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The trend of chemotherapy-induced peripheral neurotoxicity in ovarian cancer survivors and its impacts on daily life during and one year after treatment

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Summary

Purpose: To explore the trend of progression and regression of peripheral neuropathy (PN) induced by combination of carboplatin and paclitaxel, and the impacts on daily activities. *Materials and Methods:* PN was evaluated by nurse-based interview and patient-reported measures in their diary. The severity of PN scaled by National Cancer Institute Common Toxicity Criteria (NCI-CTC) before each cycle of chemotherapy and at three, six, and 12 months after drug withdrawal and coded as Grade I ~ V. *Results:* The authors enrolled 106 eligible patients with ovarian cancer who underwent six cycles of combined chemotherapy of carboplatin plus paclitaxel. No patients showed Grade IV and V of PN and it was gradually aggravated following the dose accumulation. About 29.3% of the patients presented no PN, 64.2% Grade I, and 6.6% Grade II after the third course of chemotherapy, but increased to 36.8% of Grade I, 25.5% of Grade II, and 34.9% of Grade III after the sixth course of chemotherapy. At one-year follow-up, the rate of PN still existed with the rate of 88.5%, 57.3%, and 38.7% at three, six, and 12 months after drug withdrawal. Thirty-one patients encountered accidents, such as sharp injury (14.2%), fall (9.4%), burn (3.8%), and cold injury (1.9%). *Conclusions:* A significant proportion of patients with epithelial ovarian cancer treated with carboplatin plus paclitaxel suffer long term neuropathy and it affects patient's daily activities. Specialized care is necessary to provide not only during treatment, but also months to years after drugs withdrawal.

Key words: Peripheral neuropathy (PN); Chemotherapy; Ovarian cancer; Impact; Follow-up.

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is one of common side effects of many prescribed chemotherapy drugs. CIPN results in diverse clinical symptom patterns and leads to some degree of physical problems, emotional distress, and even impairment of social role [1]. Its onset may have a strong impact on the quality of life as well as on the daily life activities of cancer patients. The combination of paclitaxel and carboplatin, as the first-line protocol for epithelial ovarian cancer, frequently induces PN, even at lower cumulative dose [2]. To the present authors' best knowledge, there are few studies assessing the clinical long-term trend of CIPN induced by combination of carboplatin and paclitaxel in female patients after treatment discontinuation. Understanding the long-term style of CIPN might be beneficial to determine the preventative strategies, inform physicians of the permanent side effects of anti-neoplastic drugs, and guide caregivers to provide pertinence nursing care during the special period. The aim of this study is to systemically record the trend of progression and regression of PN induced by combination of carboplatin and paclitaxel, and the impacts on the daily life activities of ovarian cancer patients.

Materials and Methods

Subjects and procedures

All patients with ovarian cancer scheduled for receiving carboplatin and paclitaxel chemotherapy in the hospital were enrolled into the study. Enrollment period was from June 2011 to June 2013. Enrollment criteria included (1) age ranged from 30 to 65 years; (2) epithelial ovarian cancer confirmed by pathologic diagnosis; (3) FIGO Stage I to III; (4) scheduled to receive six cycles of carboplatin plus paclitaxel; (5) no history of neuropathy disease, electrolyte disturbance, diabetes mellitus or mental disease; (6) no history of radiotherapy or chemotherapy; (7) expected life longer than one year. Exclusion criteria were (1) inability to read and write; (2) radiotherapy received during chemotherapy or within 12 months after antineoplastic drug discontinued; (3) less or more than six courses of carboplatin and paclitaxel received.

Paclitaxel at 175 mg/m^2 was administered as a three-hour intravenous infusion on the first day of chemotherapy. All patients received oral dexamethasone 15 mg administered at 12 and six hours before paclitaxel. A one- to two-hour intravenous infusion of carboplatin to an AUC of 6 was administered on the second day. Cycles were repeated at the interval of 21-28 days. This dose remained fixed for all cycles, unless toxicity necessitated a reduction.

The common symptoms of CIPN, including tingling, weakness, numbness, pain, and unable to walk or climb stairs, were listed in

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Table 1. — *The National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0.*

	Grade I	Grade II	Grade III	Grade IV	Grade V
Neuropathy, motor	Asymptomatic, weakness on exam testing only	Symptomatic weakness, interfering with function but not interfering with ADL*	Weakness interfering with ADL; bracing or assistance to walk (e.g., cane or walker) indicated	Life-threatening, disabling (e.g., paralysis)	Death
Neuropathy, sensory	Asymptomatic loss of tendon reflex or paresthesias (including tingling) but not interfering with function	Sensory alterations or paresthesias interfering with function but not interfering with ADL	Sensory alterations or paresthesias interfering with ADL	Disabling	Death

*ADL: activities of daily living.

a table in the diary. Before starting treatment, every participant was instructed how to use this table to record her symptoms, signs, and accidents that occurred due to CIPN in daily life. The task participant should perform was to tick the symptom they had on the table, or write down the additional feelings by words.

Data collection and analysis

Participants' social and clinical characteristics, including age, marital status, parity, education level, occupation, family income, diagnosis, FIGO Stage, and chemotherapy regimen were collected from medical records. CIPN was assessed by nurse-based questionnaire, physical examination, patient's diary, and scored according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0 (Table 1) [3] before each cycle of chemotherapy and at three, six, and 12 months after drug withdrawal and coded as Grade I ~ V. Meanwhile accidents occurring due to CIPN in daily life were stated by oral or diary.

All analyses were carried out using statistical Package for the Social Sciences version 16.0 software. Continuous variables were expressed as mean ± standard deviation, discrete variables as median (range), and counting data as number (percentage).

Ethical approval

This clinical study was approved by Hospital Ethical Committee. Informed consent was obtained from all participants before study commenced, including study purpose, privacy, right, and responsibility of both researchers and participant. All subjects enrolled were purely voluntary.

Results

Socio-demographic and clinical characteristics of subjects

A total of 113 epithelial ovarian cancer patients were enrolled into the study. Five patients either receiving less or more than six courses of chemotherapy were excluded. Two patients retreated from the present study due to their unwillingness to keep diary after the third cycle. The remaining106 patients ranged in age from 30 to 65 years, with a mean of 50.2 ± 8.6 years (SD). Among them, 103 patients (97.2%) were married with 95 patients (89.6%) giving birth at least to one child. Thirty-five patients (33.0%) were FIGO Stage I, 56 patients (52.8%) were FIGO Stage II, and 15 patients (14.2%) were FIGO Stage III. The follow-up rates were 98.1%, 97.2%, and 95.3% at three, six, and 12 months, respectively, after chemotherapeutic drugs were discontinued. Patient socio-demographic and clinical characteristics are summarized in Table 2.

Table 2. — *Patient social and clinical characteristics* (*n=106*).

Item		n.	%
Age (years)	30-40	14	13.2
	41-55	48	45.3
	56-65	44	41.5
Educational level (years)	< 10	43	40.6
	10-12	47	44.3
	> 12	16	15.1
Marital status	Single	3	2.8
	Married	82	77.4
	Divorced	12	11.3
	Widow	9	8.5
Parity	0	11	10.4
	≥ 1	95	89.6
Family income per month (Yuan in RMB)	≤ 100,000	17	16.0
	100,000~300,000	52	49.1
	> 300,000	37	34.9
FIGO Stage at diagnosis	I	35	33.0
	II	56	52.8
	III	15	14.2
Follow-up (months)	3	104	98.1
	6	103	97.2
	12	101	95.3

The progression and regression trend of PN induced by combination of carboplatin and paclitaxel

One hundred and six patients completed six cycles of chemotherapy on the regular dose without drug modification or dose reduction. There were no patients showing Grade IV and V of CIPN according to NCI-CTC version 3.0. The severity of CIPN was shown to gradually increase following the dose accumulation, and fade away with the withdrawal time. Specifically, the assessment after the third cycle showed that 64.2% of patients were evaluated as Grade I, 6.6% Grade II, and 29.3% cases were no CIPN, while after the sixth cycle, 36.8% in Grade I, 25.5% in Grade II, and 34.9% in Grade III. During the one-year follow-up, CIPN was observed in 88.5%, 57.3%, and 38.7% of patients at three, six, and 12 months, respectively, after chemotherapeutic drug withdrawal (Table 3, Figure 1).

Table 3. — *PN induced by combination of carboplatin and paclitaxel.*

Time	n.	None		Grade I		Grade II		Grade III	
		n.	%	n.	%	n.	%	n.	%
Cycle 1	106	83	78.3	23	21.7	0	0	0	0
Cycle 2	106	79	74.5	27	25.5	0	0	0	0
Cycle 3	106	31	29.3	68	64.2	7	6.6	0	0
Cycle 4	106	19	17.9	72	67.9	10	9.5	5	4.7
Cycle 5	106	4	3.8	37	34.9	36	34.0	29	27.4
Cycle 6	106	3	2.8	39	36.8	27	25.5	37	34.9
3 months after drug withdrawal	104	12	11.5	44	42.3	24	23.1	24	23.1
6 months after drug withdrawal	103	44	42.7	28	27.2	24	23.3	7	6.8
1 year after drug withdrawal	101	62	61.3	33	32.7	5	5.0	1	1.0

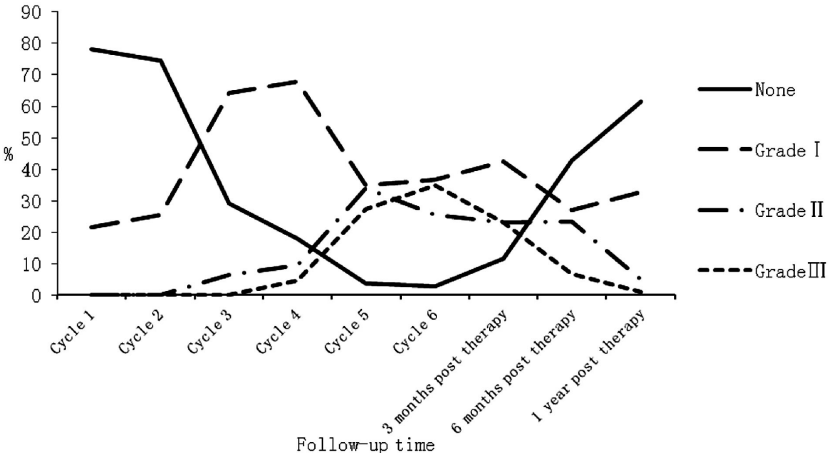

Figure 1. — Progression and regression trend of PN induced by carboplatin and paclitaxel.

Table 4. — *Patterns of CIPN and its impacts on patients" daily life.*

	N	%
Symptoms & signs		
Tingling	101	95.3
Numbness	56	52.8
Neuropathic pain	30	28.3
Loss of deep tendon reflexes (DTR)	37	34.9
Progressive neuromuscular weakness	59	55.7
Impact on daily activities		
Unable to walk ≥ 30 minutes	35	33.0
Unable to go up & down stairs	22	20.8
Assistance needed half of daily activity	54	50.9
Reluctant to join social activity	46	43.4
Sharp injury	15	14.2
Fall	10	9.4
Burn	4	3.8
Cold injury	2	1.9

The patterns of CIPN and its impact on patients' daily life

The patterns of CIPN induced by combination of carboplatin and paclitaxel were very variable. The impact on sensory impacts was more serious than that on motor. Among 106 patients, 95.3% complained of tingling, 55.7% complained of progressively neuromuscular weakness, and 50.9% patients needed assistance for half of their daily activity. Life accidents occurred in 31 patients, including sharp injury (14.2%), fall (9.4%), burn (3.8%), and cold injury (1.9%), as shown in Table 4.

Discussion

The peripheral nervous system can be vulnerable to anticancer drugs. The incidence and clinical features of CIPN are dependent on the type and dose of the agent involved. The combination of carboplatin and paclitaxel is the first-line regimen for epithelial ovarian cancer patients and has been widely used. Unfortunately, PN induced by carboplatin and paclitaxel is not rare. A retrospective research preformed by Pignata *et al.* showed that 54.2% (65/120) ovarian cancer patients receiving carboplatin and placitaxel developed CIPN [4]. Other studies also showed that up to 70% patients undergoing paclitaxel combined with either cisplatin or carboplatin could develop CIPN [2, 5]. In the present prospective study, the incidence of CIPN reached 97.2% after six cycles of chemotherapy, which was much higher than that in previ-

ous studies. The underlying reason could be that the authors used the double assessing system, both by nurses-based questionnaire and patient's self-report in the dairy. From a clinical point of view, cancer patients, to some extent, might be unwilling to actively report their CIPN because most of them would not be happy to modify treatment regimen or withdraw anticancer drugs, especially for those patients who are well-responsive to present drugs. However, the modification of chemotherapeutic drug is the common choice for doctors to limit the severity of CIPN. The double evaluation model may compensate for the hidden information and reflect the real situation. It also indicates that standard assessment instruments and procedures are needed for patients in order to make a decision with individualized treatment.

Besides the high incidence of CIPN during the treatment of carboplatin plus paclitaxel, a long-term existing side effects of CIPN in a certain proportion of patients was another difficult problem, as shown in Figure 1 and Table 3. Nicole *et al.* also found that CIPN symptoms persisted on women with ovarian cancer who underwent chemotherapy treatment up to 12 years after drug withdrawal [6]. Both above results indicated that more attention should be paid not only on the treatment period but also months to years after drug withdrawal. However, the latter is easily overlooked by both caregivers and patients themselves.

Currently, little is known about the pathogenetics of CIPN. American Society of Clinical Oncology (ASCO) Clinical Practice Guideline (2014) showed that no established agents were recommended for the effective prevention and treatment for CIPN in cancer patients undergoing treatment with neurotoxic agents [7]. The optimal management of CIPN patients is still an unmet clinical need. The modification of chemotherapeutic drug is currently the only available approach to limit the severity of CIPN in the majority of the patients. However, the delayed progression of CIPN may delay doctor's decision of drug modification, resulting in unavoidable CIPN. According to the data of Table 4, the impacts on patients' daily activities due to CIPN were obvious and accidents, such as sharp injury and fall, were not rare. It is strongly recommended that maintaining a safe environment, educating, and supporting patients to avoid accidents or injuries are of major focus of nursing care for patients with CIPN. Flow chart such as assessment and management of upper or lower extremities of CIPN is needed to guide oncologic nurses to care patient to and avoid relevant accidents. For example, if the patient has the problem of fine motor skill, sharp injury should be purposely prevented by avoiding kitchen duties. If the patient experiences progressive neuromuscular weakness, a cane, walker or wheelchair should be actively offered since fall is a concern.

The study had specific strengths. Firstly, the combined use of patients' diary and nurse-based assessment model were rarely applied in previous studies and might compensate for the hidden information and make the results more accurate. Secondly, the study clearly showed the trend of progression and regression of PN induced by carboplatin and paclitaxel from the first day of therapy to 12 months after chemotherapeutic drug withdrawal. Thirdly, follow-up rate of the samples were very high, which was up to 95.3% at 12 months after chemotherapy completion. However, the authors recognized the possible limitation of the present study. Standard evaluation scales for impacts of CIPN on patients' daily life was absent, and the findings regarding life activity impacts caused by CIPN should be further re-evaluated in future studies.

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