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Quality Surveys to Compare Chemotherapy-induced Toxicity and Quality of Life between Two Paclitaxel and Carboplatin Regimens for Ovarian Carcinoma

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Abstract

Objective: *After the JGOG 3016 trial, several studies have evaluated the effectiveness of dose-dense paclitaxel and carboplatin for advanced ovarian carcinoma. The objective of this study was to compare dose-dense paclitaxel and carboplatin (dd-TC) to conventional paclitaxel and carboplatin (c-TC) regarding chemotherapy-induced toxicity and quality of life (QoL) using EORTC questionnaire serially through six cycles of adjuvant chemotherapy.*
Materials and Methods: *Patients who received six cycles of either c-TC (carboplatin AUC(Area Under Curve) 5 mg/mL on day 1 and paclitaxel 175 mg/mL every 3 weeks) or dd-TC (carboplatin AUC 6 mg/mL on day 1 and paclitaxel 80 mg/m² on days 1, 8, and 15) were selected. Patients' QoL was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) version 3.0 and its ovarian-specific module QLQ-OV28. Clinical information was extracted from medical records.*
Results: *This study included 17 patients, including 8 in the c-TC group and 9 in the dd-TC group. The dd-TC regimen was associated with higher frequency of gastrointestinal toxicity. Other chemotherapy-induced toxicities or patient QoL were not statistically significantly different between the two treatment arms.*
Conclusions: *Patients treated with dd-TC or c-RC regimen have comparable tolerability and quality of life.*

Keywords: Ovarian carcinoma; Chemotherapy; Paclitaxel

Introduction

In Korea, the incidence and mortality of ovarian cancer are expected to increase by 2600 and 1100 annually [1]. Annual estimated cases and deaths worldwide are 220,000 and 140,000, respectively [2]. Patients with high-risk ovarian cancer are destined to receive multiple modalities of treatment, including debulking surgery and multiple courses of cytotoxic and targeted chemotherapies. Among chemotherapy regimens, paclitaxel and carboplatin are the mainstay throughout the last several decades. Despite adoption of new chemotherapeutic agents, results of several randomized trials have not shown any improvement in survival [3,4]. However, in the pivotal Japanese Gynecologic Oncology Group trial (JGOG 3016 trial), dose-dense administration of paclitaxel combined with carboplatin (dd-TC) improved progression-free survival and overall survival compared with conventional, tri-weekly paclitaxel and carboplatin (c-TC) in patients with newly

diagnosed stage II–IV ovarian cancer [5,6]. Also, quality-of-life (QoL) outcomes measured by using Functional Assessment of Cancer Therapy (FACT)-General (FACT-G), FACT-Taxane subscale (FACT-T), and FACT-Ovarian subscale (FACT-Ov) showed non-inferior results for these populations [7]. At the same time, there are conflicting data according to study population and ethnicity with regard to the survival advantage of dose-dense paclitaxel and carboplatin chemotherapy for patients with ovarian cancer [6,8].

Better survival and improved quality of life are two important issues for human study with regard to cancer management. Up to date, there are two questionnaire-based general QoL measurement tools for patients with cancer: the EORTC QLQ-C30 and the FACT-G [9,10]. Later, ovarian cancer-specific questionnaires known as FACT-O and EORTC-Ov28 were added [11,12]. These two have some common and different scales. However, few studies have investigated the Korean population with regard to QoL with dose-dense chemotherapy compared with conventional paclitaxel and carboplatin-based chemotherapy.

Thus, the objective of this study was to compare dose-dense paclitaxel and carboplatin (dd-TC) and conventional paclitaxel and carboplatin (c-TC) regarding chemotherapy-induced toxicity and quality of life during chemotherapy.

Materials and Methods

Patient enrolment

After acquisition of institutional approval, medical chart review was performed for patients with ovarian cancer who were treated in the Department of Obstetrics and Gynecology, Samsung Changwon Hospital, Korea. After standard work-up and staging operation, patients received six cycles of either c-TC or dd-TC with or without addition of bevacizumab according to risk factors. QoL was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) version 3.0 and its ovarian cancer-specific module, QLQ-OV28, every time the patient visited. Clinical information was extracted from medical records.

The study was performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki and its later amendments. The study was approved by the institutional review board of each study site, and all the patients provided informed consent prior to their inclusion in the study.

Treatment plan

Patients were randomly allocated to receive paclitaxel and carboplatin as part of either a conventional regimen (c-TC group, 8 patients) or a dose-dense regimen (dd-TC group, 9 patients). Both groups received carboplatin at a dose calculated to produce an AUC (area under the plasma concentration-time curve). Carboplatin was administered as an intravenous infusion over the course of 1 h. The c-TC group additionally received paclitaxel administered as an intravenous infusion for 3 h at a dose of 175 mg/m^2 on day 1. In the dd-TC group, paclitaxel was administered as an intravenous infusion over 1 h at a dose of 80mg/m^2 on days 1, 8, and 15. These treatments were repeated every 3 weeks for six cycles. Eligible patients had an Eastern Cooperative Oncology Group performance status of 2 or less with age of 18 to 80 years. Laboratory criteria included adequate bone marrow function (WBC count $\geq 3.5 \times 10^9$/L, neutrophil count $\geq 1.5 \times 10^9$/L, hemoglobin level ≥ 9.0 g/dL, and platelet count $\geq 100 \times 10^9$/L) and adequate liver function (serum bilirubin level ≤ 2.0 mg/dL, serum AST/ALT and alkaline phosphatase levels ≤ 2 times the upper limit of normal), and adequate renal function (serum creatinine level ≤ 1.5 mg/dL or creatinine clearance > 60 mL/min).

Quality of Life (QoL) assessment

Quality of life during chemotherapy was investigated by using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) [10] version 3.0 and its ovarian cancer-specific module, QLQ-OV28 [11] every time when patient visited the hospital for chemotherapy. The QLQ-C30 is a 30-item questionnaire consisting of the following: 1) five function scales totaling 15 items (physical-5, role-2, cognitive-2, emotional-4, and social-2); 2) three symptom scales totaling 7 items (fatigue-3, pain-2, and nausea/vomiting-2); 3) six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial impact); and 4) a global QoL scale with 2 items (overall QoL and overall general health). Among quality of life measures for patients with cancer, the QLQ-C30 has been used in ovarian cancer. Although the EORTC QLQ-OV28 has items to evaluate ovarian cancer-specific symptoms related to treatments including surgery and/or chemotherapy, the QLQ-C30 questionnaire does not include such items. The QLQ-OV28 consists of 28 items with 6 scales containing 20 items, 4 single items, and 4 items of sexual function. These six scales consist of the following: 1) 6 items of abdominal/gastrointestinal symptoms, 2) 2 items of peripheral neuropathy, 3) 2

items of hormonal symptoms, 4) 2 items of body image, 5) 3 items of attitude to disease and treatment, and 6) 5 items of chemotherapy-related adverse effects. For the four single items, patients filled out questionnaires before chemotherapy and after each cycle. If they had problems with reading and writing, the nurse and physician helped. All scales exhibited good psychometric properties. These questionnaires could be completed in a short time.

Statistical analyses

All scores were linearly transformed to values of 0-100 and analyzed according to procedures recommended by the EORTC QoL Group. Higher scores on functional scales and global QoL scale indicate higher level of functioning and better QoL, respectively. Higher scores on symptom scales indicate higher level of symptoms or problems. A difference of 10 points or more was considered to indicate clinically important difference. Predictive values of clinical factors for global QoL were analyzed with hierarchical regression models. All analyses were carried out with PASW 18 (SPSS Inc., Chicago, IL, USA).

Results

This study enrolled 17 patients, including 8 in the c-TC group and 9 in the dd-TC group (Table 1). Two patients refused chemotherapy. Neither refusal was related to chemotherapy-associated toxicity. The dd-TC regimen was associated with higher frequency of gastrointestinal toxicity than the c-TC regimen. However, other chemotherapy-induced toxicities and patient QoL were similar between the two treatment arms.

Table 1: Demographic and clinical characteristics of patients.

Categories	c-Taxol carboplatin (n=8)	Dose dense Taxol carboplatin (n=9)	P-value
Age	56.50 (45.00-66.00)	64.00 (40.00-75.00)	0.385
FIGO stage			0.813
I, II	5 (62.50)	4 (44.44)	
III	1 (12.50)	3 (33.33)	
IV	2 (25.00)	2 (22.22)	
Histology			0.845
Papillary serous	2 (25.00)	5 (55.56)	
Endometrioid	2 (25.00)	1 (11.11)	
Clear	2 (25.00)	1 (11.11)	
Transitional	1 (12.50)	1 (11.11)	
Malignant FATWO	1 (12.50)	1 (11.11)	
Optimal debulking			0.576
Optimal (<1cm)	7 (87.50)	6 (66.67)	
Suboptimal	1 (12.50)	3 (33.33)	
CA-125	47.52 (6.28-384.30)	312.00 (10.33-811.00)	0.178
Overall chemotherapy period	107.00 (43.00-147.00)	142.00 (0.00-165.00)	0.211

Eight patients had early stage (I–II) while nine patients had advanced stage (III–IV) disease. Over half (9/17 [53%]) had papillary serous pathology. Pre-surgery CA 125 tumor marker levels were 90.79 (6.28–384.3) and 296.89 (10.33–811) (Table 1). Hematologic toxicity was more frequent in the dose-dense paclitaxel carboplatin group, especially grade 3-4 neutropenia. However, fatigue was more frequent in the conventional paclitaxel-carboplatin group. We found that 27% of patients in the dose-dense study group had constipation. The dose-dense group also had longer period of chemotherapy (Table 2). Scores of Global and Functional scales of QLQ-C30 for patients in the dose-dense group are shown in Figure 1A. Patients had gradually improving status during the whole period of chemotherapy and further improvement at the end of chemotherapy, with gains greater than 10 points. In addition, their cognitive score was stable (Figure 1B). Social scores such as daily living status and family matters declined after treatment. Sexuality scores were

low through all chemotherapy cycles. Regarding symptom scales, fatigue, pain, dyspnea, and insomnia generally declined after chemotherapy but improved until the end of therapy (Figure 1C). Nausea/vomiting was improved in the middle of chemotherapy but declined with continuation of chemotherapy.

Table 2: Chemotherapy toxicity during 160 cycles (Common Terminology Criteria for Adverse Events v3.0).

Categories	c-Taxol carboplatin (n=48)	Dose dense Taxol carboplatin (n=108)	P-value
Hematologic			
Neutropinia	5 (10.4)	34 (31.5)	0.005
Anaemia	1 (2.1)	24 (22.2)	0.002
Thrombocytopenia	0 (0.0)	0 (0.0)	-
WBC decreased	5 (10.4)	38 (35.2)	0.001
Non-hematologic			
Nausea	7 (14.6)	46 (42.6)	0.001
Vomiting	1 (2.1)	26 (24.1)	0.001
Constipation	8 (16.7)	65 (60.2)	<0.001
Diarrhea	4 (8.3)	34 (31.5)	0.002
Anorexia	20 (41.7)	65 (60.2)	0.032
Fatigue	26 (54.2)	69 (63.9)	0.251
Allergy	4 (8.3)	23 (21.3)	0.048
Arthlargia	16 (33.3)	30 (27.8)	0.482
Frequency	36 (52.1)	70 (64.8)	0.133

Among other symptom scales, diarrhea worsened with the addition of chemotherapy. Financial difficulty did not cause much harm to patients (Figure 1D). Attitudes to disease/treatment according to QLQ-OV28 were stable during all chemotherapy cycles (Figure 2). However, body image and chemotherapy adverse effects worsened with chemotherapy.

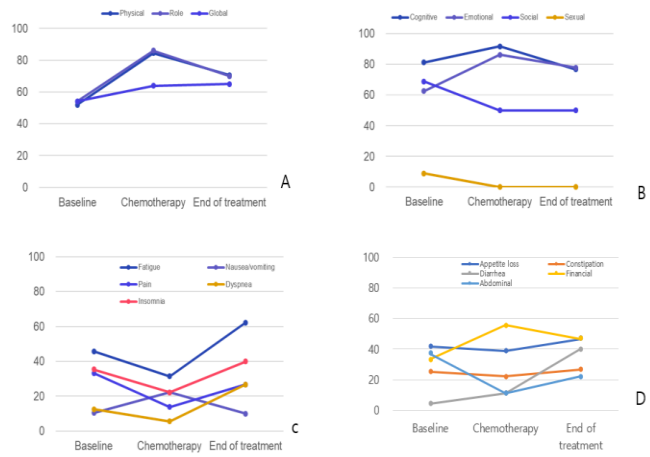

Figure 1: EORTC QLQ-C30 results of the DD-TC population.

Most patients were menopausal. They did not have severe hormonal symptoms. Peripheral neuropathy increased with chemotherapy. It might continue after therapy. Every-3-weeks and dose-dense chemotherapy showed comparable results for most parameters. However, for some parameters such as insomnia and appetite loss, dose-dense chemotherapy was better than the conventional chemotherapy (Figure 3).

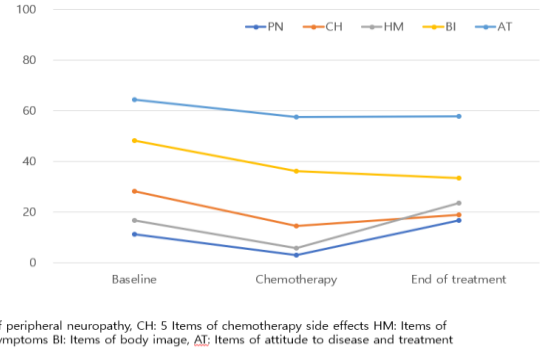

Figure 2: EORTC QLQ-OV28 results of the DD-TC population.

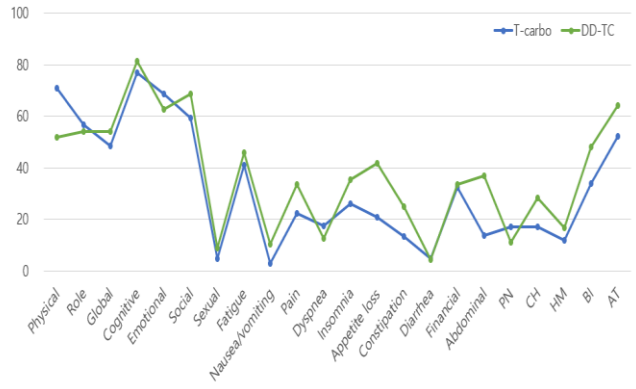

Figure 3: Comparison of DD-TC vs. 3W TC. [*Note: DD-TC: Dose-dense paclitaxel and carboplatin, 3W TC^{+}: Conventional 3 weeks paclitaxel and carboplatin (c-TC)]*.

Discussion

Assessing and evaluating chemotherapy-related symptoms based on well-established questionnaires such as the EORTC QLQ-30 and OV28 serially through chemotherapy cycles are important for patients as they can assess improvements in patient survival. To the best of our knowledge, this is the first study to compare the quality of life of patients with ovarian carcinoma in Korea between conventional and dose-dense paclitaxel carboplatin regimens using EORTC questionnaires. Sustaining moderate quality of life throughout chemotherapy is as important as survival for such patients because they receive multiple courses of chemotherapy according to their disease status.

Although questions still remain overdosing and timing of first-line treatment for patients with advanced ovarian cancer, a dose-dense paclitaxel and carboplatin regimen is found to be feasible for Korean population. However, this study has limitations in that it has a small sample size and short-term follow-up period.

There are conflicting data according to study population and ethnicity regarding the survival advantage of dose-dense paclitaxel and carboplatin chemotherapy for patients with ovarian cancer [6,8]. The quality of life has been reported to be non-inferior between groups according to FACT-G, FACT-T, and FACT-Ov [7]. EORTC QLQ-C30 and FACT-G are equally important for assessing quality of life in patients with cancer, although these questionnaires were developed in 1987 and 1993, respectively [9,10]. FACT-O and EORTC-Ov28 ovarian cancer-specific questionnaires were developed in 2001 and 2003, respectively, to supplement the general questionnaire [11,12]. The Korean versions of the questionnaires were highly compliant.

The theoretical background for dose-dense chemotherapy is known to be the Norton-Simon hypothesis [13] in which the rate of destruction of a tumor by chemotherapy is proportional to the growth rate of the same tumor in the absence of therapy. Therefore, solid tumors follow Gompertzian or sigmoidal growth [14] while bigger tumors are less susceptible to therapy [15]. However, the right number of cycles and interval time for tumor growth shrinkage remain unclear. Although long-term follow-up survival data are needed, we observed no chemotherapy delay or refusal in the present study. In addition, dose-dense chemotherapy appears to have fewer complications, consistent with results of the JGOG3016 trial, although anemia and neutropenic issues are resolved with several agents and transfusion, similar to results reported in a recent study [16].

In conclusion, this is the first study assessing quality of life using Korean versions of the EORTC-QLQ 30 and OV28 among patients with ovarian cancer receiving paclitaxel and carboplatin weekly or tri-weekly. The dose-dense regimen was associated with tolerable toxicity and health status through six cycles of adjuvant chemotherapy. This study showed that chemotherapy-induced toxicity and quality of life of patients with the dd-TC regimen were comparable to those with c-TC regimen. Continuous long-term and larger scale studies are needed in the future to confirm these results.

Conflict of Interest

None declared.

Funding

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