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Patient-reported outcomes at discontinuation of anti-angiogenesis therapy in the randomized trial of chemotherapy with bevacizumab for advanced cervical cancer: An NRG Oncology Group study

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Abstract

Introduction: To describe patient-reported outcomes and toxicities at time of treatment discontinuation secondary to progression or toxicities in advanced/recurrent cervical cancer patients receiving chemotherapy with bevacizumab.

Methods: Summarize toxicity, grade, and health-related quality of life within one month of treatment discontinuation for women receiving chemotherapy with bevacizumabin GOG240.

Results: Of the 227 patients who received chemotherapy with bevacizumab, 148 discontinued study protocol treatment (90 for disease progression and 58 for toxicity). The median survival time from treatment discontinuation to death was 7.9 months (95% CI: 5.0–9.0) for those who progressed versus 12.1 months (95% CI: 8.9–23.2) for those who discontinued therapy due to toxicities. The most common grade 3 or higher toxicities included hematologic, gastrointestinal, and pain. There were 57% (84/148) of patients who completed quality of life assessment within one month of treatment discontinuation. Those patients who discontinued treatment due to progression had a mean decline in the FACT-Cx TOI of 3.2 points versus 2.2 in patients who discontinued therapy due to toxicity. This was a 9.9 point more decline in the FACT-Cx TOI scores than those who discontinued treatment due to progression (95% CI: 2.8~17.0; p=0.007). The decline in quality of life was due to worsening physical and functional well-being. Those who discontinued treatment due to toxicities had worse neurotoxicity and pain.

Discussion: Patients who discontinued chemotherapy with bevacizumab for toxicity experienced longer post-protocol survival but significantly greater declination in quality of life than those with progression. Future trial design should include supportive care interventions that optimize physiologic function and performance status for salvage therapies.

Keywords

GOG240; Quality of life; bevacizumab; cervical cancer; patient-reported outcomes; anti-angiogenesis

INTRODUCTION

In 2014, the addition of the anti-angiogenesis agent bevacizumab to standard platinum and taxane therapy provided a survival advantage in a patient population that historically had a poor prognosis of less than or equal to 12 months.[1]The overall survivaladvantage of the chemotherapy plus bevacizumab arm in GOG240of 3.9 months (16.8 versus 12.9 months) is what led the international community to approve this regimen for standard use. However, in GOG240, 97% ultimately discontinued study protocol treatment despite having received at least 6 cycles.[1]Therefore a population of recurrent/advanced cervical cancer patients is

eligible for second or greater line chemotherapy depending on such characteristics as performances, health-related quality of lfie, toxicities and other disease factors.

Baseline quality of life is independently associated with survival in advanced cervical cancer clinical trials.[2–8] With poor baseline quality of life, patient treatment outcomes may be compromised just as significantly as other independent prognostic factors such as race, performance status, site and timing of recurrence, and prior treatment with a radiosensitizer. [9–10] Poorbaseline quality of life has also been associated with the development of toxicities, including the development of gastrointestinal (GI) toxicities and myelosuppression.[11]In GOG240, there were no significant changes in health-related quality of life reported by patients on this regimen when compared to quality of life scores of patients treated with chemotherapy alone.[2]

With patients now experiencing survival gain with systemic chemotherapy for stage IVB or recurrent cervical cancer, the next line of therapy will be debated and one must recognize and anticipate the challenges associated with this and future therapies and improve supportive care.[12]On GOG240, 45% (201/452) of patients discontinued the trial due to progression at the time of efficacy analysis and 48% (218/452) patients on this protocol received further treatment. [1.] Thus, the objective of this study was to describe quality of life and toxicities at the point when patients discontinue treatment with bevacizumab secondary to progression or toxicity as to inform future therapeutic choices.

METHODS

The GOG240protocol was a randomized phase III trial of cisplatin plus paclitaxel with and without bevacizumab versus a non-platinum doublet of topotecan plus paclitaxel, with and without bevacizumabin stage IVB, recurrent or persistent carcinoma of the cervix. A total of 452 patients were enrolled to the trial, 227 patients were randomized to chemotherapy plus bevacizumab therapy and 225 patients were randomized to chemotherapy alone therapy. [1]Patients on chemotherapy plus bevacizumab were administered paclitaxel with cisplatin, or paclitaxel with topotecan, repeated every 21 days to disease progression or toxicity. The eligible patient had primary stage IVB or recurrent/persistent carcinoma of the cervix with measurable disease and GOG performance status 0–1.[1]The patient-reported outcomesassessment includingThe Functional Assessment of Cancer Therapy – Cervix (FACT-Cx), the FACT/GOG-Neurotoxicity (Ntx) subscale (short), and a brief pain inventory (BPI) single item on worse pain in the last 24 hours were completed by patients at the five time points: baseline (prior to randomization), before cycle 2 (3 weeks post cycle 1 if treatment delayed or discontinued), before cycle 5 (12 weeks post cycle 1 if treatment delayed or discontinued), and at 6 and 9 months post cycle 1.A larger score indicates a better quality of life for the FACT-Cx and its subscales, less neurotoxicity for the FACT/GOG-Ntx subscale score, and worse pain for the BPI single item score.[2]All patients signed written, informed consent before study entry in compliance with institutional, state, and federal guidelines. After obtaining approval from the NRG Oncology ancillary data committee, a descriptive study of the toxicities and quality of life on GOG240 was undertaken. Two groups were identified: 1) those who discontinued study protocol treatment due to toxicity versus2) due to progression. The toxicity and quality of life scores within one month of

treatment discontinuation were utilized to describe the two groups. In those who discontinued therapy due to progression, data were gathered on location of progression by RECIST criteria, closest toxicity and quality of life scores, time from treatment discontinuation to death, and patient characteristics. In those who discontinued therapy due to toxicity, data were generated on the grade and type of toxicities closest to trial discontinuation, the closest quality of life score, time from treatment discontinuation to death, and patient characteristics. The change of quality of life scores from baseline were summarized with mean scores accompanied with 95% CI. The comparison of the quality of life scores between the patients discontinued due to progression or toxicities were summarized with the least squared mean differences estimated from a fitted general linear model adjusting for the assessment time points when the quality of life score were reportedsince the quality of life scores might vary across the quality of life assessment time points. There were 35 patients who discontinued treatment after 12 cycles of chemotherapy. Of them 10 patients provided quality of life assessment (at 9 months) within one month of the treatment discontinuation and were included in the analysis. The other 25 patients discontinued treatment after one month post 9-month assessment and therefore were excluded from this analysis. Since the quality of life assessments were scheduled at fixed time points and the treatment could be discontinued at any cycles, the results of quality of life outcomes in this paper are considered exploratory and limited to only those patients who discontinued treatment within 10 months post cycle 1 and provided valid quality of life outcomes within one months of treatment discontinuation.

All the statistics are descriptivesince the analysis are post hoc and exploratory and for the purpose of hypothesis generating only. No confirmatory or definitive conclusions should be derived from the analysis. All analyses were conducted using SAS/STAT software 9.4.

RESULTS

When data were retrieved on August 11, 2018, 148 (65%) patients on chemotherapy plus bevacizumab discontinued therapy (90 (61%) due to progression, and 58 (39%) secondary to toxicity) and 155 patients on chemotherapy alone discontinued therapy (117 (75%) due to progression, and 38 (25%) secondary to toxicity). A patient could have both disease progression and toxicities at the time of discontinuation however only one reason for the treatment discontinuation was documented as the primary or contributing reason for discontinuation. The demographics of this patient population is described in Table 1. The large majority of patients were between age 30 and 60, with roughly 70% of patients of White race, and roughly 75% of patients with recurrent disease. More patients on this trial had a performance status of 0 and the majority had prior platinum chemotherapy.

Younger patients were more likely to stop protocol treatment due to disease progression while older patients more likely discontinued treatment as a result of toxicities. The patients who discontinued treatment due to progression were, on average, 47 years old for those on the chemotherapy plus bevacizumab and 4 years younger ($p=0.03$) than those who discontinued the protocol due to toxicity. The patients on chemotherapy alone who discontinued treatment due to disease progression were 46 years old and were 10 years younger ($p<0.001$) than those who discontinued the protocol due to toxicity. For patients on

chemotherapy plus bevacizumab, patients who discontinued treatment due to progression were more likely to have worse baseline performance status. In the Stage IVB group, more patients discontinued due to progression than toxicity (17.8% versus 10.3).In the persistent/recurrent disease group more patients discontinued due to toxicity than progression (17.2% versus 8.9%). The prior platinum was not found to be associated with the contributing reasons (disease progression or toxicities) of treatment discontinuation.

Of all those who discontinued treatment (chemo alone or with bevacizumab, progression or toxicity), 53% completed between 1 to 6 cycles. Over half of the patients on both arms received more therapy after they came off study treatment (57% on chemotherapy plus bevacizumab and 68% on chemotherapy alone). Of the 148 patients on chemotherapy plus bevacizumab, who discontinued treatment due to either progression or toxicities, 132 have died (84 who discontinued treatment due to progression and 48 due to toxicities). Of the 155 patients on chemotherapy alone who discontinued treatment due to either progression or toxicities, 143 have died (112 who discontinued treatment due to progression and 31 due to toxicities). The median survival time from treatment discontinuation, for those with disease progression, was 7.9 months (range 0.9–39.1) for patients on chemotherapy plus bevacizumab and 6.6 months (range 0.7 ~72.1) for patients on chemotherapy alone. For those who came of therapy for toxicity, median survival time was 12.1months (1.1–56.3) for patients on chemotherapy plus bevacizumab and 15.8 months (range 1.2 ~51.6) for patients on chemotherapy alone. These median survival times are based on patients who died already (n=132 for patients on chemotherapy plus bevacizumab and n=143 for patients on chemotherapy alone).

The majority of patients who discontinued due to toxicities had experienced a grade 3 to 5 toxicity, 88% of patients on chemotherapy plus bevacizumab and 76% of patients on chemotherapy alone. Grade 3 to 5 toxicities were less in those who discontinued due to progression (54% on both arms). Of note, the majority of grade 3 to 4 toxicities were hematologic, GI, and pain in those who discontinued therapy due to toxicity. Similar toxicity trends were seen in those who discontinued therapy due to progression. More common grade 1 to 2 toxicities included constitutional, metabolic/laboratory, and neurologic. Regarding fistula formation at the time of treatment discontinuation, 12 were seen in patients on chemotherapy plus bevacizumab (5 who had progression and 7 who discontinued due to toxicities) and 2 were seen in patients on chemotherapy alone (one who progression and one who discontinued due to toxicities).

Quality of life assessments were scheduled but the assessment time points may not have been at the exact time of treatment discontinuation which is a limitation of this analysis. For example, patients who discontinued due to progression, only 54% (49/90) on chemotherapy plus bevacizumab and 66% (77/117) on chemotherapy alone therapy had quality of life assessed within one months of treatment discontinuation. For those who discontinued due to toxicities,60% (35/58) on chemotherapy plus bevacizumab and 61% (23/38) on chemotherapy alone have their quality of life assessed within one month of the treatment discontinuation. (Table 2). Baselinecharacteristics were explored for patients with quality of life data available versus those who did not have quality of life assessment within one month of their discontinuation of treatment. There were no significant characteristic/demographic

differences between patients who had versus did not have quality of life assessment at the time of treatment discontinuation whether discontinuation was due to progression or toxicity.

The changes of quality of life scores from baseline to within one month of treatment discontinuation were presented for both groups in Table 3.The patients that discontinued treatment due to toxicity had a larger quality of life deterioration from baseline than those who discontinued treatment due to progression, especially for those on chemotherapy plus bevacizumab and discontinued close to cycle 5 (Figure 1a and 1b).

After adjusting for the assessment time points, the patients who were on chemotherapy plus bevacizumab anddiscontinued treatment due to toxicities had 8.5 point (95% CI: 1.5~15.4; p=0.018) more decline on average in the FACT-Cx TOI scores than those who discontinued treatment due to progression. The decline in quality of life was due to declining physical and functioning well-being at the time of treatment discontinuation. The patients who discontinued treatment due to toxicitiesalso had worsening neurotoxicity and pain since the starting treatment than those who discontinued treatment due to disease progression.

Seventeen (20% of patients who were evaluable in this project) patients on chemotherapy plus bevacizumab and 27 on chemotherapy alone therapy did not have platinum with radiation therapy. In patients on chemotherapy plus bevacizumab, those who discontinued treatment due to toxicities declined 9.8 points (95% CI: −1.4~21) from baseline in FACT-Cx TOI score and those discontinued due to progression increased 0.2 points (95% CI: −9.7~9.3). After adjusting for assessment time, the patients who discontinued treatment due to toxicities had 7.3 points (95% CI: −11.4~26) more decline for patients on chemotherapy plus bevacizumab and 11.3 points (95% CI: −1.5~24.2) more decline for patients on chemotherapy alone in the FACT-Cx TOI score than those discontinued due to progression.

DISCUSSION

In this analysis of patients who discontinued treatment with bevacizumab and chemotherapy on GOG240, we hope to inform the design of future recurrent, persistent, or advanced cervical cancer clinical trials. This patient population has previously carried a grim prognosis with patient survival being 12 months or less.[13] Now, with platinum/taxane-based chemotherapy given with bevacizumab, there is a population of patients who have discontinued therapy on the GOG240regimensbut are still potential candidates for further therapy. The objective of this project was to describe the status of these patients at time of discontinuation of trial therapy.

The findings within this analysis could prove helpful in the design of clinical trials for this patient population. Toxicicites on this regimen were cumulative and dose-limiting and represent a third of discontinuations. The treatment team may consider improving toxicity management as opposed to discontinuing therapy. Givensurvival data after trial discontinuation is universally poor, treating teams should be motivated to improved supportive care interventions in those suffering from toxicitiesto allow these women to stay on the GOG240 regimen. As new therapies are being investigated; toxicities experienced

(especially those which forced trial discontinuation) should be addressed during future therapy.[13]

The treating physician could consider shorter length of prior regimen as a surrogate for worse quality of life and emphasis should be placed improving quality of life to impact survival outcomes. In this analysis, patients had worse pain (whether treatment- or tumor-related) and cervical cancer-related complaints if they discontinued treatment closer to trial enrollment for both those who progress and those with toxicities. In addition, worsequality of life change was more pronounced in those who discontinued treatment due to toxicity yet these patients also experienced longer post-protocol survival than those with progression. Patients who discontinue protocol-directed therapy may not only have toxicity as per Common Toxicity Criteria of Adverse Events but also have a decrement in quality of life but alo live longer. This finding highlights the need to improve the management of adverse events especially on a regimen that improves survival.

The association with a steeper quality of life decline in those with grade 3 or 4 toxicitythan with progression is an important consideration. The clinical benefit of bevacizumab, which includes a survivaladvantage, potentially allows for patients to be treated with a next line of therapy which may include other novel drugs. There may be a 7 to 9month time period after the GOG240 regimen is discontinued. Thedata here which demonstrates that progression on bevacizumabdoes not significantly alter quality of lifemay help to justify the opportunity for patients to try novel drugs for next line of therapy (as opposed to hospice care). Those who discontinued treatment due to toxicity may have on average a longer interval to death and therefore could be more ideal candidates for more aggressive next-line therapy.

Alternative quality of life or patient-reported endpoints for these second- or third-line trials could also be considered. For example, pain was also the most severe patient-reported symptom on an analysis of GOG 179/204. Although not significantly different between treatment arms on GOG240, pain and neutropenia were the most common toxicities reported at roughly 30% of all patients on each arm. Therapies for women discontinuingGOG240-type regimens could be designed with an alternative endpoint such as reduction of pain.

With the field moving into other areas of targeted therapyand immunotherapy, we propose an ideal regimen which limits hematologic, neurologic, or GI toxicity while improving pain control and limiting further declines in quality of life. Future trial design should include improved supportive care interventions to allow patients to stay on trial longer and/or optimize performance status for salvage therapies. Consideration should be made to collect patient-reported quality of life data for a period of time after discontinuation of therapy. Novel targeted agents may soon be an option after progression or toxicity from anti-angiogenesis based therapy.[14]It may be that better supportive care is needed to allow patients who are benefiting from treatment to continue because, when the treatment is stopped, there is a short overall survivalinterval.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CONFLICT OF INTEREST STATEMENT:

Dr. Chase reports personal fees received from AstraZeneca, Clovis, Roche/Genentech and Tesaro outside of the submitted work. Dr. Monk reports personal fees received from Roche/Genentech outside of the submitted work. Dr. Penson reports serving on a Scientific Advisory Board for Genentech/Roche. Dr. Oaknin reports serving on advisory boards for Roche, AstraZeneca, PharmaMar, Clovis Oncology, and Tesaro and received support for travel/accommodation from Roche, AstraZeneca and PharmaMar. Dr. Warner Huh reports receiving personal fees as consultant for Antiva, PathoVax and Li-Cor, outside of the submitted work. Dr. Richardson reports serving on the Advisory Board for Genentech and Ipsen and received personal fees, outside of the submitted report. Dr. Salani reports serving on the Speaker Bureau for Genentech as well as serving on Advisory Boards for Tesaro, Clovis, AstraZeneca and Ethicon, outside of the submitted work. Dr. Krishnansu Tewari reports serving on the Speaker's Bureau, Advisory Board for Roche/Genentech. All other coauthors have no conflicts to disclose.

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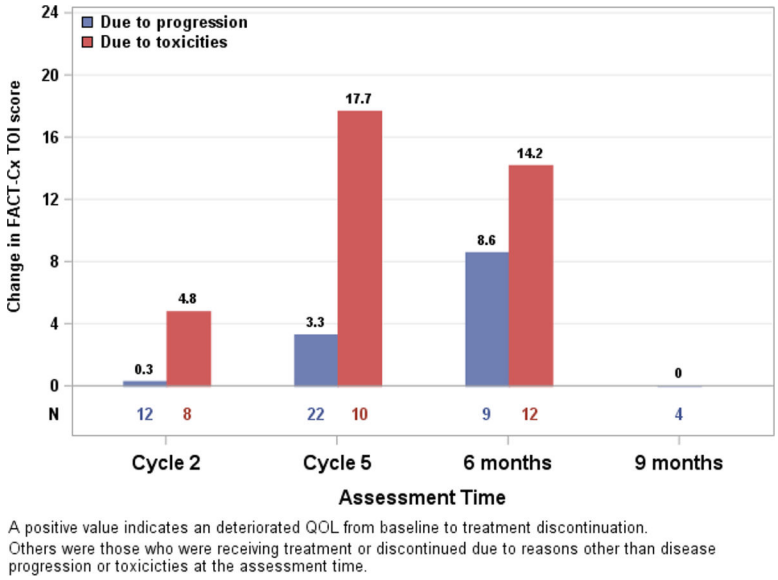

Figure 1a.

Change in FACT-Cx TOI score from baseline to treatment discontinuation for patients on chemotherapy plus bevacizumab

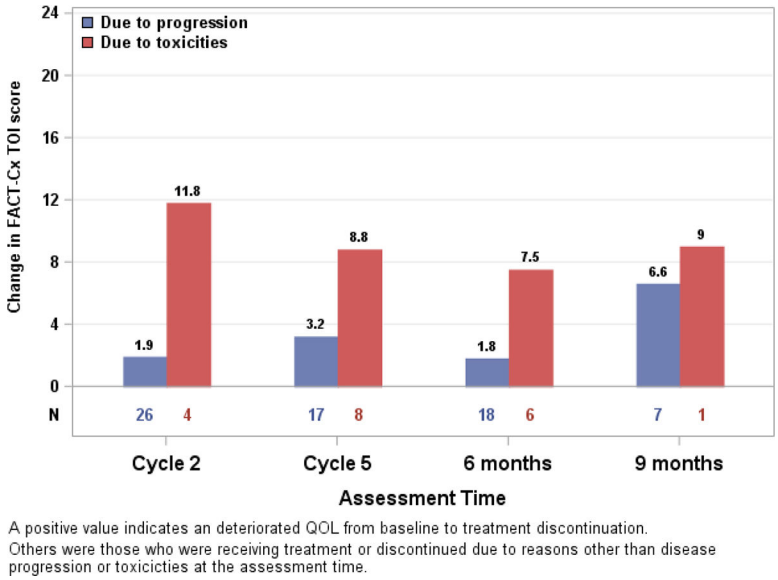

Figure 1b.

Change in FACT-Cx TOI score from baseline to treatment discontinuation for patients on chemotherapy alone therapy

Table 1.

Patient Characteristics by the reasons of treatment discontinuation

		Chemotherapy + Bevacizumab				Chemotherapy alone			
		Due to Progression N=90		Due to Toxicity N=58		Due to Progression N=117		Due to Toxicity N=38	
Characteristic	**Category**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Age Group	<30	5	5.6	1	1.7	4	3.4	1	2.6
	30–39	20	22.2	10	17.2	37	31.6	3	7.9
	40–49	29	32.2	14	24.1	38	32.5	7	18.4
	50–59	23	25.6	19	32.8	19	16.2	12	31.6
	60–69	10	11.1	9	15.5	15	12.8	9	23.7
	70–79	3	3.3	5	8.6	4	3.4	6	15.8
Race	Black	15	16.7	12	20.7	15	12.8	.	.
	Other	9	10.0	4	6.9	10	8.5	4	10.5
	White	66	73.3	42	72.4	92	78.6	34	89.5
Disease Status	Advanced	16	17.8	6	103	20	17.1	5	13.2
	Persistent	8	8.9	10	17.2	12	10.3	3	7.9
	Recurrent	66	73.3	42	72.4	85	72.6	30	78.9
Performance Status	0	47	52.2	38	65.5	71	60.7	25	65.8
	1	43	47.8	20	34.5	46	39.3	13	34.2
Prior Platinum with Radiation	No	23	25.6	12	20.7	29	24.8	10	26.3
	Yes	67	74.4	46	79.3	88	75.2	28	73.7

Table 2.

Number of patients with Quality of Life assessed within one months of treatment discontinuation

Quality of life assessed within one months of treatment discontinuation	Chemo + Bev		Chemo Alone		Total	
	Due to progression	Due to toxicities	Due to progression	Due to toxicities	Due to progression	Due to toxicities
No	41	23	40	15	81	38
Yes	49	35	77	23	126	58
Total	90	58	117	38	207	96

Table 3.

QOL score declines from baseline within one month of treatment discontinuation due to progression or toxicities (95% CI)

	Patients on Chemo + Bev		
QOL Instrument	Due to progression N=49	Due to toxicities N=35	Due to toxicities – due to progression
Physical Well Being	0.8 (−1.1~2.7)	5.3 (3.4~7.2)	5.1 (2.3~8.0)
Social Well Being	0.9 (−0.3~2.0)	−0.4 (−2.0~1.1)	−1.0 (−3.0~0.9)
Emotional Well Being	−1.7 (−3.0~−0.4)	0.3 (−1.0~1.7)	1.7 (−0.2~3.6)
Functional Well Being	0.7 (−0.8~2.2)	4.1 (2.1~6.1	3.2 (0.7~5.6)
Cervix Cancer Subscale	1.6 (−0.6~3.8)	6.1 (−0.7~3.9)	0.2 (−3.3~3.7)
FACT-Cx TOI	3.2 (−1.2~7.6)	11.0 (5.9~16.1)	8.5 (1.5~15.4)
FACT/GOG-Ntx subscale (short)	2.2 (0.9~3.6)	4.1 (2.3~5.9)	1.7 (−0.4~3.8)
BPI single item on worst pain	0.9 (0.01~1.8)	−0.8 (−1.9~0.3)	−1.9 (−3.3~−0.4)
	Patients on Chemo Alone		
QOL Instrument	Due to progression N=77	Due to toxicities N=23	Due to toxicities – due to progression
Physical Well Being	1.10.0~2.2)	4.4 (1.8~7.0)	3.3 (0.8~5.7)
Social Well Being	0.0 (−0 7~08)	2.3 (−0.6~5.1)	2.0 (−0.04~4.1)
Emotional Well Being	−1.3 (−2.2~−0.4)	−0.5 (−2.5~1.5)	0.8 (−1.2~2.9)
Functional Well Being	0.6 (−0.6~1.8)	2.4 (0.4~4.5)	1.9 (−0.6~4.5)
Cervix Cancer Subscale	0.7 (−0.6~2.0)	0.6 (−1.3~2.5)	0.3 (−2.3~2.9)
FACT-Cx TOI	2.4 (−0.7~5.0)	7.5 (2.6~12.3)	5.5 (0.1~10.8)
FACT/GOG-Ntx subscale (short)	3.0 (2.0~4.1)	4.8 (2.3~7.2)	1.7 (−0.4~3.8)
BPI single item on worst pain	0.5 (−0.3~1.4)	0.6 (−0.5~1.7)	0.3 (−1.3~1.8)

QOL=Quality of life; SD=Standard deviation; FACT-Cx TOI=Functional Assessment of Cancer Therapy-Ovarian-Trial Outcome Index; FACT/GOG-Ntx=Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity; BPI=Brief Pain Inventory; The change in QOL scores is calculated as subtract from baseline score so a positive change suggests decline in QOL, worsen in NTX, or improvement on worst pain. The least squared mean difference in QOL scores is estimated after adjusting for the QOL assessment time points.