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Neurotoxicity in Ovarian Cancer Patients on Gynecologic Oncology Group (GOG) Protocol 218: Characteristics Associated with Toxicity and the Effect of Substitution with Docetaxel: An NRG Oncology/Gynecologic Oncology Group study

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Abstract

Objectives—To describe characteristics associated with neurotoxicity (NT) in advanced ovarian cancer patients treated on Gynecologic Oncology Group 218 and examine effect of substituting docetaxel for paclitaxel in these patients.

Methods—The development of NT was defined as Common Toxicity Criteria grade (G) 1. The association between substitution with docetaxel and NT improvement was explored with generalized estimating equations adjusting for treatment cycle and NT grading at previous cycle.

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CONFLICTS OF INTEREST

Dr. Bradley Monk discloses that his institution has received grants/contracts from Genentech. Dr. Monk has received honorarium from speaker's bureaus from Roche/Genentech and has been a consultant for Roche/Genentech.

Dr. Robert Burger states that between 8/14/2011 and 8/14/2014, he served as a consultant on advisory boards for the following: Amgen; Boehringer-Ingelheim; Champions Biotechnology; Clovis Oncology; Endocyte; Fujirebio; Genentech-Roche; GlaxoSmithKline; Marshall Edwards; Oxigene; PharmaMar and Tesaro.

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

Results—Of 1,864 evaluable patients, 1,329 (71%) developed G 1 NT during the study. Nearly half appeared within the first two cycles of chemotherapy, with 31% experiencing G 2. Older patients or those with worse quality of life (QoL) scores at baseline ($p<0.05$) were more likely to experience NT. One-hundred-six patients received docetaxel as substitute for paclitaxel. Of them, 47 patients started with docetaxel at cycle one due to reaction to paclitaxel ($n=32$), fear of NT ($n=4$), other reasons ($n=11$), whereas 59 patients switched to docetaxel during cycle 2-6 due to NT ($n=32$), reaction to paclitaxel ($n=19$), and other reasons ($n=8$). Although the protocol instructed otherwise, the majority continued paclitaxel despite G 2 NT symptoms. There was no evidence that substitution with docetaxel improved NT (Odds Ratio: 1.57; 95% CI 0.98-2.54; $p>0.05$). Of 59 patients who switched to docetaxel, only seven (12%) discontinued taxane prior to chemotherapy completion. A roughly equal chance of worsening NT was reported on paclitaxel (6%) as on docetaxel (5%).

Conclusions—Age and worse QoL at baseline are associated with NT. Substitution of docetaxel did not improve NT symptoms.

Keywords

Ovarian cancer; neurotoxicity; taxane

INTRODUCTION

Microtubule-targeting agents such as taxanes are well-known for their associations with the development of neurotoxicity (NT) [1]. Previous clinical trials have indicated that peripheral neuropathy is a significant dose-limiting toxicity associated with combination chemotherapy regimens containing taxane agents. In an evaluation of the SEER (Surveillance, Epidemiology and End Results) database in 2010, the incidence of peripheral neuropathy in ovarian cancer patients was 21.5/1000 person-years [2]. In addition, it showed that women receiving combination platinum and taxane chemotherapy were three times more likely to develop peripheral neuropathy versus two times more likely to develop neuropathy when only a taxane was used (this is compared to those not receiving chemotherapy at all). From prior trials in advanced ovarian cancer patients, it can be estimated that upwards of 25% of patients on traditional six-cycle carboplatin and paclitaxel chemotherapy will develop grade (G) 2 or higher NT [3]. Despite this, carboplatin and paclitaxel continues to be the mainstay intravenous chemotherapy regimen in patients with advanced ovarian cancer based on several randomized clinical trials [3-5].

While NT may not be considered by patients to be as concerning as other symptoms such as pain or fatigue, it is more likely to be persistent and long-lasting even after discontinuation of therapy [6-7]. Up to 23% of patients may suffer from residual neuropathy 48 months after treatment, and this may have significant effects on quality of life (QoL) and activities of daily living [8]. Several management options exist once NT develops on combination platinum and taxane chemotherapy, including a dose reduction, dose delay, prolongation of taxane infusion, or replacement of the taxane with a different non-platinum agent. From Gynecologic Oncology Group (GOG) protocol 182, it is understood that reduction of the cycles of paclitaxel administered can potentially reduce the incidence of G 2 or higher peripheral neuropathy from approximately 25% to 15% [3]. Vasey, et al reported the

incidence of G2 or higher neuropathy was 11% in patients treated with docetaxel, as opposed to 30% in patients treated with paclitaxel, in combination with carboplatin [9]. Others have also reported decreased rates of NT with combinations of carboplatin with gemcitabine or pegylated liposomal doxorubicin (PLD), as opposed to paclitaxel [10-11].

In light of the above findings, treatment with docetaxel has been an acceptable alternative to paclitaxel in many GOG trials. Despite the practice of allowing patients to discontinue paclitaxel and resume treatment with docetaxel in the setting of NT, there have been no studies documenting the course of NT after dose substitution. Thus, prior to the continuous recommendation of docetaxel as an acceptable alternative to paclitaxel, an exploration into the course of toxicity after substitution should be documented. The objective of this study was to document the disease and patient characteristics associated with the development, severity, and progression of NT on the most recent completed phase III GOG trial in advanced ovarian cancer, protocol 218, and to evaluate whether replacement of paclitaxel with docetaxel results in improvement of NT once it develops.

METHODS

GOG-218 is a randomized, phase III clinical trial evaluating the addition of bevacizumab to standard carboplatin and paclitaxel chemotherapy in patients with advanced ovarian cancer [12]. While the primary objective of this trial was to compare the overall survival (OS) among patients on these regimens, a secondary objective of the main study included comparisons of the incidence of severe toxicity and the QoL of patients treated with these regimens. QoL was compared between regimens with the use of the Trial Outcome index of the Functional Assessment of Cancer Therapy-Ovary (FACT-O TOI) survey. NT was measured by the National Cancer Institute Common Toxicity Criteria Adverse Events version 3.0 (NCI-CTC v3.0). This ancillary project exploring neurotoxicity was an unplanned subset analysis.

Eligibility criteria for this ancillary data study included patients enrolled on GOG-218 who reported G 1 NT. There were no exclusion criteria. Patients were triaged according to the following algorithm if NT developed: 1) for G 2 NT on paclitaxel, one dose reduction and a treatment delay of up to three weeks to allow the NT to return to G 1; 2) for persistent G 2 NT on paclitaxel, a substitution to docetaxel; 3) for G 3-4 NT on docetaxel, a treatment delay of up to three weeks; and 4) discontinuation of docetaxel if toxicity did not return back to G 2 after 3 weeks.

Incidence and severity of NT as measured by the CTC v3.0 were collected and recorded prior to each cycle of chemotherapy. Patient and disease characteristics were investigated including age, stage of disease, performance status, and baseline FACT-O TOI scores. The development of peripheral neuropathy was defined as either sensory or motor neuropathy CTC G 1 at any cycle. The severity of NT was documented as the maximum CTC grade recorded during the study. Progression of neuropathy was diagnosed if the maximum CTC grade increased beyond that which was reported at the first time. Improvement of NT was defined as a decline in CTC grade from the previous cycle. The associations between the development, severity, and progression of peripheral neuropathy and patient's age,

performance status, disease stage, and baseline FACT-O TOI score (by quartiles) were explored using generalized linear model with adjustment for treatment assignment [13]. The association between substitution with docetaxel and the improvement of NT was explored by fitting generalized estimating equations (GEE) [14], adjusting for the treatment cycle and CTC grade at the previous cycle. All patients gave written informed consent prior to enrollment in the primary study in compliance with all local Institutional Review Board and federal guidelines.

RESULTS

One-thousand-eight-hundred-seventy-three patients were enrolled and eligible for GOG-218. Of them, 1,864 patients received at least one cycle of study chemotherapy and therefore were evaluable for evaluating chemotherapy-related peripheral neuropathy. Of those, 1,329 (71%) developed G 1 neurotoxicity. In 90% of these patients, the NT developed in the main six-cycle chemotherapy course. The worst NT could have occurred at any cycle of chemotherapy. Nearly half these patients developed NT within the first two cycles of chemotherapy, with 31% of patients developing G 2 NT, and 7% of patients developing G 3 NT (Table 1). However prior to cycle 4, 42% patients had G 1 NT, 18% had G 2 and 10% had G ≥ 3 . After 6 cycles of chemo, 17% patients had G1, 30% had G 2 and 32% had G ≥ 3 . Dose modification was made on 755 patients. Of them, 200 patients did not have NT, 316 had G 1 NT, 177 had G 2 and 62 had G 3 NT.

Patient and disease characteristics were analyzed, including age, performance status, disease stage, and baseline QoL by FACT-O TOI score. Patients with poor performance status (PS=2) or advanced disease (stage IV) tend to have less chance to develop NT (Table 2).

Although not necessarily associated with the development of NT, poor baseline QoL was significantly associated with increased severity of NT ($P=0.01$). Age groups 60-69 and ≥ 70 as well as those with pre-treatment FACT-O TOI scores in the 1st and 2nd quartiles developed more severe NT (Table 3). In regards to NT progression, age and poor baseline QoL were the only factors associated with an increased incidence of progression or worsening of the grade of NT ($P<0.05$; Table 4). Figure 1 illustrates patient and disease characteristics associated with progression of neurotoxicity.

Among the 1,196 patients who developed NT within the main six-cycle chemotherapy course, 106 patients received docetaxel as the substitute for paclitaxel. Of those, 47 patients started with docetaxel at cycle 1 due to hypersensitivity to paclitaxel ($n=32$), fear of the development of NT ($n=4$), or other undisclosed reasons ($n=11$). Fifty-nine patients were switched to docetaxel during cycles 2-6 due to the development of NT ($N=32$), reaction to paclitaxel ($N=19$), and other undisclosed reasons ($N=8$). Of the patients who were switched to docetaxel at the onset of NT, 10 underwent substitution for G 1 NT, 14 for G 2, 16 for G 3, and 1 patient for G 4 NT (Figure 2). Seven patients who had been switched to docetaxel discontinued the taxane due to persistent NT. Analysis for the effect of substitution to docetaxel on NT did not show statistical evidence of improvement of NT after substitution (Odds Ratio (OR) 1.57, 95% CI 0.98-2.54, $p>0.05$). The rates of NT progression were roughly similar between the groups, 6% for paclitaxel, compared to 5% for docetaxel.

DISCUSSION

Several clinical trials have shown differences in NT rates with combinations of docetaxel, gemcitabine, or PLD with carboplatin, as compared to paclitaxel. GOG-182, which investigated the addition of an additional cytotoxic agent including gemcitabine, PLD, or topotecan to carboplatin and paclitaxel chemotherapy, did not show differences in OS or progression-free survival (PFS), but did reveal significant differences in the rates of neuropathy among the different regimens [3]. Specifically, the doublet therapy arms, including carboplatin and topotecan or carboplatin and gemcitabine, followed by carboplatin and paclitaxel, thus resulting in only four cycles of paclitaxel, resulted in the lowest rates of peripheral neuropathy, while the standard arms of carboplatin and paclitaxel and the triple-therapy arms, which included additions of gemcitabine or PLD, resulted in the highest rates of neuropathy. This established the principle that a reduction in the dose of paclitaxel is associated with decreased rates of NT.

The SCOTROC (Scottish Randomized Trial in Ovarian Cancer) trial compared the efficacy, tolerability, and QoL outcomes of carboplatin, docetaxel to carboplatin, and paclitaxel chemotherapy [9]. Both groups had similar PFS, OS, and response rates. However, the carboplatin and docetaxel arm had significantly less overall and G₂ NT. Moreover, they noted similar global QoL scores, but substantial differences in symptom scores favoring docetaxel. The authors were able to conclude that carboplatin and docetaxel is an acceptable alternative for first-line chemotherapy in ovarian cancer.

The MITO-2 (Multicentre Italian Trials in Ovarian Cancer) trial similarly compared carboplatin and paclitaxel with carboplatin and PLD as first-line therapy [11]. Comparing toxicities between regimens, PLD was associated with significantly lower rates of NT than paclitaxel. PFS and OS was similar between the two groups, thus PLD may also be considered an alternative to paclitaxel in combination with carboplatin for first-line treatment of ovarian cancer.

Gordon et al. assessed the safety and efficacy of gemcitabine and carboplatin versus paclitaxel and carboplatin induction regimens with or without paclitaxel consolidation to assess superiority of gemcitabine [10]. PFS, the primary endpoint, was not statistically significant. OS was significantly longer for carboplatin and paclitaxel therapy in univariate analysis, however, in multivariate analysis, controlling for patient characteristics that slightly favored paclitaxel, there was no difference in OS. Toxicity profiles differed between the regimens, with the incidence of G₂ neuropathy being significantly higher (14% versus 2.2%) in the paclitaxel group compared with gemcitabine. Though not powered to demonstrate non-inferiority, the authors concluded that gemcitabine could be considered as an alternative to paclitaxel, in combination with carboplatin, in patients who may not be able to tolerate paclitaxel.

The above-mentioned studies were able to determine that NT rates were significantly decreased at the outset of chemotherapy with the above-named regimens, however, there have been no studies documenting the course of NT after a dose substitution. Though one of the aims of this GOG ancillary data study was to address whether the practice of substituting

docetaxel for paclitaxel in the setting of NT would be beneficial in improving symptoms, unfortunately, there was no statistical significance in the improvement of NT after dose substitution. Though there is not enough statistical evidence to show an association with docetaxel substitution and improvement of NT, the extremely low number of patients who actually received a dose substitution may have affected the analysis. Therefore, whether substitution with docetaxel improves NT symptoms once it develops, remains unclear. Furthermore, it may be that physicians and patients are underreporting symptoms for fear of dose reduction or substitution although this is difficult to prove retrospectively. This study also does highlight an apparent lack of adherence to planned algorithms for the management of NT given that the majority of patients were continued on paclitaxel despite the development of G 2 neuropathy.

Data from this study do reveal that age and poor baseline QoL are associated with the development of more severe and more progressive chemotherapy-induced NT. Though the increased rate of NT in elderly patients has not been consistently observed in other smaller studies, elderly patients on GOG-218 were significantly more likely to have G 3 NT. Elderly patients were also more likely to have progression of NT in this study. One recent retrospective review of paclitaxel toxicity in breast cancer patients did reveal significantly higher rates of G 3 neurosensory, neuromotor, neurocortical, and neurocerebellar toxicity in patients aged >65 years [15]. Age has been identified as an important risk factor for the development of chemotherapy-induced peripheral neuropathy, with elderly patients being more likely to have baseline peripheral neuropathy, predisposing them to the development of more severe toxicity with chemotherapy [16]. Moreover, in women receiving platinum agents in combination with paclitaxel, increasing age has been associated with increasing rates and severity of NT [17].

Patient reported outcomes are increasingly being used in clinical trials to determine tolerability of chemotherapeutic regimens and assess QoL during therapy. Traditionally, as in this study, assessment of peripheral neuropathy is made using subjective scores, such as the NCI-CTC system; however, these grades may not reflect the patient's perception of these symptoms. The GOG, in collaboration with the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System, developed a NT measurement tool, the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity (FACT/GOG-Ntx) [18]. An 11-item subscale of the FACT/GOG-Ntx was validated during GOG-177, correlating well with CTC grading, with a receiver operator curve AUC of 0.81 [19]. Incorporating psychometric data such as the FACT/GOG-Ntx may be invaluable in further evaluating the extent of neurotoxicity in patients undergoing platinum/taxane chemotherapy, as well as to assess the change in NT over time, and would be an important direction for future research.

Peripheral neuropathy is a significant dose-limiting toxicity associated with carboplatin/paclitaxel chemotherapy, management of which is limited by a paucity of data on the course of symptoms after intervention. From the current study, it does not appear that substitution of docetaxel for paclitaxel results in improvement of NT symptoms; however, results may be limited by the low rate of dose substitution in GOG-218. Therefore, use of docetaxel or other alternatives such as gemcitabine or PLD, should continue to be reasonable alternatives

perhaps especially in elderly or other populations that are high risk for NT. This study does highlight age and poor baseline QoL scores as potential risk factors for the progression of chemotherapy-induced peripheral neuropathy, yielding important factors that should be considered when starting a patient on standard carboplatin/paclitaxel chemotherapy for the primary treatment of ovarian cancer.

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RESEARCH HIGHLIGHTS

- Age and worse QoL at baseline are associated with chemotherapy-induced NT.
- Substitution of docetaxel does not improve NT symptoms, as examined in GOG 218.
- The use of non-taxane based doublets in upfront ovarian cancer therapy may be considered in certain patients.

Figure 1. Substitutions for Paclitaxel

Progression of Mean NT Grade from Onset to Worst by patient or disease characteristics.

Figure 2.
Peripheral neuropathy grade at the time of switching to docetaxel

Table 1

The chemo cycle when peripheral neuropathy first developed

Cycle	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	370	27.84	370	27.84
2	265	19.94	635	47.78
3	198	14.90	833	62.68
4	185	13.92	1018	76.60
5	106	7.98	1124	84.58
6	72	5.42	1196	90.12
>=7	133	10.01	1329	100

Table 2

Patient and Disease Characteristics Associated with the Development of Peripheral Neuropathy

Development of peripheral neuropathy					p-value
	No (N=535)		Yes (N=1329)		
Treatment Group					
CP	174	28.0	447	72.0	>0.05
CP+BEV	185	29.6	439	70.4	
CP+BEV->BEV	176	28.4	443	71.6	
Age Group					
<50	92	28.1	235	71.9	>0.05
50~59	165	27.4	438	72.6	
60~69	168	27.6	440	72.4	
>=70	110	33.7	216	66.3	
Performance Status					
0	262	28.2	667	71.8	0.007
1	218	27.1	586	72.9	
2	55	42.0	76	58.0	
Stage					
III	368	27.1	989	72.9	0.03
IV	167	32.9	340	67.1	
Baseline TOI Score *					
1 st Quartile	140	32.5	291	67.5	>0.05
1 st ~2 nd Quartile	115	25.0	345	75.0	
2 nd ~3 rd Quartile	112	26.5	310	73.5	
> 3 rd Quartile	116	26.7	318	73.3	

* 117 patients did not complete QOL assessment at baseline.

Table 3

Patient and Disease Characteristics associated with the severity of peripheral neuropathy

Severity of Peripheral Neuropathy (Grade)							
	1 (N=923)		2 (N=319)		>=3 (N=87)		P=
Treatment Group							
CP	318	71.1	105	23.5	24	5.4	>0.05
CP+BEV	304	69.2	104	23.7	31	7.1	
CP+BEV->BEV	301	67.9	110	24.8	32	7.2	
Age Group							
<50	177	75.3	51	21.7	7	3.0	<0.001
50~59	324	74.0	99	22.6	15	3.4	
60~69	303	68.9	107	24.3	30	6.8	
>=70	119	55.1	62	28.7	35	16.2	
Performance Statue							
0	474	71.1	153	22.9	40	6.0	>0.05
1	406	69.3	141	24.1	39	6.7	
2	43	56.6	25	32.9	8	10.5	
Stage							
III	684	69.2	240	24.3	65	6.6	>0.05
IV	239	70.3	79	23.2	22	6.5	
Baseline TOI Score [*]							
1 st Quartile	188	64.6	87	29.9	16	5.5	0.01
1 st ~2 nd Quartile	228	66.1	90	26.1	27	7.8	
2 nd ~3 rd Quartile	225	72.6	64	20.6	21	6.8	
>3 rd Quartile	235	73.9	66	20.8	17	5.3	

* 65 patients didn't completed baseline QOL assessment.

Table 4

Patient and Disease characteristics associated with the progression (worsening of grade) of peripheral neuropathy

Progression of Peripheral Neuropathy					
	No (N=1035)		Yes (N=294)		p-value
Treatment Group					
CP	353	79.0	94	21.0	>0.05
CP+BEV	337	76.8	102	23.2	
CP+BEV->BEV	345	77.9	98	22.1	
Age Group					
<50	195	83.0	40	17.0	<0.001
50~59	355	81.1	83	18.9	
60~69	343	78.0	97	22.0	
>=70	142	65.7	74	34.3	
Performance Statue					
0	521	78.1	146	21.9	>0.05
1	458	78.2	128	21.8	
2	56	73.7	20	26.3	
Stage					
III	768	77.7	221	22.3	>0.05
IV	267	78.5	73	21.5	
Baseline TOI Score *					
1 st Quantile	217	74.6	74	25.4	0.002
1 st ~2 nd Quantile	254	73.6	91	26.4	
2 nd ~3 rd Quantile	247	79.7	63	20.3	
>3 rd Quantile	263	82.7	55	17.3	

* 65 patients didn't completed baseline QOL assessment.