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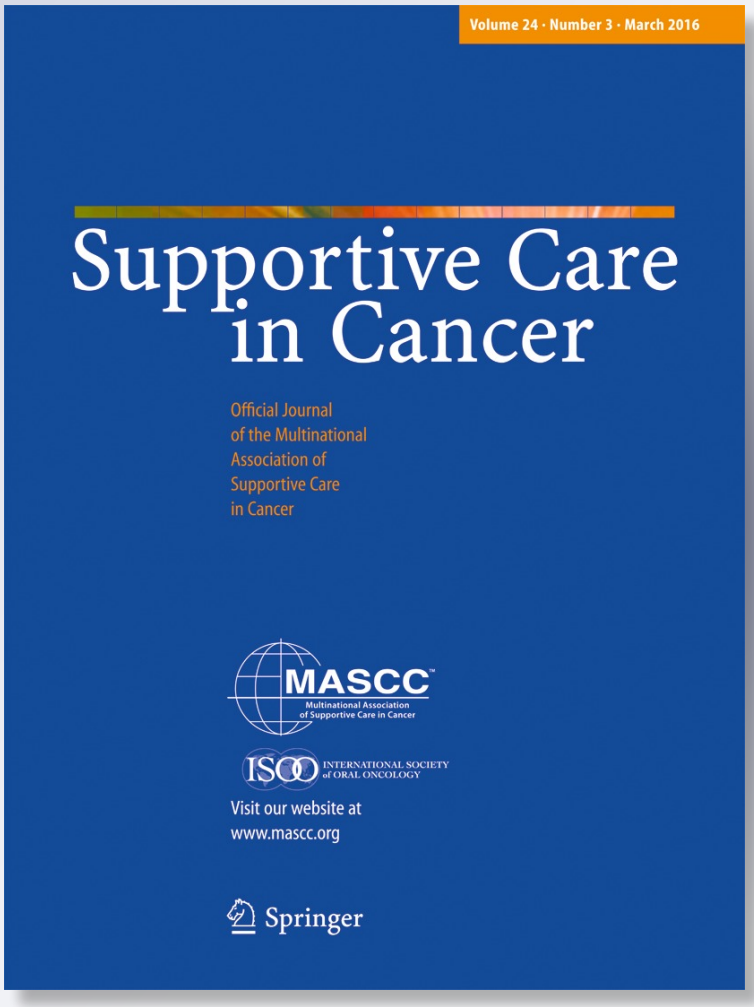


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ORIGINAL ARTICLE

# Randomized study of sequential cisplatin-topotecan/carboplatin-paclitaxel versus carboplatin-paclitaxel: effects on quality of life

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**Abstract**
*Background* A recent phase III trial compared the efficacy of cisplatin-topotecan (a topoisomerase I inhibitor) followed by carboplatin-paclitaxel (Arm 1) versus paclitaxel-carboplatin (Arm 2) in women with newly diagnosed stage IIB or greater ovarian cancer. There was a significantly lower response rate in the experimental arm compared to standard treatment, and less likelihood of normalized CA125 within the first 3 months. At 43 months follow-up, there were no significant group differences in progression-free survival. There were also significantly more side effects in the experimental arm.
*Methods* The current study examined quality of life (QoL) endpoints using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) and the ovarian cancer module, QLQ-OV28, administered prior to randomization, at day 1 of treatment cycles 3, 5, and 7, at completion of the last cycle, and at 3 and 6 months following completion of chemotherapy.
*Results* Global QoL, physical symptoms, fatigue, and role, emotional, cognitive and social function (all from the EORTC QLQ-C30) significantly improved in both treatment arms, with no significant between-arm differences. Between-group differences in pain, insomnia, and peripheral neuropathy reported while on treatment did not differ at follow-up. Nausea and vomiting improved more with standard treatment both during and after treatment. Body image significantly differed between the groups only at cycle 5 (more deterioration in Arm 2) but group differences disappeared at follow-up. A stratified analysis of global QoL by debulking surgery status found no greater effect indicating that overall improvements in QoL were unrelated to surgical recovery.
*Conclusions* There was no significant QoL advantage of cisplatin-topotecan. This finding, combined with no progression-free survival conferred by this combination, reaffirms carboplatin-paclitaxel as the standard of care for women with newly diagnosed ovarian cancer.

**Keywords** Cisplatin-topotecan · Carboplatin-paclitaxel · Ovarian cancer · Quality of life

## Introduction

Ovarian cancer is a devastating disease that is often detected in the advanced stages due to the absence or non-specific nature of early symptoms [1]. It is the leading cause of death related to gynecologic malignancy and is the 5th leading cause of death due to cancer in women in developed countries, and the 6th in developing nations according to the World Health Organization's International Agency for Research on Cancer [2]. Unfortunately, the majority of women with ovarian cancer will succumb to their disease. Although carboplatin plus

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paclitaxel remains the most widely used first line treatment for advanced epithelial ovarian cancer [3–6], there is a need for improved systemic treatment approaches.

Because topotecan, a topoisomerase I inhibitor, has mechanisms of action distinct from carboplatin and paclitaxel, it was hypothesized its addition to standard treatment might improve treatment outcomes. Following successful completion of a phase II trial of sequential doublets of cisplatin-topotecan followed by paclitaxel-cisplatin [7], the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG), in collaboration with the European Organization for Research and Treatment of Cancer—Gynecologic Cancer Group (EORTC-GCG) and the Grupo Español de Investigación en Cáncer de Ovario (GEICO) initiated a prospective randomized phase III trial (NCIC CTG OV.16) of this regimen in comparison to standard therapy.

A total of 819 Canadian and European women with newly diagnosed stage IIB or greater ovarian cancer were randomized to receive either (1) cisplatin-topotecan followed by carboplatin-paclitaxel or (2) paclitaxel-carboplatin (standard treatment) for 21 days [8]. The response rate observed in the experimental arm was significantly lower (67.9 %) compared to standard treatment (77.2 %), $p=.04$, and patients receiving standard treatment were significantly more likely to have normalized CA125 by 3 months. However, progression-free survival did not significantly differ between the groups. Significantly more patients in the standard therapy arm had allergic reactions and neurosensory side effects, whereas significantly more in the experimental arm had thromboembolic events, nausea, vomiting, febrile neutropenia, and hematological abnormalities. Overall quality of life (QoL) was reported (measured by the EORTC Quality of Life Questionnaire C30 (EORTC QLQ-C30) global score [9]) as improved over the course of treatment in both arms. No significant differences between the arms at any time point were demonstrated.

When different treatments for ovarian cancer have similar efficacy, a more detailed description of QoL outcomes may assist in patient-provider decision making by taking into account the perspective of the patient [10, 11]. Accordingly, the goal of this report was to present a more detailed analysis of QoL data from the OV.16 trial.

Prior to analyzing the QoL study findings, four hypotheses were developed in order to guide the QoL analyses: (1) We expected fatigue to be greater in patients receiving topotecan compared to standard treatment because of evidence of toxicity from the phase II trial [7]; (2) We predicted greater between-arm differences in QoL during treatment compared to differences at follow-up times; (3) We expected that individual toxicities would not necessarily affect global QoL; therefore, there would be fewer between-arm differences in global and possibly functional QoL domains; and (4) Since some symptoms were related to disease burden at baseline, overall QoL would significantly improve from baseline to follow-up in both arms as a result of effective treatments.

## Methods

### Participants

As previously described [8], women eligible for the randomized OV.16 trial were those who had newly diagnosed stage IIB to IV epithelial ovarian, peritoneal, or fallopian tube cancer; had adequate organ function; ECOG status 0 or 1 (i.e., these were well patients at study onset); were 18–75 years of age; and had completed any primary planned surgery ≤6 weeks prior to randomization. Patients provided written informed consent prior to randomization.

### Study endpoints and measures

QoL was designed as a secondary endpoint in this trial. It was assessed using the EORTC QLQ-C30 and the EORTC QLQ-OV28.

The EORTC QLQ-C30 core QoL questionnaire consists of 30 items comprising five functional scales (physical, role, emotional, cognitive, and social), global health status, and nine symptom scales and single items (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The EORTC QLQ-OV28 is a module focused on symptoms resulting from the treatment of ovarian cancer. It has 28 items that divide into seven symptom scales (abdominal/gastrointestinal symptoms, peripheral neuropathy, other chemotherapy side effects, hormonal/menopausal symptoms, body image, attitude to disease and treatment, and sexual functioning).

For both the core questionnaire and the ovarian-specific module, each scale is scored from 0 to 100 with higher scores on the functional and global domains denoting better function and lower scores on the symptom scales and individual items denoting less symptom burden. For missing items, values were imputed by calculating the mean of the remaining items as long as at least half the items for that scale were completed.

### Procedure

Women were stratified by treatment center, age (≤65 or >65), and degree of surgery (no debulking, no macroscopic residual, macroscopic residual <1 cm, macroscopic residual ≥1 cm). Patients were then randomly allocated to receive the following: *Arm 1*—four 3-weekly cycles of cisplatin 50 mg/m$^2$ intravenously over 60 min on day 1, topotecan 0.75 mg/m$^2$ intravenously for 5 days over 30 min on days 1–5 followed by four 3-weekly cycles of intravenous carboplatin AUC 5 over 30 min and paclitaxel 175 mg/m$^2$ over 3 h, both on day

1, or *Arm 2*—(standard treatment arm) the same dose and schedule of carboplatin plus paclitaxel every 3 weeks for a total of 8 cycles. Women in both arms were permitted to receive interval debulking surgery after 3 or 4 cycles of chemotherapy if they had not had optimal debulking surgery upon entry.

Participants were given QoL questionnaires to complete prior to randomization, at day 1 (pre-chemotherapy) of cycles 3, 5, and 7 while on treatment, at completion of the last cycle, and following completion of chemotherapy, at months 3 and 6 follow-up visits. Questionnaires were completed at the time of each clinic visit prior to any study-related procedures.

### Data and statistical analysis

QoL analyses were conducted on those randomized patients who provided a completed questionnaire at baseline and at least one additional post-baseline assessment. Scoring of QoL measures was based on an algorithm supplied by the EORTC Study Group on Quality of Life scoring manual [12] that transformed all raw scores to a 0–100 point scale.

We utilized the four-step guidelines for reporting QoL outcomes as endorsed by the NCIC CTG which are as follows: (1) calculation of compliance rates; (2) comparison of baseline scores between arms; (3) comparison of change scores between and within treatment arms; and (4) determination of the proportion of patients improved, stable, and worsened [13]. Compliance at any given time point was calculated as the percentage of participants who completed a questionnaire at that time point divided by all randomized participants who were expected (and alive) to complete measures within a given window.

All patients who had both QoL assessments at baseline and the given assessment point were included in the analysis. Change scores from baseline were compared between the two treatment arms with a Wilcoxon rank sum test. A positive change for the QLQ-C30 functional and global QoL domains indicated improvement whereas a positive change from baseline on the symptom domains as well as the OV28 scales indicated worsening. An analysis of the proportion improved, stable, and worsened was based on the recommendation that a change of 10 on the QLQ-C30 was perceived as clinically meaningful [14]. Thus, patients were considered to have clinically meaningful improvement if there was a change of 10 points or greater at any point compared to baseline; clinically significant worsening was determined if they obtained a score of −10 points or greater than baseline without any improvement, and a determination of stable was given if the change from baseline was between −10 and +10. Figures are presented for any domain that showed a greater than 15 point change from baseline. A chi-square test was used to compare the proportions of patients with improved, stable, and worsened symptoms between the two arms.

## Results

### Patient enrolment and characteristics

Eight hundred nineteen women were randomized between 2001 and 2005 ($n$=409 on Arm 1 and $n$=410 on Arm 2). A total of 471 were accrued in Canada by NCIC CTG-affiliated institutions, 219 from the EORTC-GCG, and 129 from GEICO. There were no apparent treatment arm differences in age, performance status, prior surgery, residual disease, cancer grade, histology, baseline CA125 levels, and presence of measurable disease at baseline (Table 1).

### Compliance with QoL assessments

Baseline questionnaires were received by 363 of the 401 eligible participants in Arm 1 and 354 of the 405 eligible participants in Arm 2. Compliance by NCIC CTG participants was excellent at baseline (98 %) and while on treatment (79 to 90 %), and very good at follow-up (75 to 82 %). Compliance by EORTC and GEICO participants was considerably lower at baseline (71 and 88 %, respectively), while 59 to 76 % and 58 to 70 %, respectively, on treatment and 45 to 50 % and 44 to 58 %, respectively, at follow-up. Although compliance rates were considerably higher for NCIC CTG participants, a sensitivity analysis comparing outcomes on this subgroup versus the entire sample showed no significant difference (data not shown) so data on the total sample are presented. As with the quality of life assessment in other advanced diseases, the compliance rate for both arms dropped over time and we found compliance rate was significantly lower for patients on Arm 1 at day 1 of cycle 3 (86.5 vs. 91.7 %; $p$=0.03) and day 1 cycle 5 (76.4 vs. 84.0 %; $p$=0.01).

### Baseline QoL characteristics

The mean and standard deviation for baseline scores are presented in Table 2. Participants in both study arms showed impairment in role function (mean scores 44 and 44 in Arms 1 and 2, respectively) and global health status (mean scores 53 and 52 in Arms 1 and 2, respectively). Fatigue was the highest rated symptom domain on the QLQ-C30 (mean score 48 and 48 for respectively Arms 1 and 2), and (negative) attitude to disease/treatment was the highest rated symptom domain on the QLQ-OV28 (mean score 56 and 55 for respectively Arms 1 and 2).

### Effects of treatment on QoL

Global QoL improved in both treatment arms, with no significant between-arm differences at any time point; this improvement was also clinically meaningful with a change score greater than 15 points beginning at the 3rd cycle of treatment

**Table 1** Baseline participant characteristics of full sample

| | Arm 1 [experimental] CT+CP<br>No. of patients (%) | Arm 2 [standard] CP<br>No. of patients (%) |
|---|---|---|
| Randomized | 409 (100) | 410 (100) |
| Eligible | 402 (98) | 402 (98) |
| Age (years) | | |
| Median | 57 years | 57 years |
| Range | (28–78) | (33–76) |
| ECOG performance status: | No. of patients (%) | No. of patients (%) |
| 0 | 138 (34) | 125 (31) |
| 1 | 271 (66) | 285 (70) |
| Site: | | |
| Ovary | 368 (90) | 362 (88) |
| Fallopian tube | 6 (2) | 15 (4) |
| Peritoneal | 33 (8) | 30 (7) |
| Other | 2 | 3 |
| Residual disease: | | |
| None/micro | 90 (22) | 92 (22) |
| Macro <1 cm | 102 (25) | 83 (20) |
| Macro ≥1 cm | 135 (33) | 149 (36) |
| No debulking | 76 (19) | 81 (20) |
| Unknown | 6 (1) | 5 (1) |
| Measurable disease | 195 (48) | 193 (47) |
| Histology: | | |
| Serous | 265 (65) | 280 (68) |
| Clear | 24 (6) | 20 (5) |
| Mixed | 31 (8) | 28 (7) |
| Endometrioid | 28 (7) | 22 (5) |
| Mucinous | 9 (2) | 10 (2) |
| Unspecified | 39 (10) | 36 (9) |
| Other | 13 (3) | 14 (3) |
| CA 125 at baseline | | |
| Median (U/mL) [range] | 212 (4–234) | 217 (4–424) |

*CT+ CP* cisplatin-topotecan followed by carboplatin-paclitaxel, *CP* carboplatin-paclitaxel

and increasing thereafter (Fig. 1). Similarly, there was no significant group difference in physical symptoms, role function, emotional function, cognitive function, and social function at any time point, with scores indicating improvement in all women over time. There were also no significant between-group differences on change scores in dyspnea, appetite loss, constipation, diarrhea, or financial difficulties on the QLQ-C30 or in abdominal/gastrointestinal symptoms, attitudes to disease and treatment, and sexual function on the QLQ-OV28 at any time point. Of note, considerably fewer patients completed the optional sexual health questions ($n$=86 and $n$=67 per arm, respectively) compared to the other QoL domains. On the individual and symptom domains of the QLQ-C30, fatigue improved with no significant between-group differences in change scores (Fig. 2; Table 3).

There were significant between-group differences in some QoL domains at individual time points during treatment, but these differences disappeared by the 6-month follow-up. For example, pain (mean change scores −23 and −16 in Arms 1 and 2, respectively; $p$=0.01) and insomnia (mean change scores −11 and −5 in Arms 1 and 2, respectively; $p$=0.02) were significantly more improved in Arm 1 relative to Arm 2 only at cycle 3. Correspondingly, peripheral neuropathy and "other chemotherapy side effects" showed significantly greater deterioration in Arm 2 relative to Arm 1 at cycles 3 (mean change scores 4 and 14 for peripheral neuropathy in Arms 1 and 2, respectively; $p$<0.0001, and 15 and 18 for other chemotherapy side effects in Arms 1 and 2, respectively; $p$=0.01) and 5 (mean change scores 8 and 25 for peripheral neuropathy in Arms 1 and 2, respectively; $p$<0.0001, and 12 and 17 for other chemotherapy side effects in Arms 1 and 2,

**Table 2** Mean baseline scores of QoL domains and symptoms by treatment arm

| QoL domain or symptom | Cisplatin-topotecan and carboplatin-paclitaxel | | | Carboplatin-paclitaxel | | |
|---|---|---|---|---|---|---|
| | No. | Mean baseline score | SD | No. | Mean baseline score | SD |
| QLQ-C30 domains | | | | | | |
| Physical | 355 | 72 | 25 | 349 | 72 | 24 |
| Role | 343 | 44 | 35 | 342 | 44 | 34 |
| Emotional | 350 | 65 | 24 | 347 | 63 | 23 |
| Cognitive | 349 | 81 | 21 | 345 | 78 | 23 |
| Social | 349 | 58 | 33 | 335 | 58 | 32 |
| Global | 349 | 53 | 25 | 344 | 52 | 24 |
| Fatigue | 353 | 48 | 26 | 350 | 48 | 25 |
| Nausea and vomiting | 351 | 13 | 22 | 349 | 14 | 23 |
| Pain | 344 | 39 | 29 | 344 | 38 | 29 |
| Dyspnea | 351 | 18 | 29 | 347 | 17 | 27 |
| Insomnia | 353 | 39 | 31 | 346 | 40 | 32 |
| Appetite loss | 351 | 34 | 34 | 349 | 34 | 34 |
| Constipation | 347 | 26 | 32 | 344 | 27 | 33 |
| Diarrhea | 349 | 11 | 23 | 345 | 11 | 20 |
| Financial difficulties | 346 | 19 | 29 | 339 | 15 | 25 |
| QLQ-OV28 domains | | | | | | |
| Gastrointestinal | 354 | 35 | 23 | 345 | 34 | 23 |
| PN | 347 | 10 | 14 | 336 | 9 | 13 |
| Other CT | 350 | 16 | 14 | 336 | 14 | 12 |
| Hormonal | 346 | 24 | 25 | 340 | 25 | 26 |
| Body image | 349 | 27 | 28 | 335 | 25 | 27 |
| Attitude | 347 | 56 | 27 | 335 | 55 | 27 |
| Sexual | 86 | 23 | 21 | 67 | 30 | 18 |

No. refers to the number of participants completing that questionnaire domain. There were no significant between-arm differences at baseline on any QoL domain

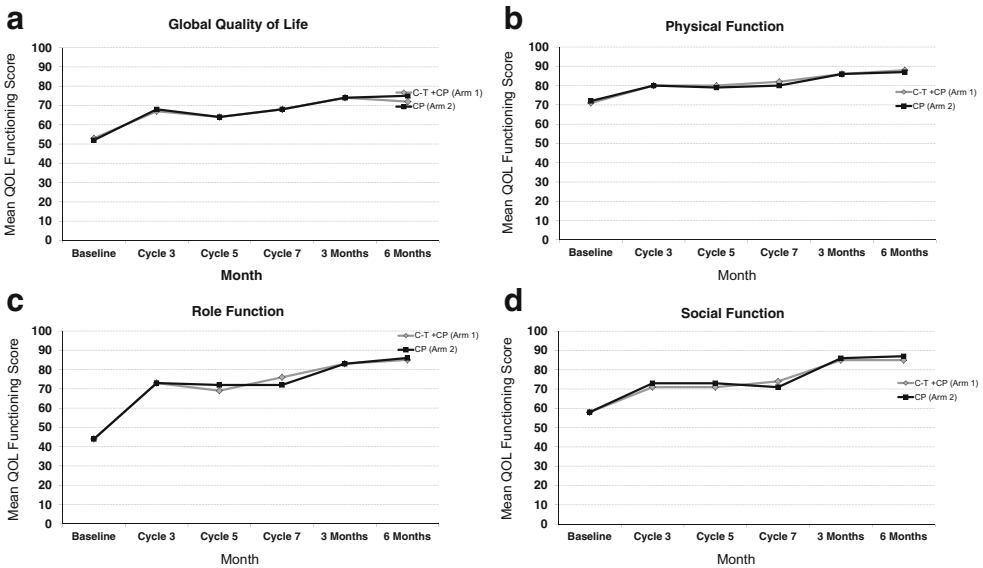


**Fig. 1** Mean scores by arm on **a** global quality of life, and functional domains: **b** physical function, **c** social function, and **d** role function. Positive change indicates improvement

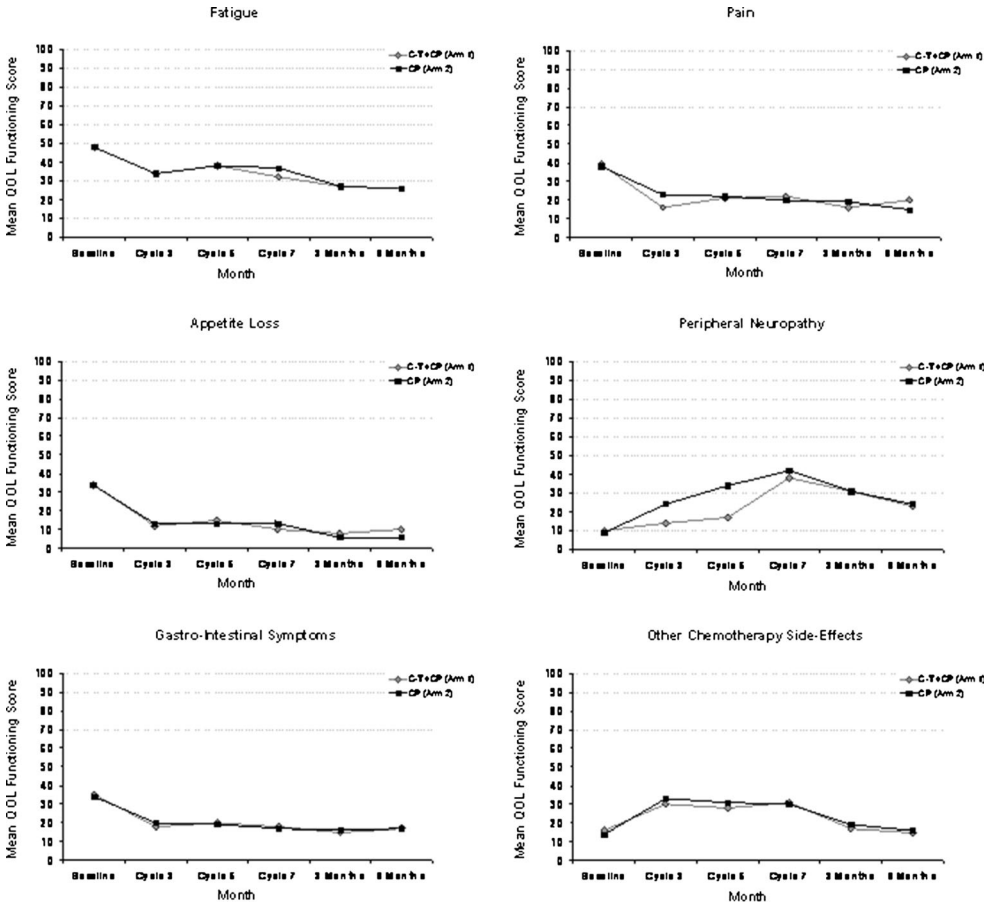


**Fig. 2** Mean scores by Arm on symptom domains: **a** fatigue, **b** pain, **c** appetite loss, **d** peripheral neuropathy, **e** gastrointestinal symptoms, and **f** other chemotherapy side effects. Negative change indicates improvement

respectively; $p=0.0007$), but scores did not significantly differ at follow-up (Fig. 2).

Hormonal/menopausal symptoms significantly differed only at 6-month follow-up, with significantly more deterioration in Arm 2 and an improvement in Arm 1 (mean change scores −3 and 2 in Arms 1 and 2, respectively; $p=0.05$). Body image was significantly more deteriorated in Arm 2 compared to Arm 1 but only at cycle 5 (mean change scores 6 and 11 in Arms 1 and 2, respectively; $p=0.03$).

Symptoms of nausea and vomiting were more significantly improved in Arm 2 at cycle 5 (mean change scores −3 and −7 in Arms 1 and 2, respectively and $p=0.03$) as well as at 6 months follow-up (mean change scores −6 and −10 in Arms 1 and 2, respectively and $p=0.05$).

### Stratified analysis comparing patients receiving initial debulking versus not receiving initial debulking surgery

As indicated in Fig. 1, there was a clinically important improvement in global QoL for patients in both arms. We carried out a stratified analysis comparing those patients who had received initial debulking surgery (Arm 1, $n=291$; Arm 2, $n=282$), to those with interval debulking surgery (Arm 1, $n=37$; Arm 2, $n=37$), and to those who did not receive debulking surgery at all during their primary treatment (Arm 1, $n=58$; Arm 2, $n=62$) to examine the question of whether recovery from surgery may have contributed to the early improvement in global QoL seen in both treatment arms. By the end of the last cycle of treatment, the overall positive change score from baseline was greater in those patients who had not received debulking surgery (Table 4), suggesting that the improvement in global QoL was unrelated to recovery from surgery.

We then repeated this analysis examining abdominal/gastrointestinal symptoms and pain (Table 4). For abdominal symptoms, the change score from baseline was greater in those who did not receive debulking surgery compared to those that did, indicating greater relief of abdominal symptoms in the former group. This was evident from the 3rd cycle of treatment onwards.

For symptoms of pain, there was also a slightly greater improvement by the end of the last cycle in those patients who did not receive debulking surgery compared to those that did (as indicated by a greater negative change score from baseline).

**Table 3** Mean change scores from baseline on QoL domains and symptoms by treatment arm (significant differences noted by domains in footnote)

| | Cycle 3 | | Cycle 5 | | Cycle 7 | | Last Cycle | | 3 month fu | | 6 month fu | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CT+CP | CP | CT+CP | CP | CT+CP | CP | CT+CP | CP | CT+CP | CP | CT+CP | CP |
| QLQ-C30 domains | | | | | | | | | | | | |
| Physical | 9 | 8 | 8 | 7 | 10 | 8 | 10 | 9 | 14 | 142 | 16 | 15 |
| Role | 29 | 29 | 25 | 28 | 32 | 28 | 29 | 31 | 39 | 40 | 40 | 42 |
| Emotional | 13 | 11 | 10 | 11 | 10 | 9 | 9 | 9 | 13 | 12. | 12 | 12 |
| Cognitive | 3 | 3 | −2 | 1 | −1 | 0 | −2 | 1 | 2 | 4.53 | 3.14 | 6.24 |
| Social | 13 | 14 | 13 | 15 | 16 | 13 | 17 | 17 | 27 | 28 | 27 | 29 |
| Global | 14 | 16 | 11 | 12 | 15 | 14 | 13 | 16 | 21 | 22 | 19 | 23 |
| Fatigue | −14 | −14 | −10 | −10 | −15 | −11 | −11 | −13 | −20 | −21 | −22 | −22 |
| Nausea and vomiting[a] | −4 | −7 | −3 | −7 | −6 | −8 | −7 | −10 | −9 | −10 | −6 | −10 |
| Pain[b] | −23 | −16 | −17 | −16 | −16 | −18 | −19 | −22 | −23 | −20 | −18 | −23 |
| Dyspnea | −6 | −6 | −3 | −5 | −3 | −2 | 1 | −1 | −6 | −4 | −5 | −4 |
| Insomnia[b] | −11 | −5 | −12 | −9 | −11 | −11 | −10 | −15 | −12 | −15 | −11 | −16 |
| Appetite loss | −22 | −22 | −19 | −22 | −25 | −22 | −25 | −26 | −26 | −28 | −24 | −28 |
| Constipation | −7 | −3 | −9 | −9 | −9 | −10 | −9 | −10 | −11 | −14 | −7 | −11 |
| Diarrhea | −6 | −7 | −3 | −6 | −5 | −5 | −5 | −4 | −6 | −5 | −4 | −56 |
| Financial difficulties | 0 | 2 | 1 | 2 | 1 | 4 | 1 | 2 | −32 | −2 | −4 | −3 |
| QLQ-OV28 domains | | | | | | | | | | | | |
| Gastrointestinal | −17 | −14 | −15 | −15 | −17 | −17 | −17 | −18 | −20 | −18 | −18 | −17 |
| Peripheral neuropathy[a, b] | 4 | 14 | 8 | 24.51 | 288 | 328 | 328 | 33 | 22 | 21 | 13 | 15 |
| Other chemo side effects[a, b] | 15 | 18 | 12 | 17 | 15 | 15 | 12 | 13 | 2 | 4 | 0 | 2 |
| Hormonal | 4 | 4 | 7 | 5 | 6 | 7 | 2 | 6 | 2 | 0 | −3 | 2 |
| Body image[a] | 7 | 8 | 6 | 11 | 8 | 14 | 11 | 12 | 1 | 3 | −4 | −1 |
| Attitude | −6 | −6 | −6 | −5 | −8 | −4 | −6 | −5 | −13 | −12 | −18 | −15 |
| Sexual | 7 | 2 | 7 | 0 | 7 | 0 | 9 | 7 | 15 | 9 | 11 | 6 |

The difference between treatment arms at each time point were analyzed with a Wilcoxon rank sum test

*CT+ CP* cisplatin-topotecan followed by carboplatin-paclitaxel, *CP* carboplatin-paclitaxel

[a] Significant difference at day 1 of cycle 5

[b] Significant difference at day 1 of cycle 3

### Proportion of patients improved

Using a 10-point difference from baseline to denote clinical significance, there was no significant between-group difference on any domain of functioning except Emotional, where there was a marginally significant greater proportion of women who improved at least once during the study in Arm 2 (69 %) compared to Arm 1 (62 %), $p=0.06$. With respect to global QoL, the proportion of patients improved on Arm 1 was the same as the proportion improved on Arm 2 at cycle 5 (48 % in each arm) with slightly more rated as worsened on Arm 1 (16 %) compared to Arm 2 (12 %) at cycle 5, though this was not statistically significant ($p=0.36$). There was a greater than 15-point change score, indicating clinically significant improvement from baseline, on role, social, fatigue, pain, appetite loss, gastrointestinal symptoms, and overall QoL while on study. There was also a greater than 15-point change, indicating deterioration from baseline, on peripheral neuropathy, while on study.

## Discussion

This trial was initially undertaken to determine if sequential doublets of cisplatin and topotecan followed by carboplatin-paclitaxel would be superior to standard treatment (carboplatin and paclitaxel); however, there were no significant between-group differences on primary endpoint of progression-free survival (mean 15 months in the experimental arm and 16 months in the standard treatment arm) [8]. Of note, we found significant group differences in compliance with QoL measures at cycle 3 and cycle 5, with patients randomized to Arm 1 showing less compliance with completing these measures. It may be due to the higher rate of toxicity as

**Table 4** Mean baseline and change scores at cycle 3 and at the end of last treatment cycle for the following: patients without debulking surgery, patients who received initial debulking surgery, and patients who received interval debulking surgery on global QoL, abdominal/gastrointestinal symptoms, and pain

| | No debulking surgery | | With initial debulking surgery | | With interval debulking surgery | |
|---|---|---|---|---|---|---|
| | CT+CP | CP | CT+CP | CP | CT+CP | CP |
| Global QoL | *n*=58 | *n*=62 | *n*=291 | *n*=282 | *n*=44 | *n*=55 |
| Baseline | 45 | 49 | 55 | 53 | 50 | 44 |
| Cycle 3 | 18 | 18 | 14 | 15 | 14 | 23 |
| End of last cycle | 23 | 23 | 11 | 14 | 21 | 30 |
| Abdominal/GI | *n*=61 | *n*=60 | *n*=293 | *n*=285 | *n*=46 | *n*=54 |
| Baseline | 42 | 44 | 33 | 32 | 42 | 42 |
| Cycle 3 | −20 | −22 | −16 | −12 | −21 | −25 |
| End of last cycle | −28 | −27 | −15 | −15 | −29 | −29 |
| Pain | *n*=60 | *n*=61 | *n*=284 | *n*=283 | *n*=45 | *n*=55 |
| Baseline | 40 | 43 | 38 | 37 | 38 | 42 |
| Cycle 3 | −23 | −12 | −23 | −17 | −22 | −18 |
| End of last cycle | −24 | −29 | −19 | −20 | −23 | −30 |

*CT+ CP* cisplatin-topotecan followed by carboplatin-paclitaxel, *CP* carboplatin-paclitaxel

observed from patients on Arm 1 (8). If more patients dropped out of QoL assessment due to the adverse events, the true differences in QoL between two arms may be of greater magnitude in a direction favoring patients on Arm 2, which would further support our conclusion that there was no significant QoL advantage of cisplatin-topotecan

An examination of QoL indices was a secondary endpoint aimed at exploring both ovarian cancer-related and treatment-related change over time. The current findings show that there was superiority in QoL domains of pain, insomnia, peripheral neuropathy, chemotherapy-related side effects, and body image in the experimental arm compared to the standard treatment arm during treatment, but that these differences disappeared by 6-month follow-up.

Although we had predicted no between-group differences on any QoL domain during and at post-chemotherapy follow-up, in fact there was a statistically significant difference between the two groups on nausea and vomiting, with a greater improvement in the standard treatment arm compared to the experimental arm at cycle 5 and at 6-month follow-up (Table 3). Although the same anti-emetics were used for participants in both arms, cisplatin was used for the first four cycles in the experimental arm, and is more emetogenic than carboplatin, likely accounting for the significant group differences in improvements on nausea and vomiting. Women in the experimental arm showed significantly greater improvement in menopausal symptoms at 6 months compared to the standard treatment arm. These findings, however, did not reach clinical significance.

Our hypotheses about fatigue were not supported. Fatigue was quite profound for patients at baseline, and both groups experienced an overall improvement in their levels of fatigue from baseline to follow-up, with no between-group differences. We also found that both groups significantly improved in global QoL over the course of treatment, and they did not significantly differ in the degree of improvement. Other domains that showed a clinically significant improvement while receiving treatment included the following: role function, social, fatigue, pain, appetite loss, and gastrointestinal symptoms.

The finding that patients in both treatment arms improved with the start of treatment was investigated further with regards to the potential role that recovery from initial debulking surgery may have played as a confounder of the treatment effects over time. A series of stratified analyses comparing patients who received versus those who did not receive debulking surgery on global QoL, abdominal/gastrointestinal symptoms, and pain revealed that the patients who did not receive debulking surgery had only slightly greater improvements in each of these domains compared to those who received surgery. This finding suggests that the overall improvement with treatment cannot be attributed to recovery from surgery.

Overall, our hypothesis about greater fatigue in the experimental arm was not supported; however, the finding that the experimental treatment led to more nausea and vomiting is perhaps not surprising given the higher rates of toxicity associated with this chemotherapy regimen. Our hypothesis about an overall improvement in QoL, regardless of treatment received, was supported.

Given the lack of significant progression-free survival advantage with cisplatin-topotecan followed by carboplatin-paclitaxel compared to standard treatment, and because most between-group differences in QoL while on treatment

disappeared by 6-month follow-up, these findings suggest that carboplatin-paclitaxel should remain the standard of care for women with newly diagnosed ovarian cancer. Moreover, the additional inconvenience, the greater side effect profile, and the added cost to the system of triplet therapy affirm our conclusion about the current standard of care. This study also found that patients' scores, in general, improved by clinically meaningful magnitudes (where they were also often statistically significant) on a number of QoL endpoints, regardless of treatment received, providing evidence that treatment is associated with improved quality of life.

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**Conflict of interest** The authors have declared no conflicts of interest.

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