

A Comparative Study on Hematological Effects of Carboplatin plus Cyclophosphamide and Carboplatin plus Paclitaxel Chemotherapy for the First Line Treatment of Epithelial Ovarian Cancer

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Objective: To compare the hematological effects of carboplatin plus cyclophosphamide, and carboplatin plus paclitaxel chemotherapy for first line treatment of epithelial ovarian cancer (EOC).

Material and Method: A retrospective study was conducted between January 2003 and May 2006 on 29 patients who received 145 cycles of carboplatin, area under the curve (AUC) 6 plus cyclophosphamide 600 mg/mm² (CC) intravenous and on 11 patients who received 65 cycles of carboplatin AUC 5 plus paclitaxel 175 mg/mm² (CP) intravenous chemotherapy for the first line treatment of epithelial ovarian cancer. They had no history of hematologic disease and complete blood count (CBC), renal function and liver function tests were normal.

Results: Both groups were similar regarding age, body mass index, performance status and stage of cancer. Hematological effects were found in 61 of 145 cycles (42.1%) in CC group and 33 of 65 cycles (50.8%) in CP group ($p = 0.05$). Twenty patients received all 6 cycles of chemotherapy in the CC group and 10 patients in the CP group. Fifteen of 20 patients (75%) and 8 of 10 patients (80%) had hematologic effect of at least one cycle found in the CC and the CP groups, respectively ($p = 0.05$). There were no treatment-related deaths in both arms.

Conclusion: Hematological effects did not differ in carboplatin AUC 6 plus cyclophosphamide 600 mg/mm² regimen and carboplatin AUC 5 plus paclitaxel 175 mg/mm² regimen and both regimens were accepted adverse effect in the first line treatment of EOC.

Keywords: Hematological effect, Carboplatin, Cyclophosphamide, Paclitaxel

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Chemotherapy is the main adjuvant treatment of epithelial ovarian cancer (EOC). The surgery is considered as an adequate treatment in low grade, tumor limited, and ovary. The role of chemotherapy, after surgery when the tumor is beyond the ovary is to increase survival rate. Currently, the first line chemotherapy in EOC is Platinum or Platinum combination^(1,2). In recent years, cisplatin has been a standard combination treatment and then replaced by carboplatin combination⁽³⁾. Carboplatin is an analog of cisplatin. It contains platinum atom surrounded in a plane by two ammonia groups

and two other ligands in cis position. This difference makes carboplatin have less nephrotoxicity, neurotoxicity, ototoxicity and emetogenesis. The exact mechanism of action of carboplatin is unknown but is believed to inhibit DNA synthesis by forming interstrand and intrastrand cross-linking of DNA molecules. Carboplatin is a cell cycle-phase nonspecific and is a radiation-sensitizing agent.

Cyclophosphamide is used for the treatment of several types of cancer in combination with other drugs. Many studies⁽⁴⁻⁵⁾ used cyclophosphamide combination with carboplatin. Cyclophosphamide is first converted by the liver to acrolein and phosphoramidate. Acrolein and phosphoramidate are active compounds.

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They slow the growth of cancer cells by interfering with the action of deoxyribonucleic acid within the cancerous cells. It is, therefore, referred to as cytotoxic drug. Cyclophosphamide also suppresses the immune system and is referred to as immunosuppressive.

Paclitaxel is a natural product with antitumor-activity. Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimmers and stabilizes microtubules by preventing depolarization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for the vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or bundles of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis. The Gynecologic Oncology Group (GOG) performed a prospective randomized trial of cisplatin 75 mg/m² plus cyclophosphamide 750 mg/m² versus cisplatin 75 mg/m² plus paclitaxel 135 mg/m² in 385 patients with suboptimal stage III and IV ovarian cancer⁽⁶⁾. The paclitaxel plus platinum combination improved median progressive-free survival 6 months. Based on this trial, paclitaxel plus cisplatin became the new standard regimen. The current clinical trial was performed in the GOG for patients with optimal stage III ovarian cancer⁽⁷⁾. The standard regimen consists of paclitaxel plus cisplatin as a previously described, which will be compared to regimen of carboplatin AUC 7.5 plus paclitaxel 175 mg/m². In the present study, there was a slight increase in time of progression and there was significantly less hematological toxicity. In another study, paclitaxel was safe and effective in combination with carboplatin for 6 cycles in patients with EOC⁽⁸⁾.

Pranangkla Hospital uses carboplatin combination for the first line treatment of EOC. The regimens are carboplatin AUC 6 plus cyclophosphamide 600 mg/m² and carboplatin AUC 5 plus paclitaxel 175 mg/m² intravenously. Not to be complacent on the efficacy of carboplatin combination regimens, the complications were considered. The important and usual complications were hematologic toxicity. Accordingly, this present study was undertaken to compare the hematologic toxicity between both regimens.

Material and Method

The retrospective study was conducted after the approval of the Ethics Committee of Pranangkla Hospital from January 2003 to May 2006. Forty (40) patients with EOC were recruited and scheduled to receive carboplatin AUC 6 plus cyclophosphamide 600 mg/m² intravenous and carboplatin AUC 5 plus

paclitaxel 175 mg/m² intravenous chemotherapy in Pranangkla Hospital. After surgery, the patients had never received chemotherapy and radiation therapy and they had no history of hematologic disease. Blood tests for bone marrow, renal and liver function were normal. They did not have any contraindication to carboplatin, cyclophosphamide and paclitaxel.

Carboplatin was administered via intravenous (IV) hour followed by cyclophosphamide (IV) hour for carboplatin plus cyclophosphamide regimen. Paclitaxel was administered (IV) 3 hours followed by carboplatin (IV) hour for carboplatin plus paclitaxel regimen. Chemotherapy was given every 28 days of 1 to 6 courses as some patients were changed to the other regimens. CBC was tested on the 7th and 28th days. Abnormal CBC profiles were recorded and rescued before the next course was given. Defined Abnormal CBC profiles by hematocrit (Hct) was less than 30%, white blood cells (WBC) count was less than 3,000 cells/mm² and platelets (Plt) count was less than 100,000 cells/mm².

Patient characteristics including age, height, body weight, body mass index, performance status defined by the Eastern Cooperative Oncology Group (ECOG)⁽⁹⁾, stage of disease and cell types were recorded. Data analysis comparing the hematological effects between the CC group and the CP group was carried out by using percentage. The characteristics and features of mean values between groups were performed using the t-test, the percentage of hematological effect was performed using the Chi-square test or Fishers' Exact test where appropriated. The P-value of less than 0.05 was judged statistically significant.

Results

Between January 2003 and May 2006, forty patients with EOC who passed the criteria for selection and met all other eligibility criteria, were identified. Twenty nine patients received (CC) and eleven patients received (CP). The mean age of CC and CP patients were 50.3 ± 13.4 years (range 20-74 years), and 49.2 ± 12.7 years (range 29-65 years), respectively. In the CC and CP groups, the mean body mass index (BMI) were 22.8, 23.5, the zero performance status (PS) were 19 patients (65.5%), and nine patients (81.8%), the number of early stage (stage I-II) were 15 patients (51.7%), and five patients (45.5%), and the most likely cell types were serous, mucinous, and endometrioid cystadenocarcinoma as shown in Table 1.

Twenty-nine patients in the CC group received 145 chemotherapeutic cycles (5.0 cycles-patient) and

Table 1. Characteristics and features

Characteristics	CC (n = 29)	%	CP (n = 11)	%	p-value
Age (years)					
Mean \pm SD	50.3 \pm 13.4		49.2 \pm 12.7		0.8
Range	20-74		29-65		
BMI					
Mean	22.8		23.5		0.6
Range	15.1-26.3		19.5-31.6		
Stage					
Early	15	51.7	5	45.5	0.7
Advance	14	48.3	6	54.5	
PS					
0	19	65.5	9	81.8	
1	3	10.3	2	18.2	
2	7	24.1	0	0.0	
Cell type					
Serous CA	6	20.7	3	27.3	
Mucinous	7	24.1	3	27.3	
Endometrioid CA	8	27.6	3	27.3	
Clear cell CA	6	20.7	1	9.1	
Undifferentiated CA	2	6.9	1	9.1	

Table 2. Hematologic effects of each cycles between CC and CP chemotherapy in EOC

Chemotherapy	CC (n = 145)	%	CP (n = 65)	%
No effect	84	57.9	32	49.2
Effect	61	42.1	33	50.8
Hct (< 30%)	40	27.6	19	29.2
WBC count (< 3,000 cells/mm ³)	7	4.8	8	12.3
PLT count (< 100,000 cells/mm ³)	1	0.7	0	0.0
Hct and WBC count	11	7.6	6	9.2
Hct and PLT count	0	0.0	0	0.0
WBC and PLT count	0	0.0	0	0.0
Hct, WBC and PLT count	2	1.4	0	0.0

² = 1.374, p = 0.24

11 patients in the CP group received 65 chemotherapeutic cycles (5.9 cycles-patient). The hematological effects in the CC group was 61 of 145 cycles (42.1%) and 33 of 65 cycles (50.8%), which was not significantly different (p = 0.05). The most common bone marrow suppression was red blood cells, white blood cells, and platelets, respectively as shown in Table 2.

Twenty patients completed the 6 cycles of chemotherapy in the CC group and 10 patients in the CP group. There were hematological effects on 15 of 20 patients (75%) of the CC group and 8 of 10 patients (80%) in the CP group. This was not significantly different (p = 0.05). The hematological effects based on the number of cycles are shown in Table 3.

Discussion

The results of the present study show similar clinical characteristics in the CC and CP groups. The hematological effects were 61 of 145 cycles (42.1%) in the CC group and 33 of 65 cycles (50.8%) in the CP group. They were less in the CC group but were not significantly different, however, the mean cycles that received chemotherapy was 5.0 and 5.9 in CC and CP groups, respectively. The patients, who received 6 chemotherapeutic cycles incompletely because of a change to other regimens, had no serious complications or mortality from chemotherapy. Bone marrow suppression was most common in red blood cells, white blood cells, and platelets, respectively. A randomized

Table 3. Hematological effects in the 6 cycles-patients

Number cycles of effects	CC patients		%	CP patients		%
No effect	5		25.0	2		20.0
Effect	15	75.0		8	80.0	
1	3		15.0	0		0.0
2	2		10.0	1		10.0
3	3		15.0	2		20.0
4	3		15.0	4		40.0
5	4		20.0	0		0.0
6	0		0.0	1		10.0
Total	20	100.0		10	100.0	

² = 0.093, p = 0.76

study of carboplatin AUC 6 intravenous with paclitaxel 175 mg/mm² intravenous was given as first line treatment in advanced EOC. Grade 1-4 hematological toxicity evaluated by percentage from 251 cycles in 45 patients has found that anemia, leucopenia, and thrombocytopenia were 76%, 68% and 28%, respectively⁽¹⁰⁾. However, the values of optimal AUC depend on cytotoxic drugs combined with carboplatin. Because cyclophosphamide has less toxicity than paclitaxel, carboplatin was given AUC 6 and 5 in CC and CP regimens, respectively.

Fifteen of 20 patients (75%) in the CC group and 8 of 10 patients (80%) in the CP group, who received a complete 6 cycles, had hematological effects of at least 1 cycle. The hematological effects were less in the CC arm group but were not significantly different. In the trial study on paclitaxel 200 mg/mm² IV, carboplatin AUC 6 IV and oral etoposide 50 mg, day 1-10 administered on 6 cycles of treatment, 270 cycles on 52 patients, it was found that anemia, leucopenia, and thrombocytopenia were in 38(75%), 22(42%) and 15(29%) patients, respectively⁽¹¹⁾. The hematological toxicity has the adverse effect of the delay in treatment of EOC⁽¹⁰⁾. Myelosuppression of carboplatin is more closely correlated with AUC of ultrafiltrable plasma concentration versus time when a patient is exposed, than it is with the administered dose. Similar relationships have been shown between AUC and antitumour effect⁽¹²⁾. The present study shows, there were not significantly different percentage of hematological toxicity and there were no treatment-related deaths in either groups. However, this study was limited in sample size.

In conclusion, hematological effects did not differ in carboplatin AUC 6 plus cyclophosphamide 600 mg/mm² regimen and carboplatin AUC 5 plus paclitaxel 175 mg/mm² regimen. However, both regimens

were accepted for their adverse effect for treatment of EOC.

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เปรียบเทียบผลกระทบท่อเม็ดเลือดในการใช้เคมีบำบัด คาร์โบพลาติน ร่วมกับ ไฮโดรฟอสฟาไมด์ และ คาร์โบพลาติน ร่วมกับแพคลิแทกเซล รักษาผู้ป่วยมะเร็งรังไข่

พิทยา วาพัฒนาวงศ์

วัตถุประสงค์: เพื่อศึกษาเปรียบเทียบผลกระทบท่อเม็ดเลือดในการใช้ยาเคมีบำบัดระหว่าง คาร์โบพลาติน ร่วมกับ ไฮโดรฟอสฟาไมด์ และ คาร์โบพลาติน ร่วมกับแพคลิแทกเซล รักษาผู้ป่วยมะเร็งรังไข่

วัสดุและวิธีการ: การศึกษาย้อนหลังระหว่าง มกราคม พ.ศ. 2546 ถึงพฤษภาคม พ.ศ. 2549 ผู้ป่วย 29 คนได้รับ เคมีบำบัด คาร์โบพลาติน AUC 6 ร่วมกับ ไฮโดรฟอสฟาไมด์ 600 มก/ตารางเมตร ฉีดเข้าเส้นเลือดดำ จำนวน 145 ครั้ง และผู้ป่วย 11 คน ได้รับ คาร์โบพลาติน AUC 5 ร่วมกับ แพคลิแทกเซล 175 มก/ตารางเมตร ฉีดเข้าเส้นเลือดดำ จำนวน 65 ครั้ง ในการรักษาผู้ป่วยมะเร็งรังไข่ ภายหลังผ่าตัดผู้ป่วยไม่เคยได้รับการรักษาด้วยยาเคมีบำบัด หรือรังสีรักษามาก่อน ผู้ป่วยไม่มีประวัติโรคเลือด การตรวจจำนวนเม็ดเลือดแดง เม็ดเลือดขาว และเกล็ดเลือดปกติ การตรวจการทำงานของไตและตับอยู่ในเกณฑ์ปกติ

ผลการศึกษา: ผู้ป่วยทั้งสองกลุ่มมีค่าเฉลี่ย อายุ ดัชนีมวลกาย สมรรถภาพร่างกาย และระยะของมะเร็งรังไข่ ใกล้เคียงกัน ผู้ป่วย 29 คน ได้รับยาเคมีบำบัด คาร์โบพลาติน ร่วมกับไฮโดรฟอสฟาไมด์ จำนวน 145 ครั้ง มีผลกระทบท่อระบบเม็ดเลือด ร้อยละ 42.1 ผู้ป่วย 11 คนได้รับยาเคมีบำบัด คาร์โบพลาติน ร่วมกับแพคลิแทกเซล จำนวน 65 ครั้ง มีผลต่อระบบเม็ดเลือด ร้อยละ 50.8 (ค่าที่ 0.05) ผู้ป่วยที่ได้รับเคมีบำบัดครบ 6 ครั้ง ในกลุ่มที่ได้รับ คาร์โบพลาติน ร่วมกับ ไฮโดรฟอสฟาไมด์ และ คาร์โบพลาตินร่วมกับ แพคลิแทกเซล จำนวน 20 คน และ 10 คน มีผลกระทบท่อระบบเม็ดเลือด อย่างน้อยหนึ่งครั้ง คิดเป็นร้อยละ 75 และ 80 ตามลำดับ (ค่าที่ 0.05) ไม่มีผู้ป่วยเสียชีวิตจากผลข้างเคียงของยาเคมีบำบัด

สรุป: ผู้ป่วยที่ได้รับเคมีบำบัด คาร์โบพลาติน AUC 6 ร่วมกับ ไฮโดรฟอสฟาไมด์ 600 มก/ตารางเมตร ฉีดเข้าเส้นเลือดดำ มีผลกระทบท่อระบบเม็ดเลือด ไม่มีความแตกต่างกับผู้ป่วยที่ได้รับ คาร์โบพลาติน AUC 5 ร่วมกับ แพคลิแทกเซล 175 มก/ตารางเมตร และทั้งสองกลุ่มมีฤทธิ์ข้างเคียงยอมรับได้ในการรักษามะเร็งรังไข่