Benefit of Electrocardiography during Front-Line Combination Paclitaxel and Carboplatin Chemotherapy for Epithelial Ovarian Cancer

Chumnan Kietpeerakool MD*,
Jitima Tiyayon MD*, Prapaporn Suprasert MD*,
Rungsrit Kanjanavanit MD**, Jatupol Srisomboon MD*

** Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Chiang Mai*
*** Department of Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai*

Objective: *To evaluate the patterns of electrocardiography (ECG), cardiac risk factors and its clinical consequence in women with epithelial ovarian cancer (EOC) who received paclitaxel and carboplatin (PC) as front line chemotherapy*
Material and Method: *The medical records and electrocardiographic data of women with EOC who received paclitaxel (175 mg/m^2) and carboplatin (AUC = 5) every 3 weeks at Chiang Mai University Hospital between January 2000 and December 2004 were reviewed for cardiac risk factors and clinical consequence.*
Results: *Among 79 women receiving PC for EOC, 43 (54.4%) had cardiac risk factors. Seventy (88.6%) women had normal ECG, the remaining nine had sinus tachycardia (5), bundle branch block (2), mild T inversion (1), and Wolff-Parkinson-White syndrome (1) before the first course of chemotherapy. Among 70 women with normal initial ECG, 8(11.4%) had sinus tachycardia, one(1.4%) had early depolarization, two (2.9%) had sinus bradycardia and three (4.3%) had sinus arrhythmia in subsequent ECG. All these cardiac disturbances were asymptomatic and needed no intervention, indicating grade 1 toxicity. The odds ratio of developing abnormal ECG in women with cardiac risk factor was 1.24(95%CI = 0.33 to 4.64, p = 0.77). Among nine patients with abnormal ECG before the first course of PC, six (66.7%) had subsequent abnormal ECG but all were asymptomatic and no worsening of abnormal ECG pattern was noted.*
Conclusion: *Although paclitaxel and carboplatin chemotherapy could induce abnormal ECG in women with either normal or abnormal prior ECG, its consequence was of no clinical significance. Therefore, the benefit of ECG before each treatment course was theoretically limited.*

Keywords: *Cardiotoxicity, Electrocardiography, Benefit, Paclitaxel, Epithelial ovarian cancer*

J Med Assoc Thai 2006; 89 (11): 1805-10
Full text. e-Journal: *http://www.medassocthai.org/journal*

Approximately 80-90% of patients with epithelial ovarian cancer require adjuvant chemotherapy after tumor debunking[1]. One of the main reasons is the advanced stage of disease at presentation that cannot be eradicated completely by surgery alone[1,2]. Chemotherapy for epithelial ovarian cancer has progressed over the past two decades, moving from the use of alkylating agents to the current standard regimen consisting of paclitaxel and carboplatin[2,3].

Paclitaxel is a taxane agent that has a unique mechanism of promoting permanent tubulin polymerization, thereby, the mitosis at the metaphase-anaphase is inhibited[2,3]. Paclitaxel has been associated with cardiac toxicity, ranging from asymptomatic arrhythmias, myocardial ischemia, and fatal myocardial infarction[4,5]. Due to this adverse effect, it is the authors' policy to perform electrocardiography (ECG) in all patients to evaluate the cardiotoxicity from previous paclitaxel

Correspondence to : Kietpeerakool C, Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand. Mobile: 0-1593-5700, E-mail: kiet_ji@hotmail.com

administration and give up chemotherapy if contraindiated. The present study, accordingly, was undertaken to evaluate the patterns of ECG before paclitaxel administration, its consequence in clinical management, and the usefulness of pretreatment ECG for cardiac toxicity surveillance in patients with epithelial ovarian cancer receiving adjuvant paclitaxel and carboplatin as frontline chemotherapy.

Material and Method

Selection of the Patients

After approval of the Research Ethics Committee, all of the medical records of patients with epithelial ovarian cancer receiving combination chemotherapy consisting of paclitaxel and carboplatin at Chiang Mai University Hospital between January 2000 and December 2004 were retrospectively reviewed. Abstracted data included patient's characteristics, cardiac risk factors, pretreatment ECG results of each treatment course, and clinical consequence in patients with abnormal ECG. Interpretation of ECG was carried out by an expert cardiologist of the Department of Medicine in the authors' hospital (RK).

Treatment Schedule

Paclitaxel was administered at the dose of 175 mg/m^2, infused over 3 hours, every 21 days. Premedication consisted of 20 mg intravenous dexamethasone, 200 mg intravenous cimetidine, 10 mg intravenous chlorpheniramine, and 25 mg oral diphenhydramine given 30 minutes before paclitaxel. After complete infusion of paclitaxel, carboplatin was administered at an area under the concentration time curve (AUC) of 5 which was calculated according to the Calvert formula[6]. The glomerular filtration rate was calculated according to the Jelleffe formula[7]. Before each treatment course, ECG was routinely investigated. The clinical consequence of all patients was followed until the completion of chemotherapy. Adverse effects were classified according to the National Cancer Institute Common Toxicity Criteria (NCI CTC)[8].

Statistical analysis

Frequency distribution was calculated for each variable with 95% confidence interval (CI). The chi-square test, or Fisher' exact test were used whenever appropriate to compare the two groups. Eight major cardiac risk factors from the medical records including the family history of premature coronary heart diseases (first-degree male < 55 years of age, first-degree female < 65 years of age), diabetes mellitus, cigarette smoking, hypertension (blood pressure > 140/90 mmHg or on antihypertensive medications), serum cholesterol > 200 mg/ml, high-density lipoprotein cholesterol (HDL-C) < 35 mg/dL, age $\geq$ 55 years, and obesity (body mass index $\geq$ 30.0 kg/m^2) were analyzed for predictive significance of abnormal ECG pattern after paclitaxel treatment in all patients. Value of p less than.05 was considered statistically significant. All statistical tests had two-sided significance.

Results

During the study period, 79 women with epithelial ovarian cancer receiving paclitaxel and carboplatin combination chemotherapy, with pretreatment ECG in all patients and total courses of treatments were varied, were reviewed for analysis. Clinical characteristics of the patients are displayed in Table 1. Mean age at diagnosis of ovarian cancer was 50.4 years (median 50.0 years, range 30-67 years). Mean parity was 1.01 (median 1, range 0-3). Forty-three (54.4%) women had cardiac risk factors including multiple risk factors (22), elevated serum cholesterol (13), hypertension (3), age $\geq$ 55 years(3), smoking(1) and obesity (1). Before the first course of paclitaxel and carboplatin chemotherapy, seventy (88.6%) women had a normal ECG, the remaining 9 (11.4%) had sinus tachycardia (5),

Table 1. Clinical characteristics of the 79 women

Characteristics	Number (%)
Parity	
Nulliparous	18 (22.8)
Multiparous	61 (77.2)
Menopausal status	
Premenopause	40 (50.6)
Postmenopause	39 (49.4)
FIGO* stage	
I	28 (35.4)
II	16 (20.3)
III	29 (36.7)
IV	6 (7.6)
Histologic subtypes	
Serous adenocarcinoma	31 (39.2)
Clear cell adenocarcinoma	24 (30.4)
Endometrioid adenocarcinoma	19 (24.1)
Others	5 (6.3)
Cardiac risk factors	
Absence	36 (45.6)
Presence	43 (54.4)

* The International Federation of Gynecology and Obstetrics

bundle branch block (2), mild T inversion (1), and Wolff-Parkinson-White syndrome (WPWS) (1).

Among 321 evaluable ECG records in 70 women with normal initial ECG, 14 women had an abnormal subsequent ECG including 8 (11.4%, 95%CI = 5.07% to 21.28%) had sinus tachycardia, 2 (2.9%, 95%CI = 0.3% to 9.9%) had sinus bradycardia, 3 (4.3%, 95%CI = 0.9% to 12%) had sinus arrhythmia, and 1 (1.4%, 95%CI = 0.03% to 7.7%) had early depolarization on subsequent treatment courses that developed in varying courses. All these cardiac disturbances were asymptomatic and needed no intervention. According to the classification of NCI CTC, these cardiotoxicities were grade 1 and chemotherapy could be continued without serious adverse events in these women. Median number of chemotherapy given prior the development of abnormal ECG was 3 courses (range 2 to 5 courses). The odds ratio of developing abnormal ECG in subsequent courses was 1.24 (95%CI = 0.33 to 4.64, p = 0.77) for women with cardiac risk factors. There was no correlation between the development of abnormal ECG and parity (p = 0.98), menopausal status (p = 0.59), and the number of treatment course (p = 0.78).

Table 2 summarizes the clinical characteristics and ECG pattern of nine women who had abnormal ECG before the first course of chemotherapy. There was neither symptomatic cardiac disturbance nor worsening of abnormal ECG pattern in subsequent courses of paclitaxel and carboplatin chemotherapy in these patients.

Discussion

Paclitaxel is currently used in the treatment of various tumors including ovarian, breast, lung, and endometrial carcinomas, which are often found in older patients[9]. Although the principle toxicity of paclitaxel is myelosupression, particularly neutropenia[9,10], it is also associated with cardiotoxicity, mainly cardiac rhythm disturbance.

Paclitaxel is formulated in a Cremophor EL vehicle to enhance drug solubility. It is postulated that Cremophor EL, not the paclitaxel itself is responsible for cardiotoxicities. The possible mechanism of cardiotoxicity is massive histamine releasing which stimulates histamine receptors in cardiac tissue, thereby resulting in cardiac conduction disturbance and arrhythmia[4]. In addition, the reported cases with myocardial infarction related to paclitaxel administration, has raised the possibility that paclitaxel may induce vasospasm and cause myocardial infarction[4,5]. However, the exact mechanism has not been elucidated so far.

Recently, Kamineni et al reported the ECG changes after paclitaxel therapy in patients with various types of cancer, mainly lung cancer with dosage of paclitaxel ranging from 75-200 mg/m^2, administered every 1-3 weeks. The majority of these patients (75.6%) received as second line chemotherapy. 8.4% of patients were treated as a single agent. The available ECG was obtained for various indications. The most common abnormal ECG pattern was sinus tachycardia occur accounting for 26%, followed by bundle branch block

Table 2. Clinical characteristics of 9 women with abnormal initial ECG

Patient	Age	FIGO stage	Cardiac riskfactor	Initial ECG	Subsequent ECG
1	52	II	no	sinus tachycardia	normal
2	49	III	no	sinus tachycardia	sinus tachycardia
3	47	III	no	sinus tachycardia	sinus tachycardia
4	40	III	smoking	sinus tachycardia	normal
5	41	II	hypercholesterolemia	sinustachycardia	normal
6	49	III	no	mild T inversion	mild T inversion
7	53	II	DM	WPWS	WPWS with sinus tachycardia
8	65	I	multiple	RBBB	RBBB
9	59	II	multiple	RBBB	RBBB

FIGO = the International Federation of Gynecology and Obstetrics
ECG = Electrocardiography
DM = Diabetes mellitus
WPWS = Wolff-Parkinson-White syndrome
RBBB = Right bundle branch block

(7%), myocardial infarction (6%), prolonged QT interval (4%), sinus bradycardia (3%), premature atrial contraction (2%), premature ventricular contraction (2%), atrial flutter (2%), and atrial fibrillation (2%)[11]. In the present study, all patients received paclitaxel (175 mg/m^2) and carboplatin (AUC 5) every 21 days as first line chemotherapy setting. Among 70 women with normal ECG before the first course of chemotherapy, sinus tachycardia was also the most frequent abnormal ECG pattern but much lower than that of the aforementioned report. Additionally, myocardial infarction and other cardiac disturbances including premature atrial contraction, premature ventricular contraction, atrial flutter, and atrial fibrillation were not observed in the present series. The different profiles of abnormal ECG pattern between these two series may be caused by the different background of the study population, the different dosage, regimens, and intervals of paclitaxel administration, and importantly, the difference in eligibility for study analysis. The ECG patterns in the present series were evaluated in women with normal initial ECG before receiving first line paclitaxel and carboplatin chemotherapy only. Women with abnormal initial ECG were analyzed separately in the present study while in the study of Kamineni et al, ECG was not routinely investigated. Direct comparison between these two series, therefore, may be unwarranted. However, based on the present findings, the cardiac toxicities of paclitaxel and carboplatin appeared minimal and were not clinically significant in women with epithelial ovarian cancer who had a normal initial ECG.

Myocardial infarction associated with paclitaxel therapy has been reported in previous studies and caused cardiac arrest in some cases[4,5,12-14]. However, this serious cardiac adverse effect was not observed in the present study.

Enhanced cardiac toxicity has been noted in combination chemotherapy of paclitaxel and other cytotoxic drugs particularly doxorubicin. Cardiac toxicity effects of paclitaxel and doxorubicin range from minimal cardiac function change to cardiomyopathy[15]. The possible pharmacokinetic interaction is that paclitaxel decreases the hepatic clearance of doxorubicin leading to a higher and longer systemic exposure of doxorubicin[16]. Carboplatin, itself, is generally thought to have a limited cardiotoxicity. When combined with paclitaxel, several reports have shown that this combination regimen does not seem to result in an increased risk of cardiac adverse effect over that of paclitaxel alone[10,17,18]. This conclusion is also supported by the present findings.

Generally, patients with preexisting cardiac diseases are often excluded from the study involving paclitaxel administration to avoid life-threatening complications. Markman et al has studied 15 patients with major cardiac diseases prior to paclitaxel therapy including congestive heart failure, severe coronary heart disease, angina, and those who received beta-blocker drugs for cardiac disturbances. There was neither symptomatic arrhythmia nor worsening of cardiac function following treatment with single paclitaxel or paclitaxel with platinum drug[19]. In the authors' series, nine patients with abnormal ECG prior to treatment with combination paclitaxel and carboplatin had conduction abnormalities and supraventricular arrhythmia in subsequent ECG. After complete treatment, there was no symptomatic cardiac disturbance or worsening of abnormal ECG patterns in these patients. Based on the data of Markman et al and the present study, paclitaxel either single or combined with carboplatin is quite safe to administer to patients with preexisting cardiac disease and/or abnormal ECG pattern. However, due to the small number of patients in both reports, additional study is needed to ensure the safety of paclitaxel administration in these high risk women.

The present study was hampered by a number of limitations including small sample size and retrospective study design that may have a potential limitation of some relevant data collection, i.e. cardiac risk factors, and other co-morbidities in some cases. However, to the best of the authors' knowledge, the usefulness of routine ECG check-up before each treatment course of paclitaxel has not been evaluated previously. Based on the findings from women with normal ECG prior to receiving paclitaxel and carboplatin in the current study, the observed incidence of abnormal ECG on subsequent investigation was low, lacked of clinical significance on the cardiac effects, and did not pose any clinical consequence to the affected patients. Therefore, routine ECG for cardiotoxicity surveillance after paclitaxel and carboplatin chemotherapy is not recommended in patients without a previous abnormal ECG pattern. However, until data that are more precise are obtained from a lager study, the benefit of routine ECG in patients who have either antecedent abnormal ECG pattern or cardiac disease is still inconclusive.

In conclusion, although paclitaxel and carboplatin chemotherapy could induce abnormal ECG in women with either normal or abnormal prior ECG, its consequence was of no clinical significance. Therefore, the benefit of ECG before each treatment course was limited.

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ประโยชน์ของการตรวจคลื่นไฟฟ้าหัวใจในผู้ป่วยมะเร็งเยื่อบุผิวรังไข่ที่ได้รับ Paclitaxel และ Carboplatin เป็นยาเคมีบำบัดอันดับแรก

ชำนาญ เกียรติพีรกุล, จิติมา ติยายน, ประภาพร สู่ประเสริฐ, รังสฤษฏ์ กาญจนวณิช, จตุพล ศรีสมบูรณ์

วัตถุประสงค์: *เพื่อประเมินความผิดปกติของผลการตรวจคลื่นไฟฟ้าหัวใจและผลทางคลินิกในผู้ป่วยมะเร็งเยื่อบุผิวรังไข่ที่ได้รับ Paclitaxel และ Carboplatin เป็นยาเคมีบำบัดอันดับแรก*

วัสดุและวิธีการ: *เป็นการศึกษาเชิงพรรณนาแบบตัดขวางโดยทำการรวบรวมข้อมูลจากเวชระเบียนของผู้ป่วยมะเร็งเยื่อบุผิวรังไข่ที่ได้รับ Paclitaxel (175 mg/m^2) และ Carboplatin (AUC = 5) ทุก 3 สัปดาห์ที่มารับการรักษาในโรงพยาบาลมหาราชนครเชียงใหม่ระหว่างเดือนมกราคม พ.ศ. 2543 ถึง เดือนธันวาคม พ.ศ. 2547*

ผลการศึกษา: *จากการรวบรวมผู้ป่วยทั้งหมด 79 รายพบว่า 43 ราย (ร้อยละ 54.4) มีปัจจัยเสี่ยงต่อโรคหัวใจ ผู้ป่วย 70 รายมีผลการตรวจคลื่นไฟฟ้าหัวใจก่อนรับยาเคมีบำบัดครั้งแรกอยู่ในเกณฑ์ปกติ ผู้ป่วยที่เหลือจำนวน 9 ราย พบความผิดปกติชนิด sinus tachycardia 5 ราย พบ bundle branch block 2 ราย พบ mild T inversion 1 ราย และพบ Wolff-Parkinson-White syndrome 1 ราย จากผลการตรวจคลื่นไฟฟ้าจำนวน 321 ครั้งในผู้ป่วย 70 ราย ที่มีผลการตรวจก่อนรับยาเคมีบำบัดอยู่ในเกณฑ์ปกติพบว่า เกิดความผิดปกติชนิด sinus tachycardia 13 ครั้ง (ร้อยละ 4.1) เกิด early depolarization 4 ครั้ง (ร้อยละ 1.3)และเกิด sinus arrhythmia 3 ครั้ง (ร้อยละ 1) โดยความผิดปกติทั้งหมดไม่มีอาการและไม่ต้องให้การรักษาเพิ่มเติม ความเสี่ยงสัมพัทธ์ (odds ratio) ต่อการเกิดความผิดปกติของการตรวจคลื่นไฟฟ้าหัวใจในผู้ป่วยที่มีปัจจัยเสี่ยงต่อการเกิดโรคหัวใจเท่ากับ 1.24 (95%CI เท่ากับ 0.33 ถึง 4.64, p เท่ากับ 0.77) ในผู้ป่วย 9 รายที่มีผลการตรวจคลื่นไฟฟ้าหัวใจก่อนรับยาเคมีบำบัดผิดปกติพบว่า 6 ราย ยังคงมีความผิดปกติในการตรวจครั้งต่อมา แต่ยังคงไม่มีอาการและผลการตรวจไม่ได้เลวลงเมื่อเปรียบเทียบกับผลตรวจครั้งแรก*

สรุป: *แม้ว่า Paclitaxel และ Carboplatin จะทำให้เกิดความผิดปกติของการตรวจคลื่นไฟฟ้าหัวใจในผู้ป่วยได้ แต่ไม่มีนัยสำคัญทางคลินิก ดังนั้นการตรวจคลื่นไฟฟ้าหัวใจก่อนการรับยาเคมีบำบัดดังกล่าวจึงมีประโยชน์น้อยทางวิชาการ*