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Health-related quality of life outcomes associated with four cisplatin-based doublet chemotherapy regimens for stage IVB recurrent or persistent cervical cancer: A Gynecologic Oncology Group study

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Abstract

Purpose—To assess the differences in health-related quality of life (HRQL) of 4 cisplatin containing doublet chemotherapy combinations in women with advanced/recurrent cervical carcinoma.

Methods—Patients were randomized to three-week cycles of paclitaxel+cisplatin (PC); vinorelbine+C (VC); gemcitabine+C (GC); or topotecan+C (TC). We report HRQL results from data available on 434 eligible patients enrolled into this 513 patient trial. HRQL was assessed with the Functional Assessment of Cancer Therapy-Cervix (FACT-Cx) the FACT/Gynecologic Oncology Group (FACT/GOG) four-item neurotoxicity scale, and the 0–10 “worst pain” item from the Brief Pain Inventory, at baseline (pre-treatment), prior to beginning cycle 2, prior to beginning cycle 5, and at 9 months after enrollment. As reported by Monk et al. (2009) [13] VC, GC and TC were found not to be superior to PC with regard to progression-free survival or overall survival.

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Conflict of interest statement

Dr. Cecelia H. Boardman is on the Speaker's Bureau at Glaxo-Smith-Kline, Merck and Eli Lilly. She is also a surgical proctor at Intuitive.

All other co-authors have no conflict of interest to declare.

Results—The trial was terminated early due to planned interim futility analysis, reducing power for HRQL analysis from 85% to 55%. Patients receiving VC, GC and TC doublets did not report significantly different HRQL, neuropathy, or pain from those who received the PC (control) doublet. Patients receiving PC tended to report worse neuropathy during treatment than patients who received other doublets (especially GC and TC), but the differences were not statistically significant.

Conclusion—None of the 3 experimental doublets was different from PC in terms of HRQL during treatment. Long-term toxicity data are inconclusive. Except where patients may wish to reduce their risk of worsening pre-treatment neuropathy, PC remains the standard of care for this disease.

Keywords

Health-related quality of life; Quality of life; Cervical cancer; Advanced; Recurrent; Clinical trial; Phase III; Chemotherapy

Introduction

Metastatic cervical cancer carries a poor survival prognosis, with small but meaningful extension of life afforded by the use of cisplatin (C) chemotherapy, either alone or in combination with agents such as topotecan [1–4]. Current treatment of advanced disease involves balancing considerations regarding toxicity with the possibility that it may palliate disease symptoms, lengthen progression-free survival (PFS) or improve overall survival (OS). The doublet regimen of paclitaxel and cisplatin (PC) has been commonly-used, based largely on its improvement of response rate (RR) and PFS compared to cisplatin alone [5]. However, in a Gynecologic Oncology Group (GOG) randomized trial comparing PC to C (GOG 169), median OS was not superior (9.7 versus 8.8 months, respectively) [5]. In a subsequent GOG comparison of topotecan/cisplatin (TC) versus C alone (GOG 179), the TC doublet was associated with significantly increased median OS (9.4 versus 6.5 months, $p=.017$) [2].

In both of these studies, the addition of a second agent to cisplatin was not associated with poorer health-related quality of life (HRQL), although in both cases the added agent contributed additional toxicity [3,5]. This suggested that the modest gains in RR, PFS and, in one case, OS, justified use of doublet chemotherapy in metastatic cervical cancer, because the additional toxicities were not associated with worsened HRQL. Because the efficacy advantages in terms of OS or PFS have been modest, and the treatments have substantial toxicity, the study of HRQL while patients receive chemotherapy for this disease has been an enduring interest.

GOG 204 was initially designed as a 2-arm trial based on the results of GOG 169 and some interesting phase I/II data with vincristine and cisplatin [6–8], with PC as the standard arm. Once the results of GOG 179 were determined, it was recognized that TC needed to be compared directly to PC, due to the improvement in OS for women treated with TC. Concurrent with this, combined gemcitabine and cisplatin (GC) was showing promise in cervix cancer cell lines and phase II studies [9–12]. Therefore, the 2-arm trial was expanded

to a 4-arm trial of doublet combinations (PC as reference arm; vinorelbine plus C (VC); TC and GC). OS was the primary endpoint, and RR, PFS, toxicity and HRQL were important secondary endpoints. In the primary efficacy analyses, VC, GC, and TC were not superior to PC in terms of OS. Median survival was 13 months for PC and approximately 10 months for the other 3 doublets. The trends in RR favored PC (29%) and VC (26% with more complete responses) over TC (23%) and GC (22%). Trends in PFS favored PC at 6 months compared to 4–5 months for the other doublets [13]. Therefore today, there is no clearly superior chemotherapy doublet for metastatic disease, although one could argue that the PC doublet has not been replaced. In such a case, the HRQL data available from the trial may help determine whether or when one or another regimen might be preferred. These HRQL results are reported here.

Patients and methods

Patient eligibility and treatment

Eligible patients were women with measurable advanced (stage IVB), recurrent, or persistent cervical cancer with squamous, adenosquamous or adenocarcinoma histology. Details of eligibility criteria are found elsewhere [13]. Patients were required to have a GOG performance status (PS) 0 or 1; recovered from the effects of recent surgery, or radiotherapy; and to be free of clinically significant infection. Participating institutional review boards approved the protocol and all patients provided written informed consent.

Chemotherapy treatment arms were as follows: PC=paclitaxel 135 mg/m² over 24 h plus cisplatin 50 mg/m² day 2 every 3 weeks; VC=vinorelbine 30 mg/m² days 1 and 8 plus cisplatin 50 mg/m² day 1 every 3 weeks; GC=gemcitabine 1000 mg/m² days 1 and 8 plus cis-platin 50 mg/m² day 1 every 3 weeks; and TC=topotecan 0.75 mg/m² days 1, 2 and 3 plus cisplatin 50 mg/m² day 1 every 3 weeks. All regimens were administered for a maximum of 6 cycles for non-responders. Patients who achieved a partial response with an acceptable level of toxicity were permitted to continue treatment with their assigned regimen beyond 6 cycles [13]. Granulocyte growth factors were permitted if febrile neutropenia occurred after dose modification for >grade 2 hematologic toxicity during the previous cycle of therapy. Response was defined according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria [14]. PFS was defined as the time from randomization until the date of last contact, documented disease progression, or death, whichever came first.

A total of 513 patients was enrolled from May 27, 2003 to Apr 30, 2007. Of the 513 patients enrolled to the trial from May, 2003 to April, 2007, 41 were entered prior to January, 2004 with either PC or VC, at which time the protocol was amended to include the GC and TC regimens. Of the 472 patients enrolled after January, 2004, 38 were found ineligible and were excluded from the analysis. This manuscript is based on 434 eligible patients, including 9 patients who never received protocol treatments (i.e., intent-to-treat analysis among eligible patients).

Health-related quality of life component

The HRQL objective in this trial was to determine if VC, GC, or TC improved HRQL when compared to the reference arm of PC. HRQL assessment was conducted at 4 times: Pre-cycle 1 (baseline); Pre-cycle 2; Pre-cycle 5; and 9 months Post cycle 1. The primary planned comparisons on HRQL, neurotoxicity, and pain were focused on assessments before the start of cycle 2 and before the start of cycle 5. It was recognized and documented in the original research protocol that the 9 month assessment would be exploratory in nature, due to the expected poor survival and follow-up by that time.

The HRQL instruments used in this trial were the Functional Assessment of Cancer Therapy-Cervix (FACT-Cx) Trial Outcome Index (TOI), for which a higher score indicates better HRQL; the FACT/GOG-Neurotoxicity 4-item Subscale (FACT/GOG-Ntx-4), for which a higher score indicates less neurotoxicity; and the Brief Pain Inventory (BPI) single item evaluating worst pain in the past 24 h, for which a higher score indicates more pain. All instruments have been widely-used in clinical research, have documented reliability and validity, and are available in English and Spanish [15–18]. Both English and Spanish language versions were used in this trial.

The Functional Assessment of Cancer Therapy-Cervix (FACT-Cx)

The FACT-Cx is the FACT-G plus a cervix cancer-specific subscale [15]. The FACT-G is a 27-item self-report quality of life (QOL) measure that includes 4 subscales (physical well-being, social well-being, functional well-being and emotional well-being) [16]. Each scale produces a score, and scores can be summed to produce a total QOL score. The FACT-Cx endpoint for this trial focuses on the aspects of HRQL that are most sensitive and responsive in clinical trials. This “Trial Outcome Index” of FACT-Cx (FACT-Cx TOI), is the summation of the Physical Well Being, Functional Well Being and Cervix Cancer Subscales. Based on guidelines from Yost and Eton [19], a clinically meaningful change for group comparisons is approximately 4–5 points.

FACT/GOG-Ntx 4-item scale

Four items from the 11-item FACT/GOG-Neurotoxicity (FACT/GOG-Ntx) subscale were included to evaluate this important side effect associated with many of the chemotherapy agents in this trial. This was the co-primary HRQL endpoint. Based on the data from a prior GOG study, these 4 questions on the 11-item scale correctly classified the vast majority of patients based on the physician reported CTC grade. These 4 questions also explain more than 50% of the variation in the total Ntx score [17]. Based on Huang et al. [17] and guidelines from Yost and Eton [19], a clinically meaningful change for group comparisons is approximately 1.5–2.0 points.

The Brief Pain Inventory (BPI)

The BPI is a 23-item, self-report instrument designed to assess pain in cancer and other diseases [18]. The BPI has demonstrated reliability and validity across cultures and languages and has been used to study the effectiveness of pain treatment [18]. To limit patient burden, we selected the most commonly-employed endpoint from the BPI which is the single item assessing “worst pain” in the past 24 h, on a 0–10 scale. The BPI single item

was added to provide secondary confirmation of FACT-Cx TOI and FACT-Ntx results. A clinically meaningful change score for group comparisons is approximately 1.0–1.5 points [18].

Analysis plan

For each of the 3 endpoints mentioned earlier, each of the 3 experimental groups (VC, GC, and TC) was compared to the control arm (PC) using a linear mixed model, adjusting for baseline HRQL scores, GOG performance status at randomization and age. Since the correlation of reported HRQL scores between the 3 time points was unknown, the covariance pattern of repeated measures was assumed to be unstructured. The assessment time points were fitted as categorical due to unequal duration. The interaction between assessment time points and treatment assignments was tested for differential effects of treatment on the HRQL scores over time. Unless the interaction was significant, the overall treatment effect was estimated by a weighted average of estimates from each time point. To reflect the observed covariance pattern of the HRQL data, the ‘empirical’ variance was used in estimating the precision of parameter estimates. Satterthwaite’s DF was used in significance testing.

Statistical power

The FACT-Cx-TOI and FACT/GOG-Ntx endpoints were the primary HRQL endpoints, and the BPI endpoint was secondary/exploratory. Given the multiple planned comparisons (6 primary and 3 exploratory), and in light of the known association (0.33) between these endpoints in previous trials, we set alpha at 0.01 for each treatment comparison with two-tailed tests of significance.

The target accrual of this study was 600 eligible patients (150 per arm) and was estimated based on clinical primary endpoint (OS). After taking into account the patients’ attrition (assuming 10% at cycle 2 and cycle 5) and noncompliance (assuming 10% at cycle 2 and 20% at cycle 5), the planned sample size would provide at least 85% statistical power to detect a difference of 0.5 standard deviations (effect size is 0.5) of each HRQL scores at a significance level of 0.01 (two-sided).

Results

This study was terminated early in April 2007 according to a planned interim analysis for futility which suggested that none of the experimental arms could be superior to PC by the end of the study. At the time of study closure, a total of 434 eligible patients (72% of the target accrual) was enrolled and 363 patients (60% of the target accrual) were eligible for analysis of HRQL data. The final sample therefore provided 71% power at assessment prior to cycle 2 and 55% power at assessment prior to cycle 5 to detect the anticipated effect size for each HRQL scores.

HRQL completion rates

At baseline, 410 (94%) patients provided valid QOL assessment (see Table 1). The completion rates dropped to 82% at the second assessment (prior cycle 2), 57% at the third

assessment (prior to cycle 5) and 29% at the last assessment (9 month post cycle 1). There is no statistically significant difference between treatment arms in terms of completion rates of QOL assessments. There were 24 patients who didn't complete the baseline QOL assessments and 47 patients didn't complete at least one follow-up assessment. These patients were excluded from the analysis; thus there are 363 patients (86 in PC, 89 in VC, 92 in GC, and 96 in TC) included in the final analysis. Among the patients in this analysis, there was no statistically significant difference between treatment groups in terms of age, race, ethnicity, performance status, tumor grade or stage of disease (see Table 2).

At baseline, no significant differences were observed between any of the 3 experimental (TC, VC, and GC) arms and the control (PC) arm in terms of FACT-Cx TOI score, Ntx-4 subscale score, or BPI single item score. Group comparisons based upon follow-up evaluations for each of the 3 priori HRQL endpoints are now presented below.

FACT-Cx Trial Outcome Index

After adjustment for the baseline scores, patients' age and performance status at randomization, there was no significant difference in observed means for any of the experimental arms and control arm were associated with the treatment assignments in terms of the FACT-Cx TOI (see Table 2 and Fig. 1a).

FACT/GOG-Ntx-4 subscale

After adjustment for the baseline scores, patients' age and performance status at randomization, there was no significant difference in observed means between any of the experimental arms and control arm in terms of the FACT/GOG-Ntx-4 subscale score (see Table 3 and Fig. 1b).

Brief Pain Inventory worst pain item

After adjustment for the baseline scores, patients' age and performance status at randomization, there was no significant difference in observed means between any of the experimental arms and control arm in terms of the BPI single item (see Table 3 and Fig. 1c).

Follow-up analysis of neuropathy

Although there were no significant differences in any of the planned comparisons (6 primary for FACT-Cx and FACT/GOG-Ntx-4; and 3 secondary for BPI), a trend toward a difference in neuropathy was noted, potentially compromised by reduced power due to earlier termination of study and increasing missing data rates at cycle 5. This trend suggested an increased patient-reported disadvantage of the PC arm. Therefore, the patient-reported data on the 4 NTX questions were further analyzed, noting that a score of 16 connotes no sensory neuropathy and a score of 0 connotes severe sensory neuropathy. In this context, previous research indicates that a difference of 1.5–2.0 points in group comparisons is clinically meaningful [17].

Table 4 reports the percentage of patients reporting any neurotoxicity (Ntx-4 score<16) and mean Ntx-4 score of those patients who reported neurotoxicity symptoms. These average Ntx-4 scores are plotted by group in Fig. 2. After adjusting the baseline Ntx-4 score, there

were no statistically significant differences between experimental regimens and the control regimen associated with the treatment assignment, in terms of the percentage of patients reporting neurotoxicity. The observed mean Ntx-4 score among those who reported neurotoxicity was lower (worse) in PC at the third and fourth assessments than those in GC or TC, but not significantly so (either statistically or clinically). The only exception was the cycle 5 comparison of PC with TC, which favored TC with what might be a clinically significant difference. However, the caution of multiple comparisons and missing data bears repeating in this context.

Discussion

The HRQL results in this trial are consistent with a lack of any significant difference in pain, neuropathy or HRQL across the 4 chemotherapy doublets in the treatment of metastatic or recurrent cervix cancer. None of the observed HRQL differences between compared doublets reached statistical significance. As context for these results, this trial failed to deliver a clearly superior alternative doublet to the PC standard, with regard to RR, PFS, or OS [13].

Three observations warrant some thought. First, early closure of enrollment reduced statistical power for the HRQL analyses. Second, the missing data rate over time increased the problem of reduced power. Although from the outset it was anticipated that the 9 month data would be regarded as exploratory, even the Pre-cycle 5 data suffered from missing data rates that cannot be ignored. Data missing in this context cannot be considered missing at random. This is a common problem in oncology HRQL research [20].

A third point, based on the available, interpretable HRQL observations, reflects an emerging trend observed in prior metastatic cervical cancer clinical trials. Specifically, when treatment of the disease has activity (such as response or delayed progression), there is indirect HRQL evidence supporting those treatments with increased efficacy, despite their increased side effects. In GOG 169 and 179, doublet chemotherapy was associated with improved clinical outcomes (RR, PFS and, in one case OS), compared to single-arm cisplatin. The combination arm was also associated with increased side effects, but no worsening of HRQL. Comparing single agent cisplatin to PC, GOG investigators found that while PC provided benefit to response rate and PFS, it did not confer a benefit to OS [5]. In the same trial, HRQL analysis showed that although PC was associated with more toxicity than C alone, there was no difference in HRQL between groups, suggesting a competing palliative benefit associated with the improved response rate and PFS associated with PC [15]. Similarly, in a subsequent GOG trial comparing C to TC, there was a TC advantage over C in survival and no difference in HRQL, suggesting again that the effects of additional toxicity may be offset by the clinical superiority of the doublet regimen [2,4]. Given the adverse impact of side effects upon HRQL, the lack of HRQL difference in the main trial comparisons can be regarded as indirect evidence of symptom/HRQL benefit associated with more efficacious therapy, offset by side effect HRQL impact. Competing explanations cannot be ruled out, such as reduced power due to missing data, non-ignorable dropout unbalanced across treatment arms, or insensitive HRQL measurement. In any event, the lack of substantial HRQL difference across these three doublets provides some reassurance that

in this disease clinical efficacy drives HRQL results. Future research efforts to improve data quality can help disentangle the complex relationships among efficacy, side effects and HRQL.

In this challenging and serious disease, the gains made by adding a second chemotherapy agent to the cisplatin base have not been extraordinary. As such, the GOG is now investigating the “non-platinum” doublet of topotecan and paclitaxel in the phase III trial GOG 0240 [21]. Interest remains high to characterize the HRQL impact of these more aggressive doublets in the management of metastatic cervix cancer. The current trial did not produce a clearly superior treatment, but in the aggregation of all efficacy endpoints, toxicities, and HRQL results, it appears as though there is support for a continued study of both the PC and TC arms. From the HRQL perspective, these regimens produced nominally (if not significantly) better patient reports of pain and physical components of HRQL (Figs. 1a and c). Given its survival superiority to C alone as reported by GOG, the TC regimen has the added appeal of producing somewhat less patient-reported neurotoxicity [2]. However, it remains the case that none of these tested doublet chemotherapy regimens was superior to the “standard” PC therapy; if there was anything then it would be marginally inferior on clinical endpoints. The absence of a clear HRQL disadvantage to the PC doublet argues for it to be maintained as standard therapy for this disease, except perhaps in cases where patients wish to reduce their risk of neuropathy over the course of therapy.

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Fig. 1.
a: Mean FACT-Cx TOI scores (FACT-Cx TOI = Functional Assessment of Cancer Therapy-Cervix Trial Outcome Index), PC = paclitaxel plus cisplatin; VC = vinorelbine plus cisplatin; GC = gemcitabine plus cisplatin; TC = topotecan plus cisplatin. b: Mean FACT/GOG-Ntx Subscale Scores (FACT/GOG-Ntx = Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity Scale), PC = paclitaxel plus cisplatin; VC = vinorelbine plus cisplatin; GC = gemcitabine plus cisplatin; TC = topotecan plus cisplatin. c: Mean BPI scores (BPI = Brief Pain Inventory), PC = paclitaxel plus cisplatin; VC = vinorelbine plus cisplatin; GC = gemcitabine plus cisplatin; TC = topotecan plus cisplatin.

Fig. 2.
Mean FACT/GOG-Ntx scores of patients reporting any neurotoxicity (FACT/GOG-Ntx = Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity Scale), PC = paclitaxel plus cisplatin; VC = vinorelbine plus cisplatin; GC = gemcitabine plus cisplatin; TC = topotecan plus cisplatin.

Table 1

Completion status of QOL assessments.

	PC	VC	GC	TC
No. of patients randomized Assessments completed	103	108	112	111
0	3	3	4	1
1	13	14	13	13
2	31	27	31	33
3	35	34	42	38
4	21	30	22	26
Pre-cycle 1				
Alive	103	108	112	111
Received and valid	94 (91%)	103 (95%)	104 (93%)	109 (98%)
Noncompliance due to				
Insufficient answer	6	1	3	1
Patient refusal	1	1	2	0
Administrative error	1	2	1	1
Other	1	1	2	0
Pre-cycle 2				
Death	3	3	2	2
Alive	100	105	110	109
Received and valid	82 (82%)	87 (83%)	93 (85%)	92 (84%)
Noncompliance due to				
Insufficient answer	3	1	4	0
Illness or toxicity	0	2	2	1
Patient refusal	1	3	3	1
Administrative error	7	5	4	12
Patient off study and loss contact	0	3	2	0
Other	7	4	2	3
Pre-cycle 5				
Death	8	17	12	15
Alive	95	91	100	96
Received and valid	60 (63%)	64 (70%)	59 (59%)	65 (68%)
Noncompliance due to				
Insufficient answer	2	0	2	1
Illness or toxicity	5	1	5	4
Patient refusal	3	5	6	2
Administrative error	8	9	8	9
Patient off study and loss contact	4	1	6	5
Other	13	11	14	10
9 months post cycle 1				
Death	37	54	50	50
Alive	66	54	62	62

	PC	VC	GC	TC
Received and Valid	28 (42%)	36 (67%)	33 (53%)	31(50%)
Noncompliance due to				
Insufficient answer	0	2	3	0
Illness or toxicity	3	3	2	2
Patient refusal	4	1	2	3
Administrative error	11	5	3	6
Patient off study and loss contact	6	2	4	8
Other	14	5	15	11

PC = paclitaxel 135 mg/m² over 24 h plus cisplatin 50 mg/m² day 2 every 3 weeks; VC = vinorelbine 30 mg/m² days 1 and 8 plus cisplatin 50 mg/m² day 1 every 3 weeks; GC = gemcitabine 1000 mg/m² days 1 and 8 plus cisplatin 50 mg/m² day 1 every 3 weeks; TC = topotecan 0.75 mg/m² days 1, 2 and 3 plus cisplatin 50 mg/m² day 1 every 3 weeks.

Table 2

Patient characteristics of the sample available for HRQL analysis.

	<u>PC</u>	<u>VC</u>	<u>GC</u>	<u>TC</u>
Characteristics	N=86	N=89	N=92	N=96
Age				
<=39	6	7	16	8
40–49	19	25	32	29
50–59	28	29	25	38
60–69	23	21	12	12
>=70	10	7	7	9
Race				
Asian	4	5	2	2
Black	16	19	20	14
Other	3	3	5	9
White	63	62	65	71
Ethnicity				
Hispanic	12	9	15	18
Non-Hispanic	67	74	74	68
Other/unspecified	7	6	3	10
Performance status				
0	48	47	50	52
1	38	42	42	44
Tumor grade				
1	4	7	4	5
2	43	40	45	48
3	38	42	43	43
Not graded	1	.	.	.
Stage				
IV	18	16	20	18
Recurrent/persistent	68	73	72	78

PC = paclitaxel 135 mg/m² over 24 h plus cisplatin 50 mg/m² day 2 every 3 weeks; VC = vinorelbine 30 mg/m² days 1 and 8 plus cisplatin 50 mg/m² day 1 every 3 weeks; GC = gemcitabine 1000 mg/m² days 1 and 8 plus cisplatin 50 mg/m² day 1 every 3 weeks; TC = topotecan 0.75 mg/m² days 1, 2 and 3 plus cisplatin 50 mg/m² day 1 every 3 weeks.

Table 3

Health-related quality of life scores by treatment group.

Assessment time	PC			VC			GC			TC		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Pre-cycle 1												
TOI	86	66.6	17.6	89	69.1	18.6	92	67.9	19.5	96	68.1	19.2
Ntx-4 subscale	84	14.4	2.9	89	13.5	3.4	91	14.2	2.9	96	14.1	3.5
BPI worst pain	74	4.0	2.8	83	3.9	3.2	86	3.3	3.0	92	3.6	3.3
Pre-cycle 2												
TOI	78	65.2	17.6	85	65.5	15.8	90	65.3	18.2	91	66.2	16.3
Ntx-4 subscale	77	14.1	3.2	86	13.3	3.6	89	13.7	3.5	91	14.2	3.2
BPI worst pain	74	3.5	2.9	81	3.5	2.8	85	3.4	3.0	85	3.6	3.1
Pre-cycle 5												
TOI	58	70.5	16.5	62	66.6	17.4	56	64.5	16.5	64	68.4	15.5
Ntx-4 subscale	56	13.1	3.5	62	13.1	3.7	55	14.1	3.0	64	14.4	2.2
BPI Worst Pain	50	3.6	3.1	59	4.0	2.7	51	3.5	3.0	59	2.5	3.0
9 months post cycle 1												
TOI	27	71.9	16.6	35	69.9	18.8	31	68.6	19.5	31	70.9	17.9
Ntx-4 Subscale	26	11.1	5.2	35	11.4	4.7	30	12.3	3.7	30	13.1	3.5
BPI Worst Pain	24	2.3	3.0	33	3.2	2.9	32	3.7	3.0	28	2.9	2.7

PC = paclitaxel 135 mg/m² over 24 h plus cisplatin 50 mg/m² day 2 every 3 weeks; VC = vinorelbine 30 mg/m² days 1 and 8 plus cisplatin 50 mg/m² day 1 every 3 weeks; GC = gemcitabine 1000 mg/m² days 1 and 8 plus cisplatin 50 mg/m² day 1 every 3 weeks; TC = topotecan 0.75 mg/m² days 1, 2 and 3 plus cisplatin 50 mg/m² day 1 every 3 weeks. TOI=Trials Outcome Index.

Ntx-4 = FACT/GOG-Neurotoxicity 4-item scale.

BPI = Brief pain Inventory.

Table 4
Frequency of patients reporting peripheral neuropathy and their mean FACT/GOG-Ntx-4 scores.

Assessment time	Regimen	No. of valid assessments	Neurotoxicity (Ntx 4<16) reported	
			No.	% mean±SD
Pre-cycle 1	PC	84	31	37% 11.7±3.4
	VC	89	42	47% 10.8±3.2
	GC	91	42	46% 12.1±3.2
	TC	96	36	38% 11.1±4.1
Pre-cycle 2	PC	77	33	43% 11.7±3.7
	VC	86	47	55% 11.1±3.6
	GC	89	42	47% 11.1±3.6
	TC	91	36	40% 11.5±3.6
Pre-cycle 5	PC	56	32	57% 10.8±3.2
	VC	62	34	55% 10.8±3.5
	GC	55	25	45% 11.8±3.3
	TC	64	30	47% 12.5±2.1
9 months post cycle 1	PC	26	16	62% 8.0±4.3
	VC	35	23	66% 9.1±4.1
	GC	30	19	63% 10.2±3.1
	TC	30	17	57% 10.9±3.3

PC = paclitaxel 135 mg/m² over 24 h plus cisplatin 50 mg/m² day 2 every 3 weeks; VC = vinorelbine 30 mg/m² days 1 and 8 plus cisplatin 50 mg/m² day 1 every 3 weeks; GC = gemcitabine 1000 mg/m² days 1 and 8 plus cisplatin 50 mg/m² day 1 every 3 weeks; TC = topotecan 0.75 mg/m² days 1, 2 and 3 plus cisplatin 50 mg/m² day 1 every 3 weeks.