The Influence of Chemotherapy-Induced Peripheral Neuropathy on Quality of Life of Gynecologic Cancer Survivors

ABSTRACT

Objective: The aim of this observational study was to investigate correlations between long-term chemotherapy-induced peripheral neurotoxicity (CIPN) and quality of life (QOL) (physical well-being, social well-being, emotional well-being [EWB], and functional well-being [FWB]) among survivors of gynecologic cancer (GC).

Methods: We aimed to assess the correlation of QOL and long-term CIPN with the temporal change in recurrence-free GC survival. Questionnaire responses and clinical data of 259 GC survivors were collected and assessed according to treatment received. The χ^2 test was used to determine the significance of correlations.

Results: Of 165 evaluable patients treated by chemotherapy, 36 patients (21.8%) developed CIPN of Common Toxicity Criteria for Adverse Events Grade ≥1 during the study. CIPN had significantly improved over time in the domain of FWB at ≥61 months after the end of chemotherapy (post-treatment4) among GC survivors (p=0.003). Furthermore, CIPN treated by more than 6 courses of the paclitaxel and carboplatin

(TC) regimen among GC survivors showed significant improvement over time in the EWB domain at 25–60 months and ≥61 months after the end of chemotherapy (post-treatment3 and 4) (p=0.037 and p=0.023) and in FWB at post-treatment4 (p<0.001).

Conclusions: Emotional and functional domains of CIPN improved over time among GC survivors treated by more than 6 courses of the TC regimen. Based on these results, further research is required to identify additional preventative or curative approaches.

Keywords: gynecologic cancer survivors, chemotherapy-induced peripheral neurotoxicity, quality of life, functional assessment of cancer therapy-general

INTRODUCTION

The incidence of gynecologic cancer (GC) has increased in recent years in Japan, with an estimated 30,964 newly diagnosed patients in 2009. [1] Rising incidence rates, earlier diagnosis, and improved treatments have caused the number of cancer survivors to increase rapidly. While quality of life (QOL) is the primary goal for most patients immediately after diagnosis, it becomes more important over the longer term. However, owing to the rising prevalence of cancer, more patients are living with the long-term side effects of cancer and its treatment, which can have a negative impact on QOL. One such common side effect is chemotherapy-induced peripheral neuropathy (CIPN), which can arise from treatment with certain chemotherapeutic agents such as taxanes, platinum derivatives and adversely affects the QOL of patients. [2, 3] CIPN affects the lower and upper limbs and comprises mixed sensory and motor effects, including loss of vibration sense and taste, paresthesia, weakness, tremor, and impaired function. [4-9] Such adverse effects are likely to reduce QOL by impairing physical well-being (PWB), social

well-being (SWB), emotional well-being (EWB), and functional well-being (FWB). Several studies have assessed the relationship between CIPN and QOL among GC survivors. [10-12] Although published data on short-term outcomes of CIPN are abundant, the long-term consequences of CIPN have not been sufficiently investigated with regard to GC survival. In the present study, we aimed to assess the correlation of QOL and long-term CIPN with the clinical characteristics and temporal change of GC survival.

MATERIALS AND METHODS

Patients

This study comprised 259 survivors who had received various treatments for GC in the authors' institution. GC survivors with recurrence were excluded. The study enrolled 103 survivors who had been treated for cervical cancer (CC) including 35 patients treated solely by surgery, 33 survivors of concurrent chemoradiotherapy (CCRT)/radiotherapy (RT) alone, 27 patients who underwent surgery plus RT/CCRT, and 8 patients treated by surgery plus chemotherapy. Of 102 survivors with endometrial cancer (EC), 44 patients underwent surgery alone and 58 patients were treated by

surgery plus chemotherapy. Of 54 survivors with ovarian cancer (OC), 9 patients underwent surgery and 45 were treated by surgery plus chemotherapy. Patients characteristics are listed in Table 1. Patients treated by RT received a combination of external irradiation and intracavitary brachytherapy (ICBT) with curative intent. RT was delivered at 2.0 Gy per fraction once daily, 5 days per week, over 5 weeks. The median dose to the whole pelvis was 50.0 Gy, and 24 Gy was administered by ICBT four times. The patients treated with CCRT received RT with cisplatin (CDDP) or nedaplatin (NED) (CDDP, 40 mg/m^2 or NED, 30 mg/m^2 by infusion weekly). Patients with CC, EC, or OC received neoadjuvant or adjuvant chemotherapy depending on FIGO stage, grade, patient preference, and physician discretion. Our standard chemotherapy consisted of 3–8 cycles of paclitaxel (175 mg/m^2 infused) and carboplatin (dosed for an area under the curve of 5) (TC). In addition to TC, docetaxel (70 mg/m^2 infused) and carboplatin (dosed for an area under the curve of 5) (DC) and gemcitabine (1,000 mg/m^2 on days 1 and 8) and carboplatin (dosed for an area under the curve of 4) (GC) were used. Cycles were repeated every 21 days. Our treatment policy used analgesics (NSAIDs and acetaminophen), and an anti-neuropathic drug (pregabalin) if the CIPN has appeared.

Questionnaires

We collected responses to questionnaires and clinical data from medical records. The questionnaires were distributed to eligible women who had been treated from January to December 2017. All participants were informed about the survey by their consultants and provided written informed consent to participate in the study. All consent was voluntary. Completed questionnaires were collected using in-hospital collection boxes. QOL was measured by the Functional Assessment of Cancer Therapy-General (FACT-G), a valid and reliable 27-item questionnaire that evaluates PWB, SWB, EWB, and FWB. The FACT-G provides a generic core of questions that are often combined with cancer site-specific questionnaires. [13, 14] According to the FACT-G, better QOL is indicated by a higher score of SWB and FWB as well as a lower score of PWB and EWB. FACT-G questionnaires were completed by GC survivors at least 12 months after treatment (post-treatment1), 13–24 months after treatment (post-treatment2), 25–60 months after treatment (post-treatment3), and >61 months after treatment (post-treatment4). CIPN was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. In this study, CIPN was classified as present when CTCAE was at least Grade 1. Patient and disease characteristics were investigated,

including cancer site, stage, chemotherapy, marital status, children, education, age, body mass index (BMI), physical activity, time asleep, cigarette use, alcohol consumption, anemia, hypoproteinemia, diabetes, and FACT-G score. This study protocol was approved by the Institutional Review Board of Okayama University Hospital (Epidemiology; No.1612-013).

Statistical analysis

Differences between groups were analyzed using Student's *t*-test for continuous variables or the Mann–Whitney U test when a normal distribution was not assumed (nonparametric test). Contingency tables were adopted to compare categorical variables. Pearson's χ^2 test was used to test for significance. A receiver-operating characteristic (ROC) curve was generated, and the area under the curve (AUC) was calculated to evaluate the discriminatory ability of each scoring system. We also examined the data in cross-tabulated form to explore CIPN. All analyses were performed using SPSS 20.0 software (SPSS, Chicago, IL, USA), and *p* values of less than 0.05 were considered significant.

RESULTS

The survivors' characteristics are summarized in Table 1. Their median age at the time of diagnosis was 53.8 years (range 23–79 years). Cancer sites were cervix (n=103, 39.8%), endometrium (n=102, 39.4%), and ovary (n=54, 20.8%). The number of patients with early stage (n=204, 79.2%) exceeded those with advanced stage (n=55, 20.8%). BMI data (kg/m^2) were as follows: <18.5 (n=28, 10.8%), 18.5–24.9 (n=157, 57.7%), 25.0–29.9 (n=50, 19.3%), 30.0–34.9 (n=17, 9.5%), 35.0–39.9 (n=4, 1.5%), and ≥40.0 (n=3, 1.2%). Education was high school or less (n=151, 58.3%), part college (n=47, 18.1%), college graduate (n=60, 23.2%), and postgraduate (n=1, 0.4%). Marital status was married (n =204, 78.8%), widow (n=28, 10.8%), single (n=16, 6.2%), and divorced (n=11, 4.2%). Two hundred survivors (77.2%) had children. Twenty-six survivors (10.0%) smoked cigarettes (>10/day), and 23 (8.9%) drank alcohol (>350 ml beer or >150 ml wine/day). Time spent asleep was <5 h/day (n =44, 16.9%), 5–8 h/day (n =194, 75.0%), and >8 h/day (n =21, 8.1%). Physical activity was <0.5 h/week (n =158, 61.0%), 0.5–2 h/week (n =55, 21.2%), and >2 h/week (n =46, 17.8%). Nineteen survivors (7.3%) had anemia (hemoglobin <10.0 g/dl), 14 (5.4%) had hypoproteinemia

(albumin <3.5 g/dl), and 24 (9.3%) had diabetes. The study enrolled 24 patients with diabetes including 19 patients treated oral hypoglycemic agents, 1 patient underwent insulin injection, and 4 patients underwent diet and exercise therapy. To alleviate pain, we used analgesics (NSAIDs and acetaminophen), and an anti-neuropathic drug (pregabalin) for each patient. We administered NSAIDs with 26 patients, and acetaminophen with 2patients. Their mean at dosing period of NSAIDs were 8.3 months (range 1–50 months) and acetaminophen were 5.0 months (range 3–7 months). And, we used an anti-neuropathic drug (pregabalin) with 29 patients. Pregabalin comprised 50mg/day (n=10), 100mg/day (n=4), 150mg/day (n=12) and 300mg/day (n=3). Their mean at dosing period of pregabalin was 9.3 months (range 1–46 months). Numbers in each questionnaire time category were post-treatment1 (n=56, 21.6%), post-treatment2 (n =50, 19.3%), post-treatment3 (n =85, 32.8%), and post-treatment4 (n =68, 26.3%). A greater percentage of patients had undergone surgery and chemotherapy (n=111, 42.9%), followed by those undergoing surgery only (n=88, 34.0%), radiation (including CCRT) (n=33, 12.7%), and surgery and radiation (including CCRT) (n=27, 10.4%). Chemotherapy regimens are summarized such as TC regimens consisted of 3 courses (n=39, 23.6%), 6 courses (n=53, 32.3%), and 8 courses (n=13, 7.9%). DC regimens

involved 3 courses (n=4, 2.4%) and 6 courses (n=3, 1.8%). The GC regimen had 6 courses (n=1, 0.6%). CDDP regimens comprised 2 courses (n=2, 1.2%), 3 courses (n=3, 1.8%), 4 courses (n=4, 2.4%), 5 courses (n=20, 12.1%), and 6 courses (n=21, 12.7%). NED regimens consisted of 7 courses (n=1, 0.6%) and 8 courses (n=1, 0.6%). Chemotherapy regimens are summarized in Table 2A. We investigated correlations among chemotherapy regimens, courses, and CIPN. Chemotherapy regimens for CIPN patients were 3 courses of TC (n=5, 12.8%), 6 courses of TC (n=20, 37.7%), 8 courses of TC (n=9, 69.2%), and 6 courses of CDDP (n=2, 9.5%) (Table 2B).

We investigated correlations among characteristics, namely cancer site, stage, chemotherapy, marital status, children, education, age, BMI, physical activity, time asleep, cigarette use, alcohol consumption, anemia, hypoproteinemia, diabetes, and CIPN. We used ROC curve analyses to predict CIPN. Chemotherapy (more than 6 courses of TC) had a significantly higher AUC (0.740) than other characteristics in terms of affecting CIPN. Additionally, OC survivors tended to have a higher AUC (0.627) than other characteristics in terms of CIPN (Figure 1 and Table 3).

We examined the association between long-term CIPN and time after the end of chemotherapy among 259 GC survivors. Long-term CIPN occurred in 35.3%, 20.5%,

15.6%, and 20.0% of 259 GC survivors undergoing chemotherapy at post-treatment1, post-treatment2, post-treatment3, and post-treatment4, respectively (Figure 2A). Associations between long-term CIPN and FACT-G scores in the 259 GC survivors at post-treatment1, 2, 3, and 4 were also examined. The mean FACT-G subscale scores of the 94 survivors with no chemotherapy treatment (Group A: post-treatment1 n=22, post-treatment2 n=11, post-treatment3 n=33, post-treatment4 n=28), 129 survivors with chemotherapy treatment without CIPN (Group B: post-treatment1 n=22, post-treatment2 n=31, post-treatment3 n=44, post-treatment4 n=32), and 36 survivors with chemotherapy treatment with CIPN (Group C: post-treatment1 n=12, post-treatment2 n=8, post-treatment3 n=8, and post-treatment4 n=8) were as follows. For PWB: post-treatment1 1.82, 3.55, and 6.08 for Groups A, B, and C, respectively; post-treatment2 4.09, 2.77, and 4.25; post-treatment3 2.76, 3.49, and 5.13; post-treatment4 2.46, 2.31, and 4.50. For SWB: post-treatment1 17.1, 16.8, and 17.2; post-treatment2 14.1, 14.5, and 18.0; post-treatment3 15.8, 15.1, and 18.5; post-treatment4 14.1, 17.0, and 18.1. For EWB: post-treatment1 6.36, 6.57, and 9.00; post-treatment2 7.73, 5.81, and 7.80; post-treatment3 6.62, 5.93, and 5.50; post-treatment4 5.64, 5.72, and 5.30. For FWB: post-treatment1 22.5, 21.3, and 20.8;

post-treatment2 18.3, 19.6, and 21.1; post-treatment3 19.6, 20.3, and 21.5; post-treatment4 19.6, 22.7, and 24.6. Associations between three groups (A, B, and C) and FACT-G subscale scores at post-treatment1, 2, 3, and 4 were also examined. Overall, FWB in Group C had showed a significant improvement over time at post-treatment4 in GC survivors (p=0.003) (Figure. 2B).

We next examined the association between long-term CIPN and time after the end of chemotherapy consisting of more than 6 courses of TC in 66 GC survivors. Long-term CIPN occurred in 58.8%, 40.0%, 30.0%, and 42.8% of the 66 GC survivors undergoing more than 6 courses of at post-treatment1, post-treatment2, post-treatment3, and post-treatment4, respectively (Figure. 3A). We also analyzed the association between long-term CIPN and FACT-G scores in the same cohort of GC survivors at post-treatment1, 2, 3, and 4. The mean FACT-G subscale scores of the 38 survivors on chemotherapy treatment without CIPN (Group A: post-treatment1 n=7, post-treatment2 n=9, post-treatment3 n=14, post-treatment4 n=8) and 28 survivors on chemotherapy with CIPN (Group B: post-treatment1 n=10, post-treatment2 n=6, post-treatment3 n=6, post-treatment4 n=6) were as follows. For PWB: post-treatment1 5.14 and 6.2 in Groups A and B, respectively; post-treatment2 3.00 and 5.17; post-treatment3 3.07 and

5.00; post-treatment4 2.38 and 3.83. For SWB: post-treatment1 14.1 and 16.7; post-treatment2 16.3 and 15.5; post-treatment3 15.1 and 17.7; post-treatment4 17.5 and 17.8. For EWB: post-treatment1 9.14 and 9.20; post-treatment2 5.89 and 9.00; post-treatment3 6.43 and 4.80; post-treatment4 5.88 and 4.30. For FWB: post-treatment1 21.7 and 21.4; post-treatment2 121.7 and 19.2; post-treatment3 19.1 and 20.8; post-treatment4 23.9 and 25.2. In the whole study cohort, CIPN survivors on the TC regimen with more than 6 courses showed significant improvement over time at post-treatment3 and post-treatment4 (p=0.037 and p=0.023) for EWB and at post-treatment4 for FWB (p<0.001). These data indicate a positive long-term effect of more than 6 courses of TC for GC survivors with regard to emotional and functional aspects (Figure 3B).

DISCUSSION

In parallel with ongoing improvements in cancer treatment options, the number of cancer survivors is continuing to grow. The disease and its treatment give rise to many symptoms and substantial impairments in domains of QOL. It is therefore important to

consider the effects of treatment on both survival and QOL of cancer survivors. To the best of our knowledge, this is the first study to evaluate correlations between QOL and CIPN over the longer term in GC survivors after the end of their chemotherapy. The long-term reversibility of CIPN remains questionable, notably in the case of platinum-based anticancer drugs and taxanes, for which CIPN may last several years after the end of anticancer chemotherapies. The health impacts of CIPN remain worrying because CIPN is associated with comorbidities such as psychological distress. [15] However, these long-term effects remain poorly studied. The degree of neurotoxicity depends on the type and combination of drugs used, the duration of administration, and the cumulative dose applied. [5, 16] Depending on the drug, sensory painful neuropathies (CDDP) or combined sensorimotor neuropathies (paclitaxel) may occur. [4-6] CIPN is also a dose-limiting adverse effect of treatment with taxanes, particularly paclitaxel, and occurs in a dose- and treatment duration-dependent manner. The threshold dose for development of taxane-induced peripheral neuropathy lies close to standard doses used in a range of chemotherapy regimens, at approximately 300 mg/m^2 for paclitaxel and 100 mg/m^2 for docetaxel. [17-19] This CIPN is a typical distal sensory neuropathy with a stocking-and-glove distribution over the hands and feet. Patients may report paresthesia,

dysesthesia, numbness, and altered proprioception. Motor weakness of hands and feet, such as vegetative disturbances, is less frequent. [7] CDDP-induced CIPN affects mostly the lower and upper limbs and includes mixed sensory and motor effects, including loss of vibration sense and taste, paresthesia, weakness, and tremor. [8, 9] With higher cumulative doses and longer times of exposure to CDDP the severity of CIPN increases, as does the likelihood of development of a chronic, irreversible neuropathy. [20, 21] Cumulative dose is the main risk factor for platinum-based drugs, specifically >200–300 mg/m^2 for CDDP. [22] Radiotherapy may increase the neurological symptoms of CDDP-induced peripheral neuropathy. [23] Depending on the agent, 30%–70% of patients receiving neurotoxic chemotherapy develop neuropathy. [24, 25] In a multicenter Italian OC trial (MITO-4), 22 out of 60 neuropathic patients (37%) treated with TC reported complete recovery in the first 2 months after the end of chemotherapy. Nevertheless, 15 patients (25%) recovered between 2 and 6 months, with 9 patients (15%) recovering after 6 months and longer. [26] Neuropathy symptoms were experienced by 51% of women with cancer, especially tingling hands/feet and numbness in fingers/toes. [27] In the present study, of 165 evaluable patients who underwent chemotherapy, 36 (21.8%) developed CIPN. Long-term CIPN occurred in 35.3%, 20.5%, 15.6%, and 20.0% of

chemotherapy-treated GC patients at least 12 months after the end treatment, 13–24 months post treatment, 25–60 months post treatment, and ≥61 months post treatment, respectively. Furthermore, long-term CIPN was present in 58.8%, 40.0%, 30.0%, and 42.8% of 66 GC survivors who underwent more than 6 courses of TC regimen at least 12 months after the end of the chemotherapy and 13–24 months, 25–60 months, and ≥61 months after treatment, respectively. Toxicity severity is critical to the successful identification of risk factors associated with CIPN. CIPN symptoms are associated with drug type, dose administered, age, comorbidities, and genetic factors. [28-31] A growing body of literature suggests that lifestyle factors, such as BMI, physical activity and pretreatment data (anemia and hypoalbuminemia) [32-35], may affect the onset and severity of CIPN in a variety of cancer patient populations. Physical activity [33] and diet [36] have been associated with diabetic neuropathy, increasing the plausibility of lifestyle factors being associated with CIPN. On investigating the correlations between each characteristic and CIPN, we discovered that undergoing more than 6 courses of the TC regimen was the variable most likely to affect CIPN. Additionally, OC patients tended to have an influence on CIPN. Interestingly, the findings of this study confirm that

cumulative dose (>1,000 mg/m^2 for paclitaxel) is the main risk factor in a significant percentage of CIPN patients.

Symptoms of CIPN such as neuropathic pain, numbness, tingling, and function loss greatly affect the physiologic and psychological status of patients and reduce their QOL. [4, 37] CIPN is associated with pain, sensory discomfort, sleep disruption, and fatigue. [38] Furthermore, symptoms associated with CIPN can affect the psychological, social, and spiritual well-being of patients. [39] Treatment-related neuropathy can serve as a constant reminder of the presence of cancer and thus contribute to anxiety and depression. [40] The inability to walk or stand for long periods of time leaves patients with CIPN unable to participate in many activities, leading to feelings of social isolation and psychological distress. [4] CIPN has also been associated with changes in physical function. However, associations between long-term CIPN and QOL have not been sufficiently investigated in GC survivors. Adverse effects may persist long term, with OC survivors reporting neuropathic symptoms negatively associated with QOL up to 12 years after treatment. For this reason, CIPN has a strong negative impact on QOL associated with recurrence, such as more cycles of chemotherapies and shorter period since the last treatment. [27] In the present study we investigated the correlations between

QOL and long-term CIPN in recurrence-free GC survivors, whereby we found that EWB and FWB scores were significantly improved over time among GC survivors who underwent more than 6 courses of TC. From these results we surmise that recurrence greatly affects QOL.

We acknowledge that our study has some limitations. The number of patients was relatively small, and the examination was performed in a single facility. Further prospective studies involving more patients and facilities would provide more definitive data with which to clarify the significance of our findings.

In conclusion, this study suggests that emotional and functional domains are improved over time in recurrence-free GC survivors with long-term CIPN who underwent more than 6 courses of the TC regimen. Based on these results, further research will be required to identify additional preventative or curative approaches.

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Figure legends

FIGURE 1. Receiver-operating characteristic curve analyses to predict chemotherapy-induced peripheral neuropathy. 1. Cancer site (ovarian cancer). 2. Stage (advanced stage). 3. More than 6 courses of TC regimen. 4. Marital status (none). 5. Children (no children). 6. Education (≥college graduate). 7. Age (>65 years). 8. BMI (≥30 kg/m^2). 9. Physical activity (<0.5 h/week). 10. Time asleep (<5 h/day). 11. Cigarettes (>10/day). 12. Alcohol (>350 ml beer/day or >150 ml wine/day). 13. Anemia (hemoglobin <10.0 g/dl). 14. Hypoproteinemia (albumin <3.5 g/dl). 15. Diabetes.

FIGURE 2. A: Chemotherapy-induced peripheral neuropathy (CIPN) in 165 gynecologic cancer (GC) survivors at least 12 months after the end of the chemotherapy (post-treatment1), 13–24 months after treatment (post-treatment2), 25–60 months after treatment (post-treatment3), and ≥61 months after treatment (post-treatment4). B: Functional Assessment of Cancer Therapy—General (FACT-G) scores and CIPN in 259 GC survivors at post-treatment1, 2, 3, and 4. There were 94 survivors with no chemotherapy treatment (Group A), 129 with chemotherapy treatment without CIPN (Group B), and 36 with chemotherapy treatment with CIPN

(Group C). PWB, physical well-being; SWB, social well-being; EWB, emotional well-being; FWB, functional well-being.

FIGURE 3. A: Chemotherapy-induced peripheral neuropathy (CIPN) in 66 gynecologic cancer (GC) survivors who underwent more than 6 courses of TC at least 12 months after the end of the chemotherapy (post-treatment1), 13–24 months after treatment (post-treatment2), 25–60 months after treatment (post-treatment3), and ≥61 months after treatment (post-treatment4). B: Functional Assessment of Cancer Therapy—General (FACT-G) scores and CIPN in 66 GC survivors who underwent more than 6 courses of TC at post-treatment1, 2, 3, and 4. There were 38 survivors with chemotherapy treatment without CIPN (Group A) and 28 with chemotherapy treatment with CIPN (Group B). PWB, physical well-being; SWB, social well-being; EWB, emotional well-being; FWB, functional well-being.