

Quantitative evaluation of chemotherapy-induced peripheral neuropathy by using intraepidermal electrical stimulation

FUMIE OYAMA, MASAYUKI FUTAGAMI, HIROE OIKIRI, ANNA TAKABAYASHI, ASAMI AKAISHI, TOMOE KODAMA, MAMI MATSUMOTO, MASAHIRO KANAMORI, MAIKA OISHI, RIE MIURA, HACHIDAI HIRAKAWA and YOSHIHITO YOKOYAMA

Department of Obstetrics and Gynecology, Hirosaki University Graduate School of Medicine, Hirosaki, Aomori 036-8562, Japan

Received November 26, 2018; Accepted March 18, 2020

DOI: 10.3892/mco.2020.2056

Abstract. Chemotherapy-induced peripheral neuropathy (CIPN) is a frequently observed treatment-related adverse effect, particularly associated with taxane-based chemotherapy, which affects the quality of life of the patients. To date, CIPN has been subjectively evaluated by patients or physicians. Intraepidermal electrical stimulation (IES) may be applied to evaluate the function of small fibers by measuring pain threshold, and assess the degree of diabetic peripheral neuropathy. The aim of the present study was to evaluate CIPN objectively by using IES. The pain threshold measured by IES in patients with gynecological cancer who underwent taxane-based chemotherapy was compared with the clinical grading scale of peripheral neuropathy (National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0). A total of 57 patients were evaluated (151 measurements). The median age of the patients was 63 years. The number of measurements with clinical grades of 0, 1 and ≥ 2 was 49, 57 and 45, respectively. The mean pain threshold was 0.1, 0.14 and 0.18 mA for grades 0, 1 and ≥ 2 , respectively. Therefore, the mean pain threshold significantly increased with the progression of the clinical grade. The measurement of pain threshold by using IES may be a reliable indicator for quantitative evaluation of CIPN.

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common side effects of chemotherapy (1). Approximately $\geq 70\%$ of patients with ovarian cancer

undergoing chemotherapy, particularly paclitaxel, develop CIPN (2). The predominant symptoms of CIPN are sensory disorder, numbness, tingling sensation and pain. Occasionally, CIPN leads to motor dysfunction. The factors affecting the development of CIPN include the type of chemotherapy, such as platinum agents, taxanes and vinca alkaloids, administration method, patient age, and pre-existing peripheral neuropathy, such as diabetes mellitus (3). One of the critical problems in CIPN is the dose-limiting toxicity of chemotherapy. Some patients who are responsive to chemotherapy are unable to continue the treatment due to CIPN. Furthermore, CIPN may be a persistent side effect. The probability of persistent CIPN 6 months after completion of chemotherapy is 15%, and the probability at 2 years after completion of chemotherapy is 11% (4). The treatment and prevention of CIPN are not yet clearly established.

CIPN can be evaluated using various methods, but there are currently no standard methods for the evaluation of CIPN, which hinders early treatment of this condition (5). The diagnosis of CIPN is mainly clinical. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (6) version 4.0, the scale most commonly used for CIPN grading, is evaluated by physicians, nurses and other clinical staff (7). The European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC-QLQ)-CIPN20 and THE Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) are commonly used as patient-based assessments (8,9). However, the assessment by physicians and patients is subjective.

There are few reports regarding the instrumentation required for quantitative evaluation (7,10-13). Intraepidermal electrical stimulation (IES) has been reported as a non-invasive and quantitative measurement method for the evaluation of diabetic neuropathy (14-16). The aim of the present study was to evaluate CIPN by using IES instruments.

Materials and methods

Subjects. This was a retrospective study that enrolled 57 patients who underwent taxane-based chemotherapy for gynecological cancer at Hirosaki University Hospital between

Correspondence to: Professor Yoshihito Yokoyama, Department of Obstetrics and Gynecology, Hirosaki University Graduate School of Medicine, 5-Zaifu-cho, Hirosaki, Aomori 036-8562, Japan
E-mail: yokoyama@hirosaki-u.ac.jp

Key words: chemotherapy-induced peripheral neuropathy, intraepidermal electrical stimulation, quantitative evaluation, paclitaxel, objective measurement

April 2017 and April 2018. The median age of the patients was 63 years (range, 40-86 years). The criteria for eligibility included i) current or previous history of taxane-based chemotherapy; ii) Eastern Cooperative Oncology Group performance status of 0-3; iii) consent to participate in this study. The exclusion criteria included pre-existing peripheral neuropathies, such as diabetic and alcoholic neuropathy, and rheumatoid arthritis. Conventional paclitaxel dose (175 mg/m^2) and a platinum-based chemotherapy (carboplatin; area under the blood concentration curve=6; cisplatin, 75 mg/m^2) with or without bevacizumab (15 mg/kg) were administered every 3 weeks. The weekly dose of paclitaxel was 80 mg/m^2 . The protocol of the present study was approved by the Institutional Review Board (IRB) of the Hirosaki University Graduate School of Medicine (IRB approval no. 2016-263). Informed consent was obtained from all the patients.

Evaluation of CIPN. CIPN was clinically evaluated by using CTCAE version 4.0. Simultaneously, CIPN was evaluated by using IES. IES instruments were used as previously described (16). Briefly, a disposable, concentric bipolar needle electrode was used for IES (NM-983W; Nihon Kohden Corp.), which consists of three concentric bipolar needle electrodes with an outer ring (1.3 mm in diameter), and the cathode is an inner needle that protrudes 0.2 mm from the outer ring (Fig. 1A). By gently pressing the electrode against the skin, the needle tip was inserted into the epidermis where the nociceptors are located, while the outer ring remained attached to the skin surface. The IES electrode was placed onto the skin of the dorsum of the hand. The temperature of the skin was maintained at $\geq 30^\circ\text{C}$. Subsequently, a stimulator (PNS-7000; Nihon Kohden Corp.) was used for IES (Fig. 1B) (14). When a button was pushed, a weak electric stimulation was delivered to the attached skin, and the patients pushed the hand switch button as soon as they felt a sensation. The stimulation was started at an intensity of 0.5 mA. Subsequently, the intensity was gradually decreased by 0.05 mA until the patients no longer felt the sensation. When the patients felt the sensation thrice at the same current intensity, this intensity was defined as the pain threshold. The evaluation was performed prior to chemotherapy and for each of the three cycles. The mean number of chemotherapy cycles administered to the patients was 7. During admission or in the outpatient clinic, the measurement was performed when the patients experienced symptoms of CIPN, such as the severe sensory disorder, numbness, tingling and pain. Even if the patients did not report CIPN symptoms, the evaluation of CIPN was performed at least every 3 cycles. The endpoint of the study was confirming the correlations between CIPN grade and the pain threshold by using PNS-7000 and CTCAE version 4.0.

Statistical analysis. Kruskal-Wallis test followed by Dunn's multiple comparison test was used for the measurement data from each group. $P < 0.05$ was considered to indicate statistically significant differences.

Results

Patient background. A total of 57 patients were enrolled in the present study, and the number of IES measurements was 151.

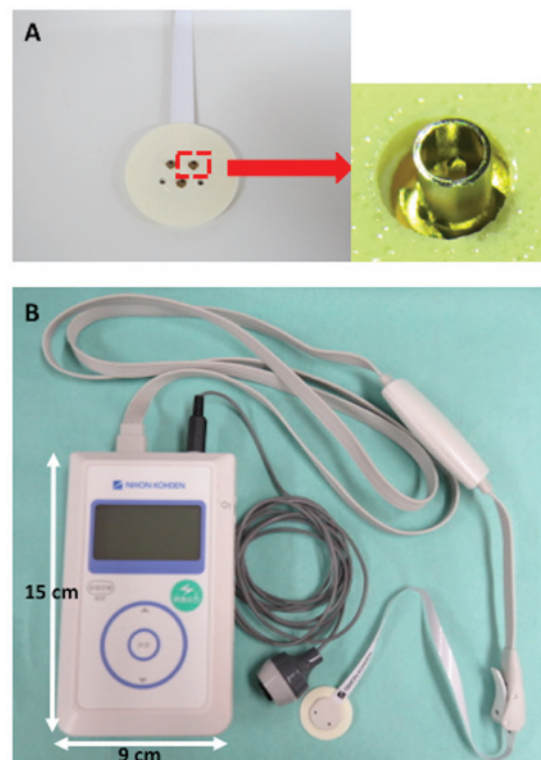


Figure 1. Intraepidermal electrical stimulation (IES). (A) A disposable, concentric bipolar needle electrode was used in the present study, which consists of three concentric bipolar needle electrodes with an outer ring (1.3 mm in diameter), and the cathode is an inner needle that protrudes 0.2 mm from the outer ring. The red arrow shows a magnified image of a needle electrode. (B) Appearance and dimensions of a IES device.

The characteristics of the patients are summarized in Table I. The median age was 63 years (range, 40-86 years). The type of cancer was ovarian in 24 cases, uterine endometrial in 20, peritoneal in 5, uterine cervical in 4, fallopian tube in 2, and primary unknown cancer in 2 cases. Chemotherapy was performed as initial treatment in 42 cases and as treatment for recurrence in 15 cases. Paclitaxel was included in all chemotherapy regimens (Table II). The number of chemotherapy cycles and the type of chemotherapy regimens are shown in Table II. Only first-line regimen was performed in most cases. The number of patients with CIPN was 54 (94.7%) (Table I).

The characteristics of patients with CIPN are listed in Table III. The number of patients with CIPN grades 1 and >2 was 31 and 23, respectively. No significant differences were found for age, type of cancer, cumulative dose of paclitaxel and treatment for CIPN between the two groups. The onset of CIPN occurred in 34 patients (63.0%) after 1 treatment cycle. Persistence of CIPN was observed in 21 (53.8%) of the 39 patients who completed chemotherapy. There was no significant correlation on between CTCAE grade and paclitaxel dose or type of chemotherapy regimen by Pearson's correlation coefficient test.

Measurement of pain threshold by using IES. CIPN measurement was performed for a mean of 1.75 times per patient. The distribution of CIPN measurements was as follows: 1 time in 32 patients, 2 times in 13 patients, 3 times in 7 patients, 4 times in 4 patients, and 5 times in 1 patient.

Table I. Patient characteristics.

Characteristics	No.
Median age, years (range)	63 (40-86)
Primary site of cancer	
Ovary	24
Uterine endometrium	20
Peritoneum	5
Uterine cervix	4
Fallopian tube	2
Primary unknown	2
Purpose of chemotherapy	
Initial treatment	42
Recurrence	15
Chemotherapy-induced peripheral neuropathy	
Yes	54
No	3

Table II. Number and type of chemotherapy regimen.

Line of chemotherapy				No. of patients
1st	2nd	3rd	4th	
TC	None	None	None	45
TC	DC	None	None	2
TC	PLD	None	None	2
TC	IAP	None	None	1
TC	CPT-11	None	None	1
TC	EC	DC	None	2
TC	DC	TC	None	2
TC	CPT-11 + PLD	T	GEM	2

TC, paclitaxel + carboplatin; DC, docetaxel + carboplatin; PLD, pegylated liposomal doxorubicin; IAP, ifosfamide + adriamycin + cisplatin; EC, epirubicin + carboplatin; CPT, irinotecan; T, paclitaxel; GEM, gemcitabine.

The association between pain threshold and clinical grading scale (NCI-CTCAE version 4.0) in 151 measurements is shown in Fig. 2. The number of measurements with clinical grades of 0, 1 and ≥ 2 was 49, 57 and 45, respectively. The mean pain threshold in grade 1 was significantly increased compared with that in grade 0 (0.1 ± 0.07 vs. 0.14 ± 0.05 mA, respectively; $P=0.024$). Similarly, the mean pain threshold in grade ≥ 2 was significantly increased compared with that in grade 0 (0.18 ± 0.12 vs. 0.1 ± 0.05 mA, respectively; $P=0.000$). The mean pain threshold in grade ≥ 2 was increased, with a marginal significance compared with that in grade 1 (0.18 ± 0.12 vs. 0.14 ± 0.07 mA, respectively; $P=0.098$). Therefore, the mean pain threshold gradually increased with the progression of clinical grading scale.

Only 2 cases suffered from grade 3 CIPN and are briefly presented below:

Case 1. A 68-year-old woman who was treated with 3 cycles of combined paclitaxel and carboplatin (TC) for stage IIIb (International Federation of Gynecology and Obstetrics) ovarian carcinosarcoma developed grade 3 CIPN after 3 cycles of TC, and the pain threshold was 0.45 mA at that time. A computed tomography scan revealed a pelvic mass 3 months after the initial surgery. The patient was treated with ifosfamide + adriamycin + cisplatin chemotherapy. The pain threshold gradually decreased by 0.05 mA and the patient displayed no CIPN at 4 months after the change in chemotherapy regimen.

Case 2. A 70-year-old woman who was treated with 2 cycles of TC as adjuvant chemotherapy for uterine endometrial cancer experienced severe numbness and tingling of her fingertips and the tips of her toes. The patient was diagnosed with grade 3 CIPN and the pain threshold at the time was 0.20 mA. TC chemotherapy was switched to docetaxel and carboplatin (DC). However, the patient suffered from ileus and severe constipation, likely caused by the DC regimen. After that, chemotherapy was discontinued due to the CIPN and those adverse effects. The symptoms subsided but became less serious after chemotherapy discontinuation.

Discussion

The frequency of CIPN in the present study was 94.7%, which is higher compared with that reported previously (17). In the present study, all regimens were paclitaxel-based. However, the results may depend on the CIPN evaluation method. Therefore, the method for evaluation is crucial. Persistence of CIPN was seen in 21 (53.8%) of 39 patients who completed chemotherapy. This percentage is markedly higher compared with that reported previously (18,19). Therefore, it is urgent to establish a standard method for the evaluation of CIPN.

CIPN has been subjectively evaluated to date. Physician-based grading scales are widely used in the clinical practice and trials, but the evaluation methods differ among physicians. Thus, the number of patient-reported evaluation methods, including EORTC-QLQ-CIPN20 and FACT/GOG-Ntx, have increased recently. However, there are several issues in the evaluation of CIPN. Some patients do not fully understand the content of the questionnaire, and a significant discordance was observed between physician- and patient-reported CIPN (5).

Therefore, a consensus-based standardized CIPN evaluation method is urgently required. One of the objective assessment methods includes the use of a nerve conduction device (11). This device demonstrated that the progression of CIPN was associated with a significant decrease in sensory nerve action potential. However, this method is not prevalent worldwide. Additional objective assessment methods include quantitative pain measurement, IES and Pain Vision[®] (7,10,12,13). These devices quantify the degree of pain by measuring the lowest perceptible current and the current at which pain is perceived. The benefits of both devices include that they are non-invasive, painless, are associated with low discomfort, and do not require special skills to operate. The disadvantages include the condition being more costly compared with subjective assessments

Table III. Characteristics of patients with CIPN.

Characteristics	Grade1 (n=31)	Grade ≥ 2 (n=23)
Age (years) \pm standard deviation	63 \pm 10.6	59 \pm 9.7
Primary site of cancer, n		
Ovary	12	9
Uterine cervix	2	2
Uterine endometrium	14	6
Fallopian tube	0	2
Peritoneum	2	3
Primary unknown	1	1
Total dose of paclitaxel, mg	1,500 \pm 1,110.4	1,440 \pm 1,064.4
Treatment for CIPN (Plural treatment was used for CIPN in some cases), n		
Herbal medicine	30	23
Pregabalin	18	16
NSAIDs	1	10
Other	0	1
Onset of CIPN, n		
After 1 cycle	18	16
After 2 cycles	9	4
After 3 cycles	3	3
After 4 cycles	1	0

CIPN, chemotherapy-induced peripheral neuropathy.

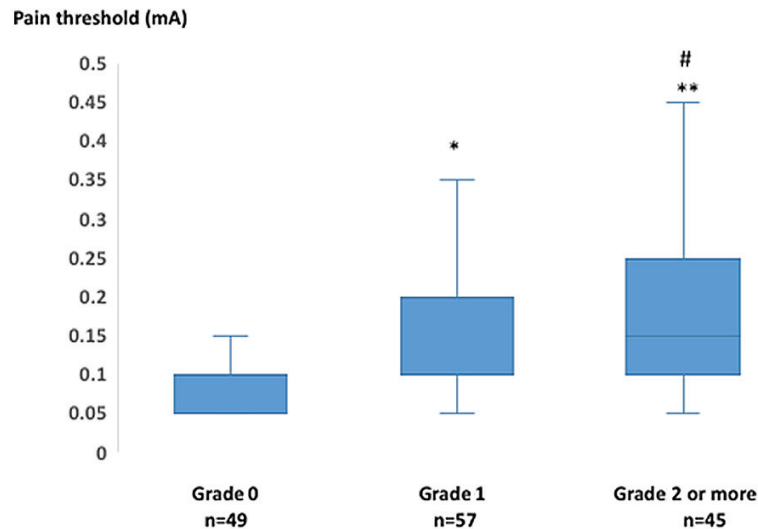


Figure 2. Association between pain threshold and clinical grading scale (National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0). * $P=0.024$, grade 0 vs. 1; ** $P=0.000$, grade 0 vs. 2; and # $P=0.098$, grade 1 vs. 2.

and the necessity of an examination room for operating the devices.

The PNS-7000 was employed to evaluate CIPN. This device was used for the quantitative measurement of diabetic neuropathy, and the results demonstrated that the mean pain threshold by PNS-7000 gradually increased with the progression of clinical grading scale. To the best of our knowledge, this is the first study to employ PNS-7000 for the assessment of CIPN. PNS-7000 may prove to be a non-invasive and

convenient tool to evaluate CIPN. The size of PNS-7000 is 15x9 cm, and its weight is 290 g, making it easy to carry and the evaluation may be performed anywhere, including at the bedside. The cost of PNS-7000 is relatively lower compared with that of other devices used for the measurement of CIPN. As regards objective assessment, the study sample was the largest to date.

Of note, PNS-7000 precisely clarified the clinical grading scale in the present study. Pain Vision[®] is a similar device,

and no difference in pain degree was observed between grades 1 and 2. These results may depend on the difference among the nerve fibers being stimulated. Pain is transmitted by three types of nerve fibers, depending on its properties. A β fibers transmit the senses of touch and pressure; A δ fibers transmit mechanical irritation, temperature and momentary pain; and C fibers transmit burning pain sensation. Pain Vision[®] mainly stimulates A β fibers. On the contrary, PNS-7000 selectively stimulates A δ and C fibers (12,14). This distinction of the type of nerve fiber may cause differences in the results. In the present study, the change in pain threshold of each case was manifested. Thus, the clinical relevance of this study is that we can determine objective CIPN.

There were several limitations to the present study. First, this study was conducted in a single institution. Although this was the largest objective study on the measurement on CIPN to date, a larger patient sample is required, and the study must be performed in a similar manner at multiple institutions. Second, the result of IES were compared with clinical grading score using CTCAE version 4.0. Third, only one CIPN measurement was performed in 32 patients. This may reflect a low compliance with the study protocol, and may add uncertainty to the study results. In future studies, we aim to compare the results with patient-reported outcomes. PNS-7000 may help physicians to confirm the grade of CIPN, which may allow for early intervention. A large randomized validation study is urgently needed to verify the observations of the present study.

In conclusion, the measurement of pain threshold by using IES may prove to be a reliable indicator for quantitative evaluation of CIPN.

Acknowledgements

The authors would like to thank all members of the Gynecologic Oncology group of Hirosaki Graduate School of Medicine for their helpful discussion and advice regarding the present study.

Funding

The present study was supported by a Grant-in-Aid for Cancer Research from the Ministry of Education, Culture, Sports, Science and Technology, Tokyo, Japan (grant no. 17K11263).

Availability of data and materials

The datasets used and analyzed during the present study are available from the corresponding author upon reasonable request.

Authors' contributions

FO, MF and YY designed the project and experiments. HO, AT, AA, TK, MM, MK, MO, RM and HH measured CIPN by using IES clinically and also evaluated the CIPN grading of the patients. FO and MF analyzed the data obtained in the present study and generated the figures. FO and YY wrote the manuscript. All the authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of our institution (IRB approval no. 2016-263). Informed consent was obtained from all the patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Wolf S, Barton D, Kottschade L, Grothey A and Loprinzi C: Chemotherapy-induced peripheral neuropathy: Prevention and treatment strategies. *Eur J Cancer* 44: 1507-1515, 2008.
2. Gaballah A, Shafik A, Elhuseiny K and Ashraf M: Chemotherapy-induced peripheral neuropathy in Egyptian patients: Single institution retrospective analysis. *Asian Pac J Cancer Prev* 19: 2223-2227, 2018.
3. Miltenburg NC and Boogerd W: Chemotherapy-induced neuropathy: A comprehensive survey. *Cancer Treat Rev* 40: 872-882, 2014.
4. Pignata S, De Placido S, Biamonte R, Scambia G, Di Vagno G, Colucci G, Febbraro A, Marinaccio M, Lombardi AV, Manzione L, *et al*: Residual neurotoxicity in ovarian cancer patients in clinical remission after first-line chemotherapy with carboplatin and paclitaxel: The Multicenter Italian Trial in Ovarian cancer (MITO-4) retrospective study. *BMC Cancer* 6: 5, 2006.
5. Park SB, Kwok JB, Asher R, Lee CK, Beale P, Selle F and Friedlander M: Clinical and genetic predictors of paclitaxel neurotoxicity based on patient-versus clinician-reported incidence and severity of neurotoxicity in the ICON7 trial. *Ann Oncol* 28: 2733-2740, 2017.
6. National Cancer Institute, Division of Cancer Treatment and Diagnosis: Common Terminology Criteria for Adverse Events (CTCAE) v4.0. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40. Accessed July 15, 2016
7. Griffith KA, Couture DJ, Zhu S, Pandya N, Johantgen ME, Cavaletti G, Davenport JM, Tanguay LJ, Choflet A, Milliron T, *et al*: Evaluation of chemotherapy-induced peripheral neuropathy using current perception threshold and clinical evaluations. *Support Care Cancer* 22: 1161-1169, 2014.
8. Wolf SL, Barton DL, Qin R, Wos EJ, Sloan JA, Liu H, Aaronson NK, Satele DV, Mattar BI, Green NB and Loprinzi CL: The relationship between numbness, tingling, and shooting/burning pain in patients with chemotherapy-induced peripheral neuropathy (CIPN) as measured by the EORTC QLQ-CIPN20 instrument, N06CA. *Support Care Cancer* 20: 625-632, 2012.
9. Haryani H, Fetzer SJ, Wu CL and Hsu YY: Chemotherapy-induced peripheral neuropathy assessment tools: A systematic review. *Oncol Nurs Forum* 44: E111-E123, 2017.
10. Doi D, Ota Y, Konishi H, Yoneyama K and Araki T: Evaluation of the neurotoxicity of paclitaxel and carboplatin by current perception threshold in ovarian cancer patients. *J Nippon Med Sch* 70: 129-134, 2003.
11. Matsuoka A, Mitsuma A, Maeda O, Kajiyama H, Kiyoi H, Kodera Y, Nagino M, Goto H and Ando Y: Quantitative assessment of chemotherapy-induced peripheral neurotoxicity using a point-of-care nerve conduction device. *Cancer Sci* 107: 1453-1457, 2016.
12. Sato J, Mori M, Nihei S, Takeuchi S, Kashiwaba M and Kudo K: Objective evaluation of chemotherapy-induced peripheral neuropathy using quantitative pain measurement system (Pain Vision[®]), a pilot study. *J Pharm Health Care Sci* 3: 21, 2017.
13. Gewandter JS, Chaudari J, Ibegbu C, Kitt R, Serventi J, Burke J, Culakova E, Kolb N, Sluka KA, Tejani MA and Mohile NA: Wireless transcutaneous electrical nerve stimulation device for chemotherapy-induced peripheral neuropathy: An open-label feasibility study. *Support Care Cancer* 27: 1765-1774, 2019.

14. Inui K and Kakigi R: Pain perception in humans: Use of intraepidermal electrical stimulation. *J Neurol Neurosurg Psychiatry* 83: 551-556, 2012.
15. Kukidome D, Nishikawa T, Sato M, Igata M, Kawashima J, Shimoda S, Matsui K, Obayashi K, Ando Y and Araki E: Measurement of small fibre pain threshold values for the early detection of diabetic polyneuropathy. *Diabet Med* 33: 62-69, 2016.
16. Suzuki C, Kon T, Funamizu Y, Ueno T, Haga R, Nishijima H, Arai A, Tomiyama M and Baba M: Elevated pain threshold in patients with asymptomatic diabetic neuropathy: An intraepidermal electrical stimulation study. *Muscle Nerve* 54: 146-149, 2016.
17. Vasey PA, Jayson GC, Gordon A, Gabra H, Coleman R, Atkinson R, Parkin D, Paul J, Hay A and Kaye SB; Scottish Gynaecological Cancer Trials Group: Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. *J Natl Cancer Inst* 96: 1682-1691, 2004.
18. Ewertz M, Qvortrup C and Eckhoff L: Chemotherapy-induced peripheral neuropathy in patients treated with taxanes and platinum derivatives. *Acta Oncol* 54: 587-591, 2015.
19. Eckhoff L, Knoop A, Jensen MB and Ewertz M: Persistence of docetaxel-induced neuropathy and impact of quality of life among breast cancer survivors. *Eur J Cancer* 51: 292-300, 2015.