RESEARCH ARTICLE

The Kampo Medicine Goshajinkigan Prevents Neuropathy in Breast Cancer Patients Treated with Docetaxel

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Abstract

Background: Goshajinkigan (GJG) is used for the treatment of several neurological symptoms. We investigated the efficacy of GJG and mecobalamin (B12) against neurotoxicity associated with docetaxel (DOC) in breast cancer patients. Materials and Methods: Sixty breast cancer patients were treated with DOC. Thirty-three patients (GJG group) received oral administration of 7.5 g/day GJG and 27 patients (B12 group) received oral administration of 1500 μg/day B12. Neuropathy was evaluated according to DEB-NTC (Neurotoxicity Criteria of Debiopharm), Common Terminology Criteria for Adverse Events (NCI-CTC) ver. 3.0, and a visual analogue scale (VAS). This study employed a randomized open design. Results: The incidence of neuropathy was 39.3% in the GJG group, and 88.9% in the B12 group ($p<0.01$). In the GJG group, grade 1 DEB-NTC was observed in 2 cases, grade 2 in 5 cases and grade 3 in 5 cases. Grade 1 NCI-CTC was observed in 7 cases, grade 2 in 6 cases, and VAS was 2.7±2.2. In the B12 group, grades 1, 2 and 3 DEB-NTC were observed in one case, 12 cases and 12 cases, respectively; and grades 1, 2 and 3 NCI-CTC were observed in 11 cases, 12 cases and one case, and VAS was 4.9±2.4. Conclusions: Concomitant administration of GJG is useful in preventing neuropathy in breast cancer patients treated with a DOC regimen.

Keywords: Breast cancer - goshajinkigan - docetaxel - peripheral neuropathy - mecobalamin

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Introduction

The treatment of breast cancer requires a multidisciplinary approach, and chemotherapy is routinely applied as an adjuvant treatment as well as for metastatic breast cancer. Thus, chemotherapy treatments that are effective, safe, and tolerable are currently being sought. Taxanes are novel antimicrotubule agents that promote the polymerization of tubulin and stabilize microtubules by preventing their disassembly. Based on their significant activity in the metastatic setting (Ravdin et al., 1995), taxanes have also been extensively tested in the adjuvant setting in many randomized trials (Henderson et al., 2003; Roché et al., 2006). Moreover, a recent meta-analysis of 13 randomized studies including 22,903 patients demonstrated that the addition of a taxane to an anthracycline-based regimen improved the disease free survival (DFS) and overall survival (OS) of high-risk early stage breast cancer patients (De Laurentiis et al., 2008). Although taxanes have become a key chemotherapeutic drug for the treatment of breast cancer, peripheral neuropathy is one of their side effects. Microtubules in the axons of the peripheral nerves are involved in axonal growth and the transport of substances. Taxanes inhibit the growth of cancer cells by disrupting the functioning of their microtubules; however, the microtubules of nerve cells are also affected by this process, which can cause neurological disorders. Vitamins (vitamin B6, vitamin B12, vitamin complexes, etc.) are sometimes used for the treatment of peripheral nerve disorders. With respect to the actions and effects of mecobalamin (B12), this agent repairs affected peripheral nerves by promoting nervous nucleic acid/protein synthesis, axonal regeneration, and myelinization, relieving swelling and pain. In Japan, B12 is the standard treatment for peripheral neuropathy (Kuwabara et al., 1999). Goshajinkigan (GJG) is a traditional Japanese medicine that is mainly used for the treatment of neurological symptoms including limb pain, cold sensation, and numbness in diabetic neuropathy (Nagaki et al., 2003; Uno et al., 2005). The incidence of docetaxel (DOC)-induced neuropathy (sensory/motor) is approximately 5% (Lee and Swain, 2006). However, in a phase II study involving patients with prostate cancer, or which this agent was recently approved in Japan, DOC at 70 mg/m^2 caused neuropathy in 20 (46.5%) of 43 patients (Naito et al., 2008), otherwise it induced neuropathy in 22 (11.5%) of 192 patients with ovarian, esophageal, or corpus uteri cancers, for which this agent at 70 mg/m^2 was approved in Japan (Muro et al., 2004; Katsumata et al., 2005). Recently, several studies reported the efficacy

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of GJG in patients with colorectal cancer (Kono et al., 2011; Nishioka et al., 2011). Therefore, we performed the present prospective randomized study to compare the effects of GJG with those of B12 against DOC-associated peripheral neurotoxicity in breast cancer patients, not with those of a placebo.

Materials and Methods

Patient selection

Patients with the following characteristics were considered to be eligible for this study: histologically proven invasive breast cancer (female); T1-3, N0-2, and M0 stage disease; an age between 20 and 70; an Eastern Cooporative Oncology Group (ECOG) performance status of 0 to 1; and normal end-organ and bone marrow function (as defined by a leukocyte count of ≥3,500/μL; an absolute neutrophil count of ≥1,500/μL; a platelet count of ≥120,000/μL; a hemoglobin level of ≥10.0 g/dL; total bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels of ≤1.5 times the upper limit of institutional normal (ULN); and a creatinine level of ≤1.5 times the ULN. The eligible patients had to have normal cardiac function, as defined by a left ventricular ejection fraction (LVEF) of ≥50% on an echocardiogram and an ECG without evidence of uncontrolled arrhythmia.

Patients were excluded for the following reasons: pre-existing ≥grade 2 peripheral neuropathy; prior chemotherapy or hormone therapy as neoadjuvant or adjuvant therapy; a history of cancer or evidence of metastatic disease; being pregnant or nursing; allergies to polysorbate 80; or any uncontrolled or severe intercurrent illness including unstable angina, myocardial infarction within the past 6 months, or severe infection. Patients who participated in other clinical trials were excluded.

The institutional review board approved the protocol, and written informed consent was obtained for all patients.

Study design and treatment

DOC therapy was administered on an outpatient basis, and the patients were premedicated with an antiemetic treatment involving a combination of 5-hydroxytryptamine-3 receptor antagonists and corticosteroids. The patients were treated with TC (75mg/m^2 DOC and 600 mg/m^2 cyclophosphamide) every 3 weeks for 4 cycles, DOC alone (100mg/m^2) every 3 weeks for 4 cycles, and XT (900mg/m^2 capecitabine administered orally twice a day on days 1-14 plus 60mg/m^2 DOC) every 3 weeks for 6 cycles. After chemotherapy, trastuzumab was administered to the HER2-positive breast cancer patients. Granulocyte colony-stimulating factor (filgrastim or lenograstim) could be used if the patient's neutrophil count fell to <500/μL or febrile neutropenia developed.

At the time of randomization, patients were stratified by the type of chemotherapy and by age. Patients were then randomized by a dynamic allocation procedure that balanced marginal distribution of the above stratification factors. The patients were randomly assigned to receive GJG or B12. GJG (7.5 g/day divided into 2-3 doses) (Tsumura and co., Japan) was orally administered before or between meals each day during the DOC therapy, whereas B12 (1500 μg/day) was orally administered after meals each day during the DOC therapy. Adverse effects were evaluated on Days 1 and 8 according to the usual attendance schedule by five nurses from the outpatient chemotherapy clinic. The patients were evenly assigned to receive GJG or B12 in advance. Thus, the design ensured that variable evaluations by the nurses could not result in statistical differences between the two drugs. Study treatment was continued as long as DOC therapy or 6 cycle of XT therapy.

Patient evaluation

The study employed randomized open control design. The patients enrolled in this study were first evaluated at the baseline (prior to chemotherapy). The peripheral neuropathy evaluations were based on the Neurotoxicity Criteria of Debiopharm (DEB-NTC) (Inoue et al., 2011), the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCI-CTC) (Trotti et al., 2003) (Table 1), and a visual analogue scale (VAS) (Huskisson, 1974). The VAS questionnaire was completed after the DOC chemotherapy. For the VAS, a straight 10 cm line was drawn. The left end of the line; i.e., 0 cm, represented "no pain", and the right end of the line; i.e., 10 cm, represented "extreme pain". The subjects were asked to indicate the pain that they were experiencing by touching or making a mark on the appropriate part of the line.

Statistical analysis

The primary objective of this trial was the incidence of peripheral neuropathy. The secondary objective was treatment compliance. The expected incidence of peripheral neuropathy in the GJG group was 30%, and at least lower than 46.5% which is the incidence of peripheral neuropathy in the literature (Naito et al., 2008). It was estimated that analysis of 54 patients was required for a statistical power of 70% with a one-sided alpha error of 5%. A total enrollment of 60 patients was required for 90% of the enrolled patients to be evaluable for GJG efficacy.

Table 1. Criteria of Neurotoxicity According to the NCI-CTC and DEB-NTC Scales

Grade	NCI-CTC	DEB-NTC
1	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling), but not interfering with function	Within 7 days
2	Sensory alteration or paresthesia (including tingling) interfering with function, but not interfering with ADL	More than 7 days
3	Sensory alteration or paresthesia interfering with ADLFunctional impairment interfering with ADL	
4	Disability –	
5	Death	

*NCI-CTC: National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0; DEB-NTC: Neurotoxicity Criteria of Debiopharm; ADL: activities of daily living

The statistical significance of differences between the two groups was assessed using the chi-squared test, Student's-t test, or Mann–Whitney U test as appropriate. All statistical tests were two-sided and employed a significance level of 0.05.

Results

Patients' characteristics

Fifty-seven patients (GJG group, 33; B12 group, 27) were enrolled between May 2009 and April 2011 (Table 2). Their median age was 58 years (range, 33-70 years). All patients had an ECOG performance status of 0; 28% were premenopausal; 45% were hormone receptor-positive, 34% were HER2-positive, 26% had stage I disease; 70% had nuclear grade 2 to 3 disease, 72% had undergone mastectomy, and 16% had received neo-adjuvant chemotherapy. No characteristics differed significantly among the groups according to the chi-square test.

Treatment administration

All treatment regimens were generally well tolerated. The overall mean relative dose intensity (RDI) for DOC was 99.2% in the GJG group and 99.1% in the B12 group. The total DOC dose was 338.5 mg/m^2 in the GJG group and 340 mg/m^2 in the B12 group (Table 3).

Peripheral neuropathy

Peripheral neuropathy occurred significantly less frequently in the GJG group (39.3%) than the B12 group (88.9%) (p<0.01) (Table 4). According to the DEB-NTC, grade 1, 2 and 3 neuropathy was seen in 2, 5 and 6 cases in the GJG group, respectively. According to the NCI-CTC, grade 1 and 2 neuropathy was observed in 7 and 6 cases in the GJG group, respectively. According to the DEB-NTC, grade 1, 2 and 3 neuropathy was observed in one, 12 and 12 cases in the B12 group. According to the NCI-CTC, grade 1, 2 and 3 disease was observed in

Table 2. Baseline Characteristics

	GJG (n=33)	B12 (n=27)
Median age, yrs (range)	58 (35 - 70)	55 (33 - 69)
Stage: I/IIA/IIB/III	14 / 7 / 8 / 4	13 / 7 / 5 / 2
Nuclear grade: 1/2/3	9 / 15 / 9	9 / 9 / 9
Surgical procedure: Bp/Bt	10 / 23	6 / 21
ER positive (%)	73	70
HER2 positive (%)	33	37
Chemotherapy		
TC/DOC/XT	19 / 13 / 1	15 / 11 / 1
Neoadjuvant/Adjuvant	6 / 27	4 / 23

*GJG: Goshajinkigan; B12: mecobalamin; Bp: partial mastectomy; Bt: total mastectomy; TC: docetaxel and cyclophosphamide; DOC: docetacel; XT: capecitabine and docetaxel

Table 3. Treatment Administration

	GJG	B12
Completion rate (%)	100	100
RDI (%)	99.2	99.1
Total dose of DOC (mg/m^2)	338.5	340

*GJG: Goshajinkigan; B12: mecobalamin; RDI: relative dose intensity; DOC: docetaxel

Table 4. Peripheral Neuropathy

		GJG	B12	p value
Incidence (%)		39.3	88.9	p<0.01
DEB-NTC (%)	Grade 1	6	4	
	Grade 2	15	44	
	Grade 3	18	44	p<0.01
NCI-CTC (%)	Grade 1	21	41	
	Grade 2	18	44	
	Grade 3	0	4	p<0.01
VAS		2.7±2.2	4.9±2.4	p<0.01

*GJG: Goshajinkigan; B12: mecobalamin; DEB-NTC: Neurotoxicity Criteria of Debiopharm; NCI-CTC: National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0; VAS: visual analogue scale

Table 5. Criteria of Neurotoxicity According to the NCI-CTC and DEB-NTC Scales

	GJG		B12	
	All grades	Grade 3/4	All grades	Grade 3/4
Hematologic toxicities				
Leucopenia	55	39	56	37
Neutropenia	55	39	59	37
Febrile neutropenia	3	3	0	0
Anemia	0	0	0	0
Thrombocytopenia	0	0	0	0
Non-hematologic toxicities				
Fatigue	45	6	51	15
Nausea/Vomiting	36	0	33	5
Anorexia	33	6	48	11
Stomatitis	27	0	30	0
Diarrhea	21	0	19	0
Rash/Eczema	18	0	19	0
AST, ALT	9	0	11	0
Nail change	27	0	26	0
Peripheral edema	18	0	26	0

*GJG: Goshajinkigan; B12: mecobalamin; AST: aspartate aminotransferase; ALT: alanine aminotransferase

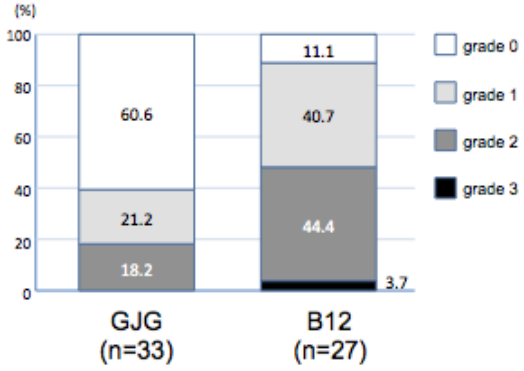

Figure 1. Incidence of Peripheral Neuropathy (NCI-CTC). GJG: Goshajinkigan; B12: mecobalamin

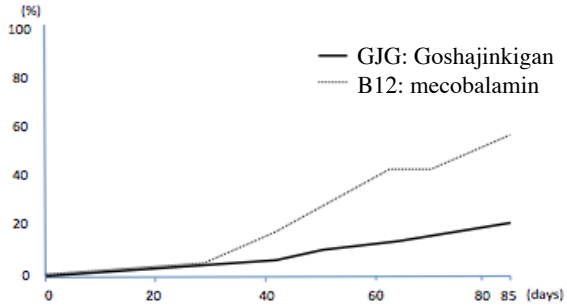

Figure 2. The Frequency of Grade 2 or More Peripheral Neuropathy after Chemotherapy

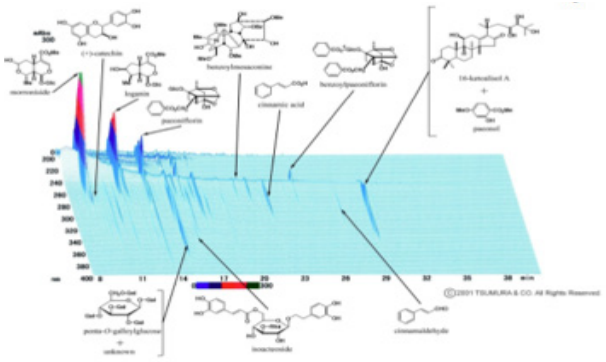

Figure 3. 3D HPLC Pattern of Goshajinkigan

11, 12 and one case, respectively (Figure 1). The mean VAS scores for numbness after chemotherapy were 2.7 in the GJG group and 4.9 in the B12 group ($p<0.01$). The incidence of grade 2/3 peripheral neuropathy was lower in the GJG group than the B12 group (Figure 2). As for other effects, there was no significant difference between the treatment groups (Table 5).

Discussion

Incidence of neurotoxicity is different between GJG and B12 group in breast cancer patients treated with DOC regimen. Use of B12 for this indication would not be recommended since it may actually increase the incidence of neurotoxicity. This study is the first prospective control study to prove the efficacy of GJG against DOC-induced peripheral neuropathy for breast cancer patients. GJG is comprised of 10 herbs, each of which contains numerous active ingredients (Figure 3). Two mechanisms have been suggested for the alleviating effects of GJG on peripheral neurotoxicity (Hu et al., 2003; Gotoh et al., 2004; Yamada et al., 2005). The first is that GJG promotes the release of dynorphin, and thus, improves numbness/pallesthesia via the opiate system. The second is that GJG promotes nitric oxide production, and thus, improves the circulation and the blood supply to the nerves. In addition, it was reported that GJG reduced the expression levels of transmitter proteins and sensory receptors associated with C-fiber activation (Imamura et al., 2008). This effect might be one of the mechanisms by which GJG prevents taxane-induced neuropathy.

Taxane-induced peripheral neuropathy is generally sensory in nature, and, as with the vinca alkaloids, the taxane dose is the primary predictor of its development (Swain and Arezzo, 2008). The clinical manifestations include symmetric painful paresthesia or numbness in a stocking-glove distribution, shaking, impaired proprioception, sensory ataxia, gait disturbance, and occasional weakness (Stubblefield et al., 2009). These symptoms have a variable clinical course and are resolved after treatment discontinuation (Argyriou et al., 2008). The onset dose for neuropathy of any grade ranges from 100 to 300 mg/m^2 for paclitaxel (PTX) and from 75 to 100 mg/m^2 for DOC. The frequency of taxane-associated peripheral neuropathy is correlated with the cumulative dose delivered and the dose per treatment cycle (Carlson and Ocean, 2011). In a randomized phase III study of metastatic breast cancer, the mean cumulative dose that induced the onset of ≥grade 2 peripheral neuropathy was 371 mg/m^2 for DOC and 715 mg/m^2 for PTX (Jones et al., 2005). In general, the incidence of taxane-related grade 3/4 sensory neuropathy appears to be higher for PTX (both castor oil– and albumin-based formulations) than DOC (Swain and Arezzo, 2008). In the adjuvant treatment of node-positive or high-risk node-negative breast cancer, grade 3/4 neuropathy was significantly more common after treatment with weekly PTX than with weekly DOC (27% *vs* 16%; $p<0.0001$) (Sparano et al., 2008). Across various trials, the incidence of grade 3/4 peripheral neuropathy ranged from 2-32% for PTX and from 0-17% for DOC (Swain and Arezzo, 2008).

Although the incidence of neuropathy appears to be higher for PTX than for DOC, it is important to control peripheral neurotoxicity during DOC treatment in order to allow its continued administration. In Japan, a phase II study involving patients with prostate cancer, or which this agent was recently approved, DOC at 70 mg/m^2 caused neuropathy in 46.5% of patients (Naito et al., 2008), otherwise it induced neuropathy in 11.5% of patients with ovarian, esophageal, or corpus uteri cancers, for which this agent at 70 mg/m^2 was approved (Muro et al., 2004; Katsumata et al., 2005). However, no study that examined Japanese patients has reported neuropathy in patients with breast, gastric, lung, or head and neck cancers, for which this agent at 60 mg/m^2 was approved. In this study, the incidence of DOC-induced neuropathy was evaluated by the nurses from the outpatient chemotherapy clinic experienced in the management of chemotherapies. Nevertheless, this incidence was apparently higher than that reported by the assumed domestic clinical study, partly due to a higher dose of DOC adopted in our hospital, as well as a possibly different evaluation method for adverse effects, relative to the domestic clinical study. On the other hand, when including NCI-CTC grade 1-4 used primarily to evaluate taxane-induced neuropathy, the incidence of neuropathy was within the previously-reported range. The incidence of taxane-induced neuropathy has varied markedly among the reports. Thus, when comparing the reported studies, we should pay attention to the evaluation method of individual studies. It is difficult to control this side effect because the mechanisms underlying the development of neuropathy have not been clarified. The most widely accepted proposed mechanism for taxane-induced peripheral neuropathy is that an atrophic effect starting at the distal nerve endings, followed by changes in Schwann cells, the neuronal body, or axonal transport and the downregulation of the expression of proteins and other components involved in active neuronal intracellular transport play the most significant roles in the induction of taxane-induced peripheral neuropathy (Argyriou et al., 2008). Several types of neuroprotective agent have been tested as treatments for taxane-induced neuropathy in animal and clinical models (Lee and Swain, 2006). Currently, lamotrigine (RAO et al., 2008), amifostine (NCT00078845), dimesna (NCT00077311), and BNP7787 (NCT00039780) are being evaluated as treatments for the prevention of taxane-induced neuropathy in phase II or III clinical trials.

It is extremely difficult to appropriately evaluate the incidence and severity of chemotherapy-induced peripheral neuropathy. The NCI-CTC-evaluation criteria are the most widely used system for assessing peripheral neuropathy, but the 5 grades of this system are not capable of reflecting exact details and subtle changes (Trotti et al., 2003). Peripheral neuropathy is classified into 3 grades in the DEB-NTC (Inoue et al., 2011). The definitions of grade 1 and grade 2 neurotoxicities differ between the two scales. The NCI-CTC places major emphasis on the severity of a range of objective neuropathies that have no effect on daily living, whereas the DEB-NTC places importance on the duration of the peripheral neurotoxicity (Table 1). As the symptoms and severity of peripheral neuropathy are largely subjective in nature, it is logical that assessments of neuropathy should be based, at least in part, on self-reported patient data. For these reasons, patient-based assessment instruments such as the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (Fact/GOG-Ntx) (Calhoun et al., 2003), the QLQ-CIPN20 of the European Organization for Research and Treatment of Cancer (EORTC) (Postma et al., 2005), and the Patient Neurotoxicity Questionnaire (PNQ) (Hausheer et al., 2006) have been used in combination with or instead of physician-based instruments. VAS is a long-established and excellent instrument for evaluating subjective symptoms (Huskisson, 1974). This patient-based assessment system is widely employed to estimate sensation in many fields, such as cancer pain (Smith et al., 2002) and neuropathic pain (Gilron et al., 2005). Although a few studies have compared the utility of VAS with other methods for assessing peripheral neuropathy (Takemoto et al., 2012), VAS questionnaires appear to be easy for patients to fill in, and it also easy for physicians to tally up VAS results.

A limitation of this study was that placebo was not used as a control group and it was not double-blind design and the number of patients was small. Nevertheless, our findings suggest that DOC-associated peripheral neurotoxicity can be suppressed by the administration of GJG. By reducing side effects, it may become possible to medicate a high dose of DOC and also a long period of time and a prognosis improvement effect may be shown. It will be necessary to confirm the usefulness of GJG by performing larger prospective studies in the future.

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