Quality-of-life outcomes from a randomized phase III trial of dose-dense weekly paclitaxel and carboplatin compared with conventional paclitaxel and carboplatin as a first-line treatment for stage II–IV ovarian cancer: Japanese Gynecologic Oncology Group Trial (JGOG3016)


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Background: Dose-dense weekly paclitaxel (Taxol) and carboplatin (dd-TC) improved survival compared with conventional tri-weekly paclitaxel and carboplatin (c-TC) as a first-line chemotherapy for newly diagnosed stage II–IV ovarian cancer in the Japanese Gynecologic Oncology Group 3016 trial. We report the quality-of-life (QoL) results from this trial.

Patients and methods: A total of 637 patients were randomly assigned to receive c-TC or dd-TC (c-TC, n = 319; dd-TC, n = 312) and were asked to complete a QoL assessment at baseline, just after the third and sixth chemotherapy cycles, and at 12 months after randomization. QoL was assessed using Functional Assessment of Cancer Therapy (FACT)-general (FACT-G), FACT-taxane subscale (FACT-T), and FACT-ovary subscale (FACT-Ov). The overall QoL and that according to each subscale were analyzed using mixed-effects models adjusted for treatment and time.

Results: Baseline QoL assessment was completed by 204 out of 319 (63.9%) and 200 out of 312 (64.1%) patients in the c-TC and dd-TC groups, respectively. In these groups, the compliance rates with regard to QoL assessment were 74.5% and 73.0%, respectively, after three chemotherapy cycles; 86.8% and 86.9%, respectively, after six chemotherapy cycles; and 74.2% and 71.6%, respectively, at 12 months after randomization. The overall QoL did not differ significantly between the two treatment groups up to 12 months after randomization (P = 0.46). However, QoL according to the FACT-T subscale was significantly lower in the dd-TC group than in the c-TC group (P = 0.02).

Conclusion: dd-TC does not decrease overall QoL compared with c-TC.

Clinical trial information: NCT00226915.

Key words: carboplatin, neurotoxicity, ovarian cancer, paclitaxel, quality of life

Introduction

Ovarian cancer is the sixth most common cause of cancer death of women in developed countries, with an estimated 220 000 cases and 140 000 deaths occurring annually worldwide [1]. The standard treatment for advanced ovarian cancer has been surgery and platinum-based combination chemotherapy.

Paclitaxel and carboplatin administered every 3 weeks have been used as the standard first-line intervention. In spite of attempts to improve this combination chemotherapy by adding other drugs, the results of several randomized trials have not shown any improvement in survival [2, 3]. The addition of bevacizumab, a humanized vascular endothelial growth factor-neutralizing monoclonal antibody, to standard combination chemotherapy resulted in a significant improvement in progression-free survival (PFS) compared with chemotherapy alone, but only by modest improvement (2–4 months) [4, 5]. Moreover, further consideration needs to be given to the...
addition of bevacizumab because of its high cost and toxic effects such as hypertension and bowel perforation [6].

In the Japanese Gynecologic Oncology Group trial (JGOG 3016 trial), dose-dense administration of paclitaxel combined with carboplatin (dd-TC) improved PFS and overall survival (OS) compared with conventional, tri-weekly paclitaxel and carboplatin (c-TC) in patients with newly diagnosed stage II–IV ovarian cancer [7, 8]. The dd-TC group showed a significantly better median PFS than the c-TC group [28.1 versus 17.5 months, hazard ratio (HR) 0.75, 95% confidence interval (CI), 0.62–0.91; P = 0.0037], and the 5-year OS rate was higher in the dd-TC group than in the c-TC group (58.6% versus 51.0%, HR 0.79, 95% CI, 0.63–0.99; P = 0.0448) according to 6.4-year follow-up data [8]. The frequency of grade 3 or 4 anemia was higher in the dd-TC group than in the c-TC group, but the frequency of other toxic effects was similar between the two groups.

These benefits are likely to be reflected in patients’ quality of life (QoL), and the assessment of QoL is a critical end point if the treatment shows improved survival but also has the potential for increased toxicity. We aimed to compare the QoL of patients receiving dd-TC and c-TC in the JGOG 3016 trial.

patients and methods

eligibility

This study was coordinated by the Japanese Gynecologic Oncology Group (JGOG) and was designed as a randomized, multicenter, non-blinded phase III trial (JGOG 3016) [7]. The details of the trial have been reported previously. Briefly, the eligible patients had a histologically or cytologically confirmed diagnosis of stage II–IV epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer. Other inclusion criteria were age of 20 years or more; an Eastern Cooperative Oncology Group performance status of 0–3; and adequate bone marrow, renal, and hepatic function. Patients were excluded if they had an ovarian tumor with a low malignant potential or a synchronous or metachronous (within 5 years) malignancies other than carcinoma in situ. All patients provided informed consent before enrollment in this study. The study protocol was approved by the institutional review boards at all participating centers.

treatment plan

Patients were randomly assigned to receive paclitaxel (Taxol) and carboplatin as part of either a conventional regimen (conventional therapy group, c-TC group) or a ‘dose-dense’ regimen (dose-dense therapy group, dd-TC group). Both groups received carboplatin at a dose calculated to produce an area under the plasma concentration–time curve of 6 mg/ml/min on day 1 of a 21-day cycle. Carboplatin was administered as intravenous infusion over the course of 1 h. The c-TC group additionally received paclitaxel administered as intravenous infusion for 3 h at a dose of 180 mg/m² on day 1. In the dd-TC group, paclitaxel was administered as intravenous infusion over 1 h at a dose of 80 mg/m² on days 1, 8, and 15. The treatments were repeated every 3 weeks for six cycles. Patients with measurable lesions who had a partial response or complete response received three additional cycles of chemotherapy.

QoL assessment

QoL was assessed using the following validated patient self-reported questionnaires: Functional Assessment of Cancer Therapy (FACT)-general (FACT-G), FACT-Taxane subscale (FACT-T), and FACT-Ovary subscale (FACT-Ov). FACT-G (Version 4) is a 27-item self-reporting QoL measure developed and validated among cancer patients for use in clinical trials [9]. It contains four subscales measuring physical well-being, social well-being, emotional well-being, and functional well-being. Each subscale contains seven, seven, six, and seven items, respectively. The FACT-T subscale is a 16-item self-reporting questionnaire focusing on patient-reported neurotoxicity symptoms and concerns [10]. The FACT-Ov subscale is an 11-item self-reporting questionnaire focusing on well-being related to ovarian cancer [11].

The FACT questionnaires use a five-point response scale: 0 referred to not at all; 1, a little bit; 2, somewhat; 3, quite a bit; and 4, very much. The range of possible scores was 0–108 for FACT-G, 0–64 for FACT-T, and 0–44 for FACT-Ov. In FACT-G, the range of possible scores for the physical, social, emotional, and functional subscales were 0–28, 0–28, 0–24, and 0–28, respectively.

Patients were asked to complete the QoL assessment at four time points: baseline (before treatment), after the third and sixth chemotherapy cycles, and at 12 months after randomization. At the third and sixth cycle, patients were given questionnaires at day 1, which were completed at home and mailed to the researchers within 3 weeks. The QoL assessment was not obligatory in the study, and we collected the data on patients who cooperated in the QoL assessment. If treatment was delayed, the corresponding QoL assessment was to be completed as near to the scheduled time point as possible.

statistical analyses

To assess QoL, scores were computed if more than 80% of items were answered in the overall FACT-G and more than 50% of items in the FACT-T, FACT-Ov, and FACT-G subscales. The baseline completion rate was calculated for each treatment arm, and compliance rates at subsequent time points were defined as the proportion of patients completing QoL assessment based on the number of patients who completed QoL assessment at baseline. QoL assessments were collected irrespective of the patients’ disease status. Differences in patient characteristics between treatment arms were calculated using the χ² test. The mean scores and standard deviation at baseline and at each time point were calculated for the overall scale (the sum of all subscales) as well as for the physical, social, emotional, functional, taxane, and ovary subscales.

To examine whether the follow-up QoL scores were affected by the treatment, a linear mixed effects model was applied and adjusted for the effects of time and treatment [12]. All QoL analyses were restricted to those patients who completed baseline QoL assessment.

results

patient characteristics

Between April 2003 and December 2005, a total of 637 patients were enrolled in the study. Of these, 319 patients were randomized to the c-TC group and 318 were randomized to the dd-TC group. Two hundred and four (63.9%) patients in the c-TC group and 200 (64.1%) patients in the dd-TC group completed baseline QoL assessment. Baseline characteristics did not differ significantly between the two treatment groups (Table 1).

compliance with QoL assessment

The compliance rates for QoL assessment in the c-TC and dd-TC groups were 74.5% (152/204) and 73.0% (146/200), respectively, after three cycles of treatment; 86.8% (132/152) and 86.9% (127/146), respectively, after six cycles of treatment; and 74.2%...
and 71.6% (91/127), respectively, at 12 months after randomization (Table 2). These differences were not significant across time points.

There was no patient with disease progression at third and sixth chemotherapy cycles, but there were 17 and 10 patients with disease progression in the c-TC and dd-TC groups, respectively, at 12 months after randomization.

QoL on treatment

The arms did not differ significantly with respect to the overall QoL score (Figure 1, Table 3) at any of the time points. QoL according to the physical, social, emotional, functional, taxane, and ovary subscales also did not differ significantly between the groups at any time point (Figure 2; Table 3).

Figure 1 shows the baseline and changes in the mean scores for overall QoL scale of each group. The mixed linear model was fitted for the overall QoL scale. The reported scores did not change over time in each group, and there was no statistical difference between two groups ($P = 0.46$). Both groups presented nearly stable scores during the assessment period, and the interaction of time and treatment was not statistically significant.

Figure 2 shows the baseline and changes in the mean scores for physical subscale, social subscale, emotional subscale, functional subscale, taxane subscale, and ovary subscale. The mixed linear model was fitted for these subscales. Among subscales, only the FACT-T subscale showed statistically significant difference between treatment groups. The FACT-T subscale of the dd-TC group showed significantly lower QoL than that of the c-TC group ($P = 0.02$). However, there was no statistical difference of QoL between two groups in physical subscale ($P = 0.90$), social subscale ($P = 0.24$), emotional subscale ($P = 0.23$), functional subscale ($P = 0.20$), and ovary subscale ($P = 0.11$).

We additionally analyzed QoL in patients without disease progression. The FACT-T subscale of dd-TC showed lower QoL than that of c-TC, although it was not statistically significant ($P = 0.06$). There was no statistical difference of QoL between two groups in overall ($P = 0.25$), physical subscale ($P = 0.97$), social subscale ($P = 0.18$), emotional subscale ($P = 0.17$), functional subscale ($P = 0.20$), and ovary subscale ($P = 0.11$).

**discussion**

This trial showed that dd-TC significantly improved PFS and OS compared with c-TC in patients with newly diagnosed advanced ovarian cancer. The toxicity of dd-TC was comparable to that of c-TC, except for grade 3 or 4 anemia.
Measurement of QoL was the secondary end point of the JGOG 3016 study. The aim of this current study was to test the hypothesis that dose-dense weekly administration of paclitaxel has a significant effect on the impact of QoL relative to the tri-weekly administration of paclitaxel. We found that there was no significant difference in the overall QoL between the two groups, suggesting that the PFS and OS benefit of dd-TC was not achieved at the expense of QoL.

In this study, QoL only according to the taxane subscale was worse for patients treated with dd-TC than for those treated with c-TC ($P = 0.02$). The incidence of paclitaxel-induced peripheral neurotoxicity (PIPN) depends on several factors, including the cumulative dose delivered [13], the dose per treatment cycle [14], the schedule of treatment administration [15, 16], and dose intensity [15]. In the phase III Cancer and Leukemia Group B (CALGB) 9840 trial for the treatment of metastatic breast cancer comparing weekly administration of paclitaxel (80 mg/m$^2$) with the administration of paclitaxel (175 mg/m$^2$) every 3 weeks, grade 3 neuropathy occurred more commonly with weekly dosing (24 versus 12%, $P = 0.0003$) and the dose intensity was higher with the weekly regimen [15]. In our original study, the mean delivered dose intensity of paclitaxel was higher in the dd-TC group than in the c-TC group [63.0 mg/m$^2$ per week (SD 13.0) versus 51.7 mg/m$^2$ per week (SD 10.6)], suggesting that the dose-dense administration of paclitaxel increased the severity of PIPN and impaired QoL due to neurotoxicity. In our study, the frequency of grade 3 or 4 neurotoxicity was found to be similar in both groups (dd-TC, 7% versus c-TC, 6%). The proportion of patients who received six or more cycles of treatment was lower in the dd-TC group (62%) than in the c-TC group (73%), which may explain why the frequency of neurotoxicity was apparently similar between the two groups. We additionally examined QoL in patients without disease progression. The taxane subscale showed a similar trend, although it was not statistically significant ($P = 0.06$).

### Table 3. Quality-of-life scores according to the overall questionnaire and the subscales in both treatment arms

<table>
<thead>
<tr>
<th>Assessment time point</th>
<th>Domain</th>
<th>Conventional tri-weekly paclitaxel and carboplatin</th>
<th>Dose-dense weekly paclitaxel and carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean score</td>
<td>SD</td>
<td>Mean score</td>
</tr>
<tr>
<td>Before treatment$^a$</td>
<td>Overall</td>
<td>154.2</td>
<td>23.3</td>
</tr>
<tr>
<td></td>
<td>Physical</td>
<td>19.4</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td>Social</td>
<td>22.4</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>Emotional</td>
<td>15.2</td>
<td>5.7</td>
</tr>
<tr>
<td></td>
<td>Functional</td>
<td>15.6</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td>Taxane</td>
<td>53.9</td>
<td>9.8</td>
</tr>
<tr>
<td></td>
<td>Ovary</td>
<td>27.2</td>
<td>6.3</td>
</tr>
<tr>
<td>After 3 cycles$^b$</td>
<td>Overall</td>
<td>153.3</td>
<td>22.8</td>
</tr>
<tr>
<td></td>
<td>Physical</td>
<td>19.4</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>Social</td>
<td>21.1</td>
<td>5.4</td>
</tr>
<tr>
<td></td>
<td>Emotional</td>
<td>15.8</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td>Functional</td>
<td>15.5</td>
<td>6.3</td>
</tr>
<tr>
<td></td>
<td>Taxane</td>
<td>53.6</td>
<td>10.2</td>
</tr>
<tr>
<td></td>
<td>Ovary</td>
<td>27.6</td>
<td>5.6</td>
</tr>
<tr>
<td>After 6 cycles$^c$</td>
<td>Overall</td>
<td>157.3</td>
<td>22.5</td>
</tr>
<tr>
<td></td>
<td>Physical</td>
<td>20.5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Social</td>
<td>21.7</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td>Emotional</td>
<td>16.3</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td>Functional</td>
<td>15.5</td>
<td>7.2</td>
</tr>
<tr>
<td></td>
<td>Taxane</td>
<td>55.2</td>
<td>9.8</td>
</tr>
<tr>
<td></td>
<td>Ovary</td>
<td>27.5</td>
<td>5.8</td>
</tr>
<tr>
<td>12 months after randomization$^d$</td>
<td>Overall</td>
<td>150.5</td>
<td>25.9</td>
</tr>
<tr>
<td></td>
<td>Physical</td>
<td>19.1</td>
<td>5.4</td>
</tr>
<tr>
<td></td>
<td>Social</td>
<td>21.6</td>
<td>4.8</td>
</tr>
<tr>
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<tr>
<td></td>
<td>Functional</td>
<td>15.3</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Taxane</td>
<td>51.6</td>
<td>12.1</td>
</tr>
<tr>
<td></td>
<td>Ovary</td>
<td>26.7</td>
<td>6</td>
</tr>
</tbody>
</table>

QoL, quality of life; SD, standard deviation.

$^a$Conventional tri-weekly paclitaxel and carboplatin, $n = 204$; dose-dense weekly paclitaxel and carboplatin, $n = 200$.

$^b$Conventional tri-weekly paclitaxel and carboplatin, $n = 152$; dose-dense weekly paclitaxel and carboplatin, $n = 146$.

$^c$Conventional tri-weekly paclitaxel and carboplatin, $n = 132$; dose-dense weekly paclitaxel and carboplatin, $n = 127$.

$^d$Conventional tri-weekly paclitaxel and carboplatin, $n = 98$; dose-dense weekly paclitaxel and carboplatin, $n = 91$. 
This study has a number of limitations. The completion rate of the QoL questionnaires was not high at baseline, nor was the compliance rate throughout the study. The reason for a missed assessment was not documented in the trial. The extent of missing data likely biases estimates of the mean improvement in QoL with time because patients with deteriorating QoL scores are less likely to fill out the questionnaires. This bias may result in some spurious improvements in QoL scores with time in both treatment groups. However, the completion rate of baseline QoL assessment and the rates of compliance across time points were

Figure 2. Box plot showing the baseline and changes in quality-of-life scores according to the Functional Assessment of Cancer Therapy-General (FACT-G) subscales: (A) physical, (B) social, (C) emotional, (D) functional, (E) taxane (FACT-T), and (F) ovary (FACT-O) for each treatment group.
similar between the treatment groups (Table 2). This might negate the potential for biases that could be caused by missing data. Moreover, the QoL assessment tool used in this study was sufficiently reliable to detect clinically significant differences in QoL.

In conclusion, this study showed that the overall QoL did not differ between the dose-dense administration of paclitaxel combined with carboplatin and conventional tri-weekly paclitaxel combined with carboplatin in patients with newly diagnosed advanced ovarian cancer. As it has also been shown that dd-TC improves survival compared with c-TC, these results suggest that dd-TC is the better treatment choice in this patient population. In this trial, QoL according to the taxane subscale was significantly lower in the dd-TC group than in the c-TC group. These findings justify further investigation into the prevention and treatment of neurotoxicity in order to improve QoL.

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disclosure

NK received honoraria and research funding from Nippon Kayaku Co., Ltd. The remaining authors have declared no conflicts of interest.

references


appendix

The following institutions participated in this study: the Jikei University Kashiwa Hospital, National Cancer Center Hospital, Kitasato University Hospital, Keio University Hospital, Toho University Ohashi Medical Center, Osaka City General Hospital, Iwate Medical University Hospital, Niigata Cancer Center Hospital, The Jikei University Third Hospital, The Jikei University Aoto Hospital, Kure Medical Center, Shikoku Cancer Center, Kinki University Hospital, National Defense Medical College, The Jikei University Hospital, St. Marianna Medical University School of Medicine, Kagoshima City Hospital, Okayama University, Tohoku University, Nagoya City University, Chiba University, Oita University, Kyoto Prefectural University of Medicine, Koye General Hospital, Hokkaido Cancer Center, Kurume University, Kyoto Daini Red-cross Hospital, Osaka Saiseikai Suita Hospital, Tsukuba University, Ashihikawa Medical University, Hirosaki University, Tokyo Medical University, Shizuoka Cancer Center, Ashihikawa Red-cross Hospital, Hamamatsu Medical University, Shinshu University, Yokohama City University, Niigata University Medical and Dental Hospital, Dokkyo Medical University, Aichi Cancer Center, Saga University, Hokkaido University, Nagoya University, Kochi Medical Center, Showa University, Teikyo University, Toho University Omori Medical Center, Hiroshima University, Nikko Memorial Hospital, Shimane Prefectural Central Hospital, Mazda Hospital, Saga Koseikan Hospital, Jichi Medical University, Chiba Cancer Center, Saint Marianna University Toyoko Hospital, Nagasaki City Hospital, Sapporo Medical University, Tokai University, Yamanashi Prefectural Central Hospital, Kobe Medical Center, Shiga University of Medical Science, Saitama Social Insurance Hospital, Matsuzaka Central Hospital, Hyogo Cancer Center, Toyohashi Municipal
Physician-assessed and patient-reported outcome measures in chemotherapy-induced sensory peripheral neurotoxicity: two sides of the same coin


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Background: The different perception and assessment of chemotherapy-induced peripheral neurotoxicity (CIPN) between healthcare providers and patients has not yet been fully addressed, although these two approaches might eventually lead to inconsistent, possibly conflicting interpretation, especially regarding sensory impairment.

Patients and methods: A cohort of 281 subjects with stable CIPN was evaluated with the National Cancer Institute—Common Toxicity Criteria (NCI-CTC v. 2.0) sensory scale, the clinical Total Neuropathy Score (TNSc©), the modified Inflammatory Neuropathy Cause and Treatment (INCAT) sensory sumscore (mISS) and the European Organization for Research and Treatment of Cancer CIPN specific self-report questionnaire (EORTC QOL-CIPN20).

Results: Patients’ probability estimates showed that the EORTC QLQ-CIPN20 sensory score was overall more highly related to the NCI-CTC sensory score. However, the vibration perception item of the TNSc had a higher probability to be scored 0 for EORTC QLQ-CIPN20 scores lower than 35, as vibration score 2 for EORTC QLQ-CIPN20 scores between 35 and 50 and as grade 3 or 4 for EORTC QLQ-CIPN20 scores higher than 50. The linear models showed a significant trend between each mISS item and increasing EORTC QLQ-CIPN20 sensory scores.

†Equally contributed to the paper.
‡See appendix for the complete list of participating centers and investigators.

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