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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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 depolymerization. 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/m^2 plus cyclophosphamide 750 mg/m^2 versus cisplatin 75 mg/m^2 plus paclitaxel 135 mg/m^2 in 385 patients with suboptimal stage III and IV ovarian cancer. The paclitaxel plus platinum combination improved median progression-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. 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/m^2. 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.

Pranangklao Hospital uses carboplatin combination for the first line treatment of EOC. The regimens are carboplatin AUC 6 plus cyclophosphamide 600 mg/m^2 and carboplatin AUC 5 plus paclitaxel 175 mg/m^2 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 Pranangklao 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/m^2 intravenous and carboplatin AUC 5 plus paclitaxel 175 mg/m^2 intravenous chemotherapy in Pranangklao 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/mm^2 and platelets (Plt) count was less than 100,000 cells/mm^2.

Patient characteristics including age, height, body weight, body mass index, performance status defined by the Eastern Cooperative Oncology Group (ECOG), 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 29-65 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
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
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 mg²/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). 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 both 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.

### References


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เปรียบเทียบผลกระทบต่อเม็ดเลือดในการใช้เคมีบำบัดคาร์โบพลาตินร่วมกับไซโคลฟอสฟาไมด์ และคาร์โบพลาตินร่วมกับแพคลิแทกเซล รักษาผู้ป่วยมะเร็งรังไข่

พิทักษ์ วัฒนาวงศ์

วัตถุประสงค์: เพื่อศึกษาและเปรียบเทียบผลกระทบต่อเม็ดเลือดจากการใช้ยาเคมีบำบัดระหว่าง คาร์โบพลาติน ร่วมกับไซโคลฟอสฟาไมด์ และ คาร์โบพลาตินร่วมกับแพคลิแทกเซล รักษาผู้ป่วยมะเร็งรังไข่

วัสดุและวิธีการ: การศึกษานี้มีผู้ป่วยทั้งหมด 29 คน ที่ได้รับการรักษาด้วยคาร์โบพลาติน AUC 5 ร่วมกับไซโคลฟอสฟาไมด์ 600 มก./ตารางเมตร ฉีดเข้าเส้นเลือดดำ จำนวน 145 ครั้ง และผู้ป่วยทั้งหมด 11 คน ที่ได้รับการรักษาด้วยคาร์โบพลาติน AUC 5 ร่วมกับแพคลิแทกเซล 175 มก./ตารางเมตร ฉีดเข้าเส้นเลือดดำ จำนวน 65 ครั้ง ในการรักษาผู้ป่วยมะเร็งรังไข่ ภายหลังผ่าตัดผู้ป่วยได้รับการรักษาด้วยยาเคมีบำบัดและรักษาภายนอกด้วย รังสีรังสีรักษาภายนอก ผู้ป่วยรักษาและข้อมูลการใช้ยาเคมีบำบัดรวมถึงผลข้างเคียงที่เกี่ยวข้อง

ผลการศึกษา: ผู้ป่วยทั้งหมดมีเม็ดเลือดขาวต่ำหรือลดลง ซึ่งมีแนวโน้มต่ำกว่าร้อยละ 42.1 ผู้ป่วย 11 คนได้รับการรักษาด้วยคาร์โบพลาติน AUC 5 ร่วมกับไซโคลฟอสฟาไมด์ จำนวน 65 ครั้ง มีผลข้างเคียงระดับมีผลต่ำเลือด ระดับ 50.8 (ค่าที่ 0.05) ผู้ป่วยทั้งหมดมีผลข้างเคียงระดับ 6 ครั้ง ระดับ 50.8 (ค่าที่ 0.05) ผู้ป่วยทั้งหมดมีผลข้างเคียงระดับ 6 ครั้ง ในผู้ป่วยที่ได้รับการรักษาด้วยคาร์โบพลาติน ร่วมกับไซโคลฟอสฟาไมด์ และ คาร์โบพลาตินร่วมกับแพคลิแทกเซล จำนวน 20 คนและ 10 คน มีผลข้างเคียงระดับมีผลต่ำเลือดอย่างน้อยหนึ่งครั้ง คิดเป็นร้อยละ 75 และ 80 ตามลำดับ (ค่าที่ 0.05) ไม่มีผู้ป่วยยืนยันอาการหลุดคิวของยาเคมีบำบัด

สรุป: ผู้ป่วยที่ได้รับการรักษาด้วยคาร์โบพลาติน AUC 5 ร่วมกับไซโคลฟอสฟาไมด์ 600 มก./ตารางเมตร ซึ่งต่ำกว่าการใช้เม็ดเลือด ไม่มีผลต่ำต่ำกว่าร้อยละ 42.1 ผู้ป่วยที่ได้รับการรักษาด้วยคาร์โบพลาติน AUC 5 ร่วมกับแพคลิแทกเซล 175 มก./ตารางเมตร และที่มีผลต่ำต่ำกว่าร้อยละ 42.1 ผู้ป่วยได้รับการรักษาด้วยเคมีบำบัดและรักษาภายนอกด้วย รังสีรังสีรักษาภายนอก