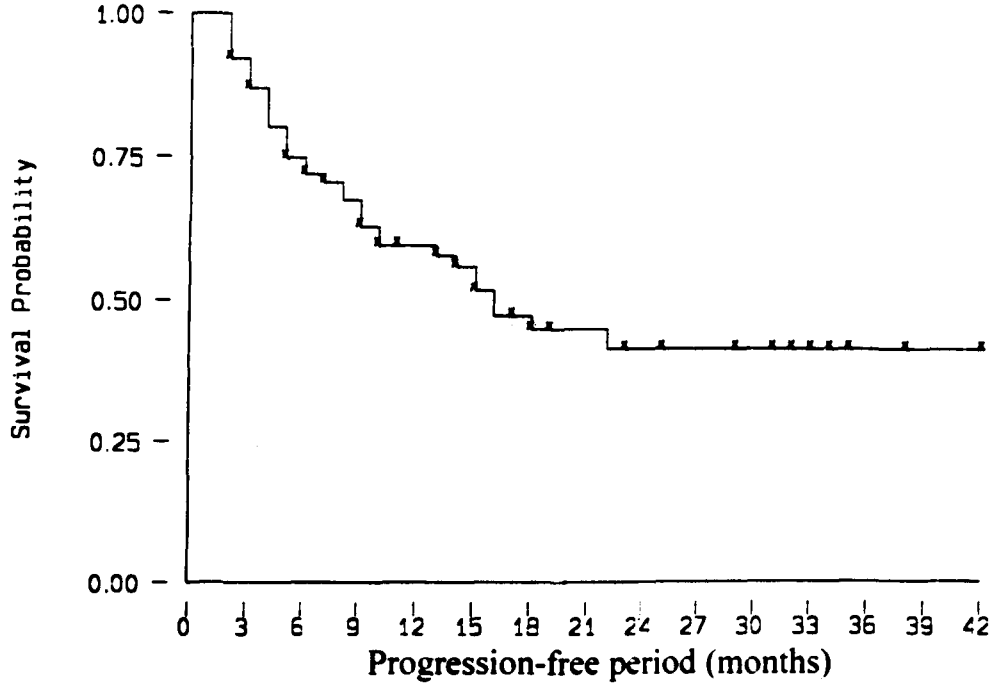

Fig. 2. Overall progression-free survival curve.

The follow-up among the patients ranged from 4 - 42 months (median 14 months). The over all survival of the 77 patients is shown in Fig.1 with the 3-year survival rate of 64 per cent. Patients in the early stage had a significantly longer survival than those in the advanced stage (P=0.030). The overall progression-free survival curve is shown in Fig. 2. The median progression-free interval was 16 months for the whole group. Fig. 3 shows survival of patients receiving cisplatin (CDDP) compared to those who received carboplatin. There was no significant difference in survival between the two groups and the same is true for the progression-free interval. In patients with advanced stage (n=45), the overall survival did not differ significantly among those who underwent optimal surgery (residual disease < 2.0 cm) and those who had suboptimal surgery (residual disease > 2.0 cm.) (P=0.532). However, the progression-free survival was significantly longer among patients who had optimal surgery (P= 0.001) (Fig. 4).

There were 13 patients with clear cell carcinoma. Of the 13, 6 were in the early stage and 7 were in advanced stage. Seven (53.8%) patients, 2 (33.3%) in the early stage and 5 (71.4%) in the advanced stage, died of the disease. All the remaining 6 patients except one are alive without disease.

Toxicities from chemotherapy are shown in Table 3. There was no death from chemotherapy in this study. The most common toxicity was nausea/vomiting followed by anemia and leucopenia.

Of the 15 patients who were lost to follow-up during treatment, 13 received cisplatin while 2 received carboplatin; 2 were in early stage and 13 were in advanced stage. All of the 15 patients were lost to follow-up within the first 3 cycles of chemotherapy. Concerning the address of the lost cases, 6 lived in Bangkok while the remaining 9 were out of Bangkok (5 central part, 3 north-eastern and 1 northern part).

DISCUSSION

This study presents the treatment outcome of EOC patients who received "standard" therapy, surgery followed by 4-6 courses of platinum-based combination chemotherapy (cisplatin or car-

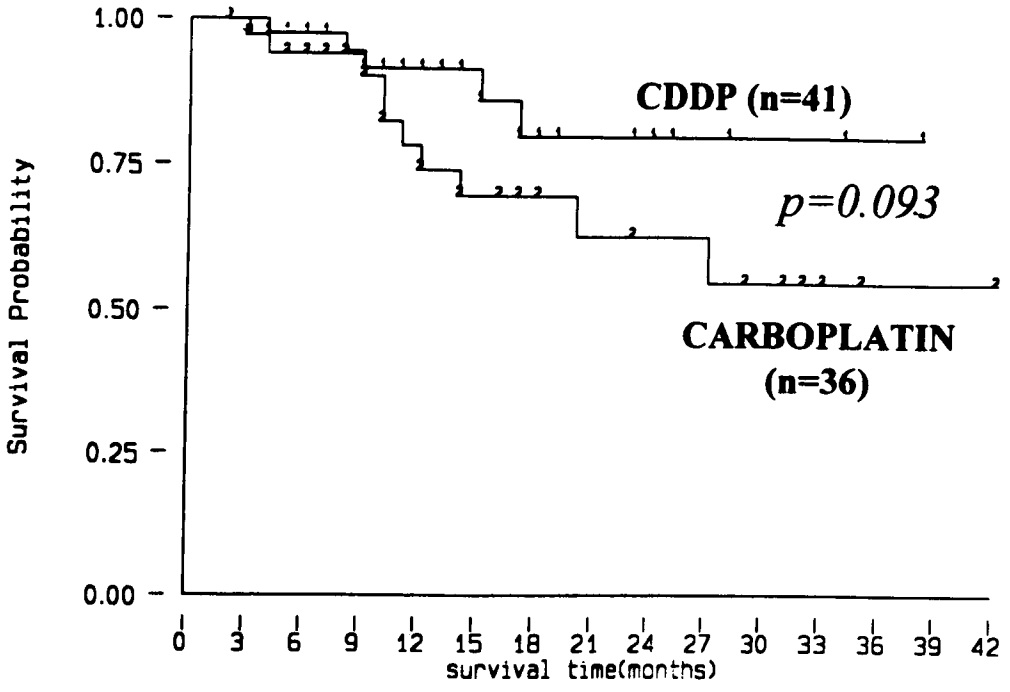

Fig. 3. The survival curve according to chemotherapy.

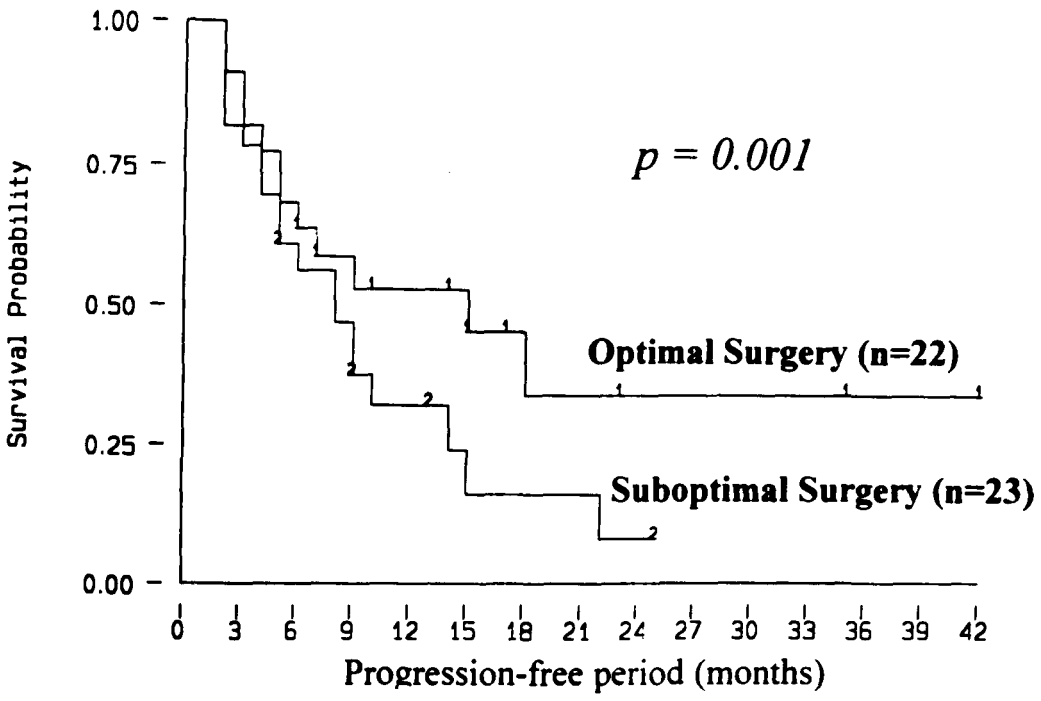

Fig. 4. The progression-free survival curve according to surgery in late stage.

Table 3. Major toxicities (worst ever) observed in patients (n = 77).

Toxicities	No. of patients with WHO toxicity grade				
	0	1	2	3	4
Anemia	29	25	17	6	-
Leucopenia	60	5	8	4	-
Thrombocytopenia	76	1	-	-	-
Nausea/Vomitting	10	51	15	1	-
Neurological	73	3	1	-	-
Renal	64	10	3	-	-

boplatin + cyclophosphamide), from a single institution. The volume of patients presented here is quite large with a good follow-up rate among those who completed the treatment. Most of our patients belonged to the low to middle income group. Cisplatin rather than carboplatin was usually prescribed to the patients of the lower income group.

Mucinous cystadenocarcinoma was the most commnon histological type found in this study, the same was true in the study of ovarian cancer in Thailand reported by The International Agency for Research on Cancer (IARC)[1]. This finding was different from studies of western countries where serous tumors was the most common type among the EOC[4,5]. Borderline tumors were not included in this study because they are a special category that represent an unusual spectrum of ovarian disease. Long-term evaluation and follow-up will be required to better elucidate its natural biology[6].

Our results of treatment i.e. the overall 3-year survival rate of 64 per cent and the mean progression-free interval of 16 months for the whole group were comparable to many studies previously reported[7-9]. In our previous study, at

the time when up to 12 courses were given and the dose of platinum and cyclophosphamide were lower, we achieved the over all 3-year survival of 41 per cent[2]. In this study, we had a very good result with patients in the early stage (FIGO stages I, II), the 3-year survival was 84 per cent. For patients in the late stage (FIGO stages III, IV), the 3-year survival was 45 per cent (see Fig. 1). We found no significant difference in survival between patients who received cisplatin and those who received carboplatin which is in accordance with previous reports[10,11]. However, patients who received cisplatin were more likely to delay chemotherapy between courses because of rising serum BUN/creatinine levels, especially in the latter part of treatment, besides vigorous hydration prior to each course of chemotherapy. Moreover, patients who received cisplatin, at the beginning of treatment, had a drop out rate more often (24% *vs* 5.3%) than that of carboplatin. One of the reasons was the severe nausea/vomiting associated with cisplatin.

In this study, patients who underwent optimal debulking surgery had slightly better survival than those who had suboptimal surgery, but the difference was not statistically significant (P=0.532). However, the progression-free survival was significantly longer in patients with optimal surgery which was in accordance with previous reports[12,13]. Most of our patients who were in the advanced stage and later found to have clinically complete response to chemotherapy rarely accepted to undergo second-look laparotomy. Only 3 out of 16 patients did agree to have the procedure.

There are reports which showed that patients with clear cell carcinoma had a poor prognosis[7,14]. In this study 54 per cent of patients, 33 per cent in the early stage and 71 per cent in the late stage had died of the disease at the time of this report.

The toxicities from chemotherapy encountered in this study were moderate but manageable. Nausea/vomiting and myelosuppression were among the most common findings. We chose to delay the chemotherapy in most cases of myelosupression, which is often seen in patients receiving carboplatin, instead of giving the hematopoietic growth factors to keep the cycle on schedule.

(Received for publication on August 7, 1997)

REFERENCES

1. Vatanasapt V, Martin N, Sriplung H, et al. Cancer in Thailand 1988-1991. IARC Technical Report No.166, International Agency for Research on Cancer, 1973.
2. Linasmita V, Sakornratanakul P, Ittisiriwait N, et al. Survival in patients treated with platinum-based combination with cyclophosphamide for advanced ovarian adenocarcinoma: Ramathibodi experience. Mahidol University Annual Research Abtracts. 1994: 33.
3. WHO Handbook for reporting results of cancer treatment. WHO Offset Publication No. 48, Geneva: World Health Organization, 1979.
4. Cannister SA. Cancer of the ovary. N Engl J Med 1993; 329: 1550-9.
5. Ozols RF, Rubin SC, Thomas G, Robboy S. Epithelial ovarian cancer. In: Hoskins WJ, Perez CA, Young RE, eds. Principle and Practice of Gynecologic Oncology, 2nd, ed.Philadelphia, Lippincott - Raven Publisher, 1997: 924-5.
6. Link CL, Jr., Reed E, Sarosy G, Kahn EC. Borderline ovarian tumors. Am J Med 1996; 101: 217-25.
7. Pettersson F. Annual Report on the results of Treatment in Gynecological Cancer. International Federation of Gynecology and Obstetrics. Vol. 22, Stockholm, Sweden 1994.
8. Young RC, Walton LA, Ellenberg SS, et al. Adjuvant therapy in stage I and II epithelial ovarian cancer. Results of two prospective randomized trials. N Engl J Med 1990; 322: 1021-7.
9. Albert DS, Green S, Hannigan EV, et al. Improved therapeutic index of carboplatin plus cyclophosphamide - versus cisplatin plus cyclophosphamide : final report of the Southwest Oncology Group of a phase III randomized trial in stages III and IV ovarian cancer. J Clin Oncol 1992; 10: 706-17.
10. Swenerton KD, Pater JL. Carboplatin in the treatment of carcinoma of the ovary. The National Cancer Institute of Canada experience. Sem Oncol 1992; 19: 144-9.
11. Aabo K, Adams M, Albert DS, et al. Chemo-

therapy in advanced ovarian cancer: a overview of randomized clinical trials. BMJ 1991; 303: 884-93
12. Griffith CT, Parker LM, Fuller AF Jr. Role of cytoreductive surgical treatment in the management of advanced ovarian cancer. Cancer Treat Rep 1979; 63: 235-40.
13. Wharton JT, Edwards CI, Rutledge FN. Long-term survival after chemotherapy for advanced epithelial ovarian carcinoma. Am J Obstet Gynecol 1984; 148: 997-1005.
14. Omura GA, Brady MF, Homesley HD, et al. Long-term follow-up and prognostic factors analysis in advanced ovarian carcinoma. The Gynecologic Oncology Group experience. J Clin Oncol 1991; 9: 1138-50.

การรักษาผู้ป่วยมะเร็งรังไข่ชนิด Epithelial Carcinoma โดยยาเคมีบำบัดชนิด Platinum หรือ Platinum Analogue ร่วมกับ Cyclophosphamide : ประสบการณ์ของโรงพยาบาลรามาธิบดี

วสันต์ ลีนะสมิต, พ.บ., F.A.C.O.G., สฤกพรรณ วิไลลักษณ์, พ.บ.*, สมเกียรติ ศรีสุพรรณดิฐ, พ.บ.*, สมศักดิ์ ตั้งตระกูล, พ.บ.*, สัญชัย บัลลังโพธิ์, พ.บ.*, ณัฐพงศ์ อิศรางกูร ณ อยุธยา, พ.บ.**

ได้รายงานผลการรักษาผู้ป่วยมะเร็งรังไข่ชนิด Epithelial carcinoma จำนวน 92 รายที่ได้ยาเคมีบำบัดชนิด platinum หรือ platinum analogue ร่วมกับ cyclophosphamide หลังผ่าตัด ในระหว่างเดือนมกราคม พ.ศ. 2536 ถึง ธันวาคม พ.ศ. 2538 ขนาดของยา cisplatin 75 mg/m^2/d IV, D1 + cyclophosphamide 600 mg/m^2/d IV, D1 ให้ทุกๆ 3 สัปดาห์ หรือ carboplatin 300 mg/m^2/d IV, D1 + cyclophosphamide 600 mg/m^2/d IV, D1 ให้ทุกๆ 4 สัปดาห์ โดยให้ 4 cycles ในผู้ป่วยที่โรคอยู่ในระยะต้น และ 6 cycles ในผู้ป่วยที่โรคอยู่ในระยะลุกลาม มีผู้ป่วย 15 รายที่ขาดการติดต่อในระหว่างได้ยาเคมีบำบัดจึงทำให้เหลือผู้ป่วย 77 รายที่สามารถประเมินผลการรักษาได้ ระยะเวลาติดตามผู้ป่วย 4–42 เดือน (เฉลี่ย 14 เดือน) พบอัตราการอยู่รอด (overall survival) 3 ปี = 64% และ median progression–free interval = 16 เดือน ไม่พบมีความแตกต่างกันในอัตราการอยู่รอดของผู้ป่วยที่ได้รับยาเคมีบำบัด cisplatin กับผู้ป่วยที่ได้รับยา carboplatin (P=0.093). ผู้ป่วยที่ได้รับการผ่าตัดจนเหลือ residual disease < 2 ซม. มี progression–free interval นานกว่าผู้ป่วยที่ได้รับการผ่าตัดที่เหลือ residual disease > 2 ซม. (P=0.001). 54% ของผู้ป่วยมะเร็งรังไข่ชนิด clear cell carcinoma เสียชีวิต ผู้ป่วยที่ได้ยาเคมีบำบัด cisplatin มีอัตราการขาดการติดต่อขณะได้ยาสูงกว่า (24% *vs* 5.3%) ผู้ป่วยที่ได้ยา carboplatin. ผลข้างเคียงจากยาเคมีบำบัดอยู่ในระดับปานกลาง

* หน่วยมะเร็งวิทยานรีเวช, ภาควิชาสูติศาสตร์–นรีเวชวิทยา, คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี, มหาวิทยาลัยมหิดล, กรุงเทพฯ 10400