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Peripheral Neurotoxicity in Gynecologic Oncology Patients who Received Paclitaxel

Abstract

Background & Aim: Peripheral neurotoxicity is the frequent adverse effect of paclitaxel. This drug is commonly used in gynecologic oncology patients. However, the incidence rate of this toxicity was limited especially in Thai patients. We conducted this prospective study to identify the incidence rate of peripheral neurotoxicity in chemo naive gynecologic cancer patients who received paclitaxel.

Methods: Between June 2014-October 2015, 40 patients who planned to received paclitaxel 175 mg/m^2 plus carboplatin AUC = 5 were interviewed about the neurotoxicity by using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) for Adverse Events version 3.0. score before received the subsequent cycle of chemotherapy. The basic data and the grade of TNS were recorded.

Results: The mean age was 55.6 years and 77.5% were diagnosed as ovarian and endometrial cancer. The patients were interviewed before received cycle 2 in 40 cases, cycle 2-6 in 30 cases and at 1,2 and 3 months after cycle 6 in 30,25 and 6 cases, respectively. From 251 cycles of chemotherapy, the incidence rate of sensory impairment was 60.6%. Of these, was grade 1 at 55.4% and grade 2 that developed after 2 cycles at 5.2% while the incidence rate of motor impairment was only 7.9% and all were grade 1. However, 15.9% felt worse about neurotoxicity from the previous cycle of chemotherapy.

Conclusion: 60.6%of the patients who received paclitaxel reported sensory neurotoxicity which became worse after 2 cycles whereas a minority of the patients reported motor impairment.

Keywords: Peripheral neurotoxicity; Paclitaxel; Gynecologic cancer

Research Article

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Abbreviations: NCI-CTC: National Cancer Institute Common Toxicity Criteria; ADL: Activities of Daily Life

Introduction

Paclitaxel is commonly used with carboplatin as standard chemotherapy in the treatment of gynecologic cancer patients especially in cases of ovarian and endometrial cancer [1]. The principle mechanism of paclitaxel is to stabilize microtubules, block the late G2 mitotic phase of the cell cycle by polymerization and induce cell death while the action of carboplatin is predominantly at the interstrand DNA cross -link [2,3]. The major side effect of paclitaxel is peripheral neuropathy and has been previously reported to be as high as 60% [4]. The pathogenesis of this event is believed to be the interference of many systems such as microtubule-based axonal transportation, macrophage activation at both the dorsal root ganglion and peripheral nerve and spinal cord microglial activation [2]. Whereas the neurotoxicity caused by carboplatin was reported as being very low, only 6%, in the former study [5]. However, when a paclitaxel plus carboplatin regimen was used there were additive effects regarding peripheral neuropathy [2]. Typically, patients affected by paclitaxel induced peripheral neuropathy presented with paresthesia, numbness, and/or neuropathic pain in a stocking-and-glove distribution and myalgia. This toxicity can show minimal improvement a long time after stopping treatment [4]. Although paclitaxel and carboplatin are widely used in Thai gynecologic oncology patients, the incidence and severity of peripheral neuropathy in these patients were unclear. Hence, we conducted this prospective study to evaluate the incidence of paclitaxel plus carboplatin induced peripheral neuropathy.

Materials and Methods

After approval by the Research Ethics Committee of the Faculty of Medicine of Chiang Mai University, the chemo naive gynecologic oncology patients with whom it was planned to treat with a paclitaxel and carboplatin regimen between June 2014 and October 2015 were invited to participate in the study. The schedule of chemotherapy consisted of paclitaxel 175 mg/m^2 and carboplatin AUC 5 given intravenously (IV) for 3 hours and 1 hour, respectively. The premedication of dexamethasone (20 mg IV), H1 antagonists chlorpheniramine (10 mg IV) and diphenhydramine (50 mg PO), H2 antagonist ranitidine (50 mg IV), and antiemetic ondansetron (8 mg IV) were given 30 minutes before starting chemotherapy. The interval of each cycle was 3-4 weeks and the total number of cycles was 6-9, the variation depending on the decision by the physician. All the participants were interviewed by one of our researchers (W.U, N.P) about the neurotoxicity using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0) [6] before receiving the subsequent cycle of chemotherapy. The same researcher conducted the interviews

at the follow-up after the course of chemotherapy, usually every 3 months in the first year. The NCI-CTC score was divided into 5 grades, 1 to 5 in both sensory and motor neuropathy. Briefly, the sensory neuropathy scales equate to the following: grade 1 means asymptomatic loss of tendon reflex or paresthesia while grade 2 and 3 reveal more paresthesia without and with interfering to activities of daily life (ADL), respectively. Grade 4 means disabling and grade 5 is death. About motor neuropathy, grade 1 means asymptomatic weakness and grade 2 reveals more weakness but not interfering with ADL while grade 3 means greater weakness which does interfere with ADL, grade 4 is life- disabling and grade 5 is death. The patients were also asked about the comparable symptom in comparison with the previous cycles of chemotherapy, classifying them at three levels; better, same or worse. The basic clinical data including any underlying disease that might be affecting the neuropathy and the grade of neuropathy were recorded.

Results and Discussion

Results

There were 40 patients enrolled onto the study with a mean age of 55.6-years old. The basic clinical data is presented in Table 1. The most common diagnosis was ovarian cancer followed by endometrial cancer, cervical cancer, fallopian tube cancer and primary peritoneal adenocarcinoma. Four patients had underlying disease that might affect the neuropathy level. These include diabetes mellitus (3 cases) and rheumatoid arthritis (1 case). Most patients received 6 cycles of chemotherapy (33 cases, 82.5%) whereas the remaining received 1, 4 and 9 cycles in 1, 5 and 1 patient, respectively. Thus, from a total of 229 cycles, 251 interviews were completed to evaluate the neuropathic symptoms at the nine-follow-up times. These results are shown in Table 2. The rate of sensory neuropathy was 60.6% and most of them (55.4%) were grade 1 and the remaining 5.2% were grade 2. All of the neuropathic symptoms involved numbness in a stocking and glove distribution. Regarding motor neuropathy, the incidence was only 7.9%. All 7.9% developed grade 1 symptoms of myalgia. During receipt of 6 cycles of chemotherapy a range of levels of sensory neuropathy, between 30.0-70.0%, was recorded between the 1st and 7th follow up time. However, 3.3-33% of the patients reported the symptoms of neuropathy worsened at each follow up time while total worsening of symptoms was reported in 15.9% of cases. Nearly 60% reported the same symptoms from 251 totals follow up times as showed in Table 3. Of the 4 patients who had the underlying diseases, diabetes mellitus and rheumatoid arthritis, all developed grade 1 sensory and motor neuropathy.

Discussion

The incidence of peripheral neuropathy in patients who received carboplatin plus paclitaxel in the present study was 60.6%. This incidence rate was closely in line with a previous report by Argyriou et al. that studied peripheral neuropathy in 21 adult non-myeloid malignancy patients who received carboplatin AUC 5 plus paclitaxel 175 mg/m^2 for 6 courses and found 66.6% of them developed peripheral neuropathy [7]. Another paper gave an explanation of taxane-induced reporting that only peripheral neuropathy might be from an inability of paclitaxel to cross the blood-brain barrier, therefore only peripheral neurons are affected [8]. Recent evidence revealed that the important activating factor as regards taxane-induced neuropathy is the accumulation of a dosage of more than 1,000 mg/m^2, the prior or concomitant administration of platinum compounds, pre-existing peripheral neuropathy from several medical conditions, and a 3-hour's infusion time [4]. However, in the present study, 30% of the patients developed grade 1 sensory neuropathy even when they only received one cycle, this number reaching 70% in the subsequent courses. This result was supported a previous publication from Pachman et al [9] that mentioned the peripheral neuropathy from chemotherapy could be started within weeks to months after initial treatment and reach a peak at, or after, the end of treatment and most cases are only partially reversible, and some cases can be permanent. In our patients, about 15% felt worse after they received the former cycle.

Table 1: Basic clinical data (N=40).

	N (%)
Mean age (SD)	55.60 (9.48)
Diagnosis	
Corpus	8 (20.0)
Cervix	4 (10.0)
Ovary	23 (57.5)
Tube	3 (7.5)
PPA	2 (5.0)
Stage	
I	14(35.0)
II	7(17.5)
III	17(42.5)
IV	2(5.0)
Mean dose of paclitaxel (mg;SD)	258.65 (29.64)
Mean dose of carboplatin (mg;SD)	491.62 (123.66)
Mean BMI (kg/m^2;SD)	22.92 (5.38)
Underlying disease	
None	23(57.5)
Diabetes mellitus	3(7.3)
Rheumatoid arthritis	1(2.5)
Current drug use	
None	29(72.5)

Regarding the motor neurotoxicity from paclitaxel, the incidence from the present study was only 7.9% all developing grade 1. This incidence was less than that cited in the previous report by Freilich et al. that found an incidence rate of motor neuropathy of 17% in 54 prospectively followed patients. The symptom was mild proximal muscle weakness and reversible.

The etiology of this motor neuropathy might be from the taxane induced distal axonopathy and proximal denervation [10]. To work towards the prevention of this toxicity, the American Society of Clinical Oncology recently carried out a systematic review from 48 randomized controlled trials and summarized that no agents recommended for the prevention of chemotherapy induced peripheral neuropathy and for the treatment of this neuropathy, the best evidence showed a moderate recommendation of prescribing duloxetine with inconclusive evidence from treatment with tricyclic antidepressants, gabapentin and blacofen topical gel that are all frequently effective in the management of other causes of neuropathy. Therefore, when prescribed these drugs to treat chemotherapy induced neuropathy, the patients needed to be informed about the limited benefit evidence [11]. The limitation of the present study was the low number of the patients enrolled onto the study and the short follow up time after completion of the course of chemotherapy. However, with the minimal data available to date of taxane-induced peripheral neuropathy, especially in Thai patients, this study can be viewed as a piece of pilot research does reflect the real-life practice because a relatively simple method was used to evaluate the neuropathy, as is used in everyday medicine.

Table 2: Neurotoxicity in accordance with National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0).

Follow up Grade	Sensory							Motor						
	None	1(%)	2(%)	3	4	5	Total	None	1(%)	2	3	4	5	Total
1	28	12(30.0)	-	-	-	-	40	34	6(15.0)	-	-	-	-	40
2	13	17(56.7)	-	-	-	-	30	28	2(6.7)	-	-	-	-	30
3	10	18(60.0)	2(6.7)	-	-	-	30	28	2(6.7)	-	-	-	-	30
4	9	18(60.0)	3(10.0)	-	-	-	30	27	3(10.0)	-	-	-	-	30
5	9	19(63.3)	2(6.7)	-	-	-	30	27	3(10.0)	-	-	-	-	30
6	9	18(60.0)	3(10.0)	-	-	-	30	28	2(6.7)	-	-	-	-	30
7	10	19(63.3)	1(3.3)	-	-	-	30	29	1(3.3)	-	-	-	-	30
8	11	13(52.0)	1(3.3)	-	-	-	25	25	-	-	-	-	-	25
9	-	5 (83.3)	1(3.3)	-	-	-	6	5	1(3.3)	-	-	-	-	6
Total	99	139(55.4)	13(5.2)	-	-	-	251	231	20(7.9)	-	-	-	-	251

Table 3: Descriptive symptoms of neurotoxicity.

Follow up Time Grade	Better (%)	Same (%)	Worse (%)	Total
1	7(17.5)	21(52.5)	12(30.0)	40
2	-	20(66.7)	10(33.3)	30
3	-	24(80.0)	6(20.0)	30
4	2(6.7)	24(80.0)	4(13.3)	30
5	1(3.3)	24(80.0)	5(16.7)	30
6	4(13.3)	25(83.3)	1(3.3)	30
7	10(33.3)	15(50.0)	5(16.7)	30
8	6(24.0)	11(44.4)	7(28.0)	25
9	1(16.7)	4(66.7)	2(33.3)	6
Total	24 (9.6)	147(58.6)	40(15.9)	251

Conclusion

In conclusion, 60.6% of the chemo naive patients treated with paclitaxel plus carboplatin developed peripheral neuropathy but this was limited to grade 1-2, only a minority of the patients reporting motor impairment. Physicians should be aware of this toxicity, checking for its occurrence at every visit during the surveillance time.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

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