Clinical Study Protocol

A randomized, open-label phase II study on the preventive effect of goshajinkigan against peripheral neuropathy induced by paclitaxel-containing chemotherapy: The OLCSG2101 study protocol

Naoki Nakamura[a], Go Makimoto[b], Takaaki Tanaka[a], Yuka Kato[c, e], Isao Oze[d], Toshiyuki Kozuki[e], Toshihide Yokoyama[f], Hirohisa Ichikawa[g], Shoichi Kuyama[h], Naofumi Hara[i], Yoshinobu Maeda[a], and Katsuyuki Hotta[c]

[a]Department of Hematology, Oncology, and Respiratory Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, [b]Department of Allergy and Respiratory Medicine, [c]Center of Innovative Clinical Medicine, Okayama University Hospital, Okayama 700-8558, Japan, [d]Division of Cancer Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya 464-8681, Japan, [e]Department of Respiratory Medicine, Shikoku Cancer Center, Matsuyama 791-0280, Japan, [f] Department of Respiratory Medicine, Kurashiki Central Hospital, Kurashiki 710-8602, Japan, [g]Department of Respiratory Medicine, KKR Takamatsu Hospital, Takamatsu 760-0018, Japan, [h]Department of Respiratory Medicine, Iwakuni Clinical Center, Iwakuni 740-8510, Japan, [i]Department of Respiratory Medicine, Okayama Rosai Hospital, Okayama 702-8055, Japan.

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Corresponding author:

Go Makimoto, Department of Allergy and Respiratory Medicine, Okayama University Hospital, 2-5-1 Shikata-cho Kita-ku, Okayama 700-8558, Japan

Phone: +81-86-235-7227, Fax: +81-86-232-8226, E-mail: gmakimoto5@okayama-u.ac.jp

https://orcid.org/0000-0002-0638-8435

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Abbreviations

PTX, paclitaxel; CIPN, chemotherapy-induced peripheral neuropathy; GJG, goshajinkigan; QOL, quality of life; CTCAE, common terminology criteria for adverse events; NSCLC, non-small cell lung cancer; CBDCA, carboplatin; PNQ, patient neurotoxicity questionnaire; TTF, treatment failure

Abstract

Background: Paclitaxel (PTX) is an essential cytotoxic anticancer agent and a standard treatment regimen component for various malignant tumors, including advanced unresectable non-small cell lung cancer, thymic cancer, and primary unknown cancers. However, chemotherapy-induced peripheral neuropathy (CIPN) caused by PTX is a significant adverse event that may lead to chemotherapy discontinuation and deterioration of the quality of life (QOL). Although treatment modalities such as goshajinkigan (GJG), pregabalin, and duloxetine are empirically utilized for CIPN, there is no established evidence for an agent as a preventive measure. We designed a randomized phase II trial (OLCSG2101) to investigate whether prophylactic GJG administration can prevent the onset of CIPN induced by PTX.

Methods: This study was designed as a two-arm, prospective, randomized, multicenter phase II trial. The patients will be randomly assigned to either the GJG prophylaxis arm (Arm A) or the GJG non-prophylaxis arm (Arm B), using cancer type (lung cancer or not) and age (<70 years or not) as adjustment factors. A total of 66 patients (33 in each arm) will be enrolled.

Discussion: The results of this study may contribute to better management of CIPN, which can enable the continuation of chemotherapy and maintenance of the patient's QOL.

Ethics and Dissemination: Ethical approval was obtained from the certified review board of Okayama University (approval no. CRB21-005) on September 28, 2021. Results will be published in peer-reviewed journals and presented at national and international conferences.

Trial registration: Japan Registry of Clinical Trials (registration number jRCTs061210047).

Keywords: Kampo, CIPN, prophylaxis, neuropathy, taxane

1. Introduction

Paclitaxel (PTX) is a cytotoxic anticancer agent that is a part of the standard treatment regimen for several malignant tumors, including inoperable advanced or recurrent non-small cell lung cancer (NSCLC), thymic cancer, and cancers of unknown primary origin. However, PTX often induces peripheral neuropathy, and it has been reported that 39% of patients with NSCLC undergoing carboplatin (CBDCA) + PTX therapy develop grade 2 or higher peripheral sensory neuropathy [1].

Chemotherapy-induced peripheral neuropathy (CIPN) is a significant adverse event that impedes chemotherapy continuation and decreases patients' quality of life (QOL), and yet, its detailed mechanisms remain largely unknown. Treatments such as goshajinkigan (GJG), pregabalin, and duloxetine are used empirically, albeit with limited efficacy [2]. For instance, in a trial comparing duloxetine to placebo in patients experiencing painful CIPN following the cessation of platinum or taxane agents, the duloxetine group showed a significant reduction in pain (reduction in the numeric rating scale score) compared with the placebo group [3]. However, the pain did not resolve completely, suggesting that treatment initiated after CIPN onset is unlikely to result in complete pain elimination.

Furthermore, no drugs with proven efficacy in CIPN prevention are currently available [2]. When CIPN is observed, the primary management strategies involve postponing or reducing the dosage of the causative agent or altering or discontinuing the chemotherapy regimen, which

underscores the potential impact of CIPN prevention on improving cancer treatment outcomes and enhancing the patients' QOL.

GJG, a traditional Japanese herbal medicine, has been reported to be effective against diabetic neuropathy [4]. In the context of CIPN prevention, a double-blind, randomized phase III trial assessed the prophylactic effect of GJG against CIPN in patients undergoing modified FOLFOX6 therapy (with oxaliplatin) after colorectal cancer surgery. The study found a higher incidence of grade 2 or higher CIPN in the GJG group (50.6%) compared to the placebo group (31.2%), leading to early termination of the trial due to negative outcomes [5].

However, prophylactic administration of GJG for CIPN has not been discontinued due to all anticancer agents. This is because agents commonly associated with CIPN, such as platinum compounds, taxanes, vinca alkaloids, and bortezomib, can cause pathologically distinct types of nerve damage depending on the individual drug. CIPN resulting from platinum compounds, such as oxaliplatin, primarily affects the cell bodies, whereas taxanes, such as PTX and docetaxel, as well as vinca alkaloids, which have a microtubule-damaging effect, lead to axonal damage, often presenting clinically as glove- and stocking-type of neuropathies that begin at the distal extremities. The pathological differences in the nerve damage caused by the respective causative agents not only underlie their different mechanisms of action but may also indicate the need for distinct prevention and treatment strategies. In other words, although GJG prophylaxis for oxaliplatin-induced CIPN may have been ineffective, different outcomes may be observed for CIPN caused by anticancer agents that lead to axonal damage.

A trial demonstrated favorable GJG outcomes for CIPN prevention in patients undergoing docetaxel-containing chemotherapy for breast cancer. In this non-blind randomized trial comparing the effects of GJG with vitamin B12, the incidence of CIPN was significantly lower in the GJG group (39.3%) than in the vitamin B12 group (88.9%). Moreover, when the severity of CIPN was classified according to the common terminology criteria for adverse events (CTCAE) ver3.0, there was a significantly lower incidence of grade 2 or higher CIPN in the GJG group. These findings suggest the potential value of GJG in preventing CIPN in patients with breast cancer undergoing docetaxel-containing chemotherapy [6], in contrast to the outcomes observed for oxaliplatin-induced CIPN.

Animal studies for evaluating the prophylactic use of GJG for PTX-induced CIPN have also been conducted. In rats, the administration of PTX alone led to a significant decrease in the pain threshold compared to controls, whereas the PTX + GJG group showed a temporary decrease in the pain threshold, followed by a return to the control levels, indicating the suppressive effect of GJG on mechanical allodynia [7].

In summary, non-clinical studies have demonstrated GJG efficacy in mitigating taxane-induced hyperalgesia, and GJG administration in patients with breast cancer has been shown to suppress the onset of docetaxel-induced CIPN. These findings led to the formulation of the current research plan to evaluate the potential usefulness of GJG prophylaxis in preventing PTX-induced CIPN.

2. Patients and Methods

2.1 Objective

The objective of this study is to elucidate the prophylactic effects of GJG against peripheral neuropathy induced by chemotherapy regimens containing PTX.

2.2 Study Design

This is a two-armed, prospective, randomized, multicenter, phase II trial. Figure 1 presents an overview of the study design. Written informed consent will be obtained from all patients before any screening or inclusion procedures. This study will be conducted in compliance with the principles of the Declaration of Helsinki, and the protocol has been approved by the Certified Review Board of Okayama University (approval no. CRB21-005) on September 28, 2021, and registered with the Japan Registry of Clinical Trials (registration number jRCTs061210047).

2.3 Endpoints

The study's primary endpoint is the proportion of patients developing grade 2 or higher CIPN based on the CTCAE version 5.0 by the completion of four chemotherapy cycles. The secondary outcome measures are as follows: 1) time from chemotherapy initiation to the onset of grade 2 CIPN. 2) CIPN incidence and severity at the end of each chemotherapy cycle are evaluated using CTCAE grades and the patient neurotoxicity questionnaire (PNQ). 3) The relative PTX dose intensity. 4) Adverse events other than peripheral neuropathy. 5) The proportion of patients

developing grade 2 or higher CIPN by the completion of four chemotherapy cycles, excluding patients to whom four cycles could not be administered for reasons other than CIPN. 6) The duration of time to treatment failure (TTF). The PNQ is a tool used to assess the severity of peripheral neuropathy in patients, particularly those undergoing chemotherapy. Peripheral neuropathy is a common side effect of certain cancer treatments, causing symptoms such as numbness, tingling, and pain in the hands and feet. The PNQ is designed to be patient-reported, allowing individuals to self-assess the extent of their symptoms [8]. It typically includes questions that cover the following aspects:

1. Sensory Symptoms: Questions addressing the presence and intensity of sensory symptoms like numbness, tingling, or burning sensations. We also evaluate how neuropathy affects the patient's ability to perform routine tasks and activities.

2. Motor Symptoms: Questions about motor symptoms, such as weakness or difficulty in performing daily activities. We also evaluate how neuropathy affects the patient's ability to perform routine tasks and activities.

The responses are usually evaluated on a five-point scale, allowing for a quantitative assessment of the severity of symptoms. This helps clinicians monitor changes over time, evaluate the impact of treatment interventions, and make necessary adjustments to the patient’s treatment plan. The PNQ is collected before every cycle of treatment and 3-4 weeks after the fourth cycle of treatment.

2.4 Eligibility Criteria

All patients who meet the inclusion criteria will be invited to undergo screening. The main inclusion and exclusion criteria are presented in Table 1.

2.5 Randomization

After the eligibility criteria have been confirmed to have been met by a patient, their registration will be performed by e-mail. The minimization method will be employed to assign patients randomly to either the GJG prophylaxis arm (Arm A) or GJG non-prophylaxis arm (Arm B), using the cancer type (lung cancer or not) and age (<70 years or not) as adjustment factors.

2.6 Intervention

In Arm A, starting from the morning of the first day of CBDCA + PTX chemotherapy, patients will take GJG at a dose of 7.5 g (three sachets) divided into 2–3 doses per day (the timing of administration, whether before, between, or after meals, has not been specified). This regimen will be continued for at least 21 days after the fourth chemotherapy cycle (day 22). In this trial, the patient's "Sho" (a term in traditional Japanese medicine referring to a patient's particular syndrome or condition based on the subjective and objective findings) will not be considered. The timing of GJG administration may be changed over the course of the trial. In Arm B, no prophylactic treatment will be administered for CIPN. Upon the development of grade 2 or higher CIPN, initiation of symptomatic treatments commonly used as standard care, including GJG, will be considered. If an intervention for peripheral neuropathy is required, or if a reduction,

discontinuation, or extension of the interval between PTX administrations is necessary due to peripheral neuropathy, it will be judged as grade 2 or higher.

2.7 Follow-up

The TTF will be assessed until the point at which chemotherapy containing CBDCA + PTX or its maintenance therapy is discontinued for any reason (including disease progression, treatment toxicity, or patient preference) or until the progression of the primary disease or patient death.

For all assessments other than TTF, evaluations will be conducted 21–28 days after the administration of the fourth cycle of chemotherapy comprising CBDCA + PTX, which corresponds to days 22–29.

2.8 Statistical Consideration

This study will evaluate the prophylactic effects of GJG against peripheral neuropathy induced by chemotherapy regimens that include PTX. The study's primary endpoint is the proportion of patients developing grade 2 or higher CIPN based on the CTCAE version 5.0 by the completion of four chemotherapy cycles.

In a non-blinded randomized trial comparing patients undergoing docetaxel-containing chemotherapy for breast cancer, who were allocated to either a GJG group or vitamin B12 group, the incidence of grade 2 or higher CIPN was 18.2% in the GJG group and 48.1% in the vitamin B12 group [6]. Based on these results, it was assumed that the incidence of grade 2 or higher

CIPN would be 50% without prophylactic medications such as GJG and 20% with GJG prophylaxis. Setting an alpha error of 0.1 (two-sided) and power (1-β) of 0.75, a sample size of 27 patients per group or a total of 54 patients is required.

Furthermore, in a trial on patients with advanced or recurrent squamous NSCLC who had not received chemotherapy, the completion rate of four cycles of PTX when administered with CBDCA + pembrolizumab was 78.7%, and 1.2% of the discontinuation cases were attributable to grade 3 or higher peripheral neuropathy [9]. Considering that approximately 20% of patients may not complete four cycles of chemotherapy for reasons other than CIPN, potentially leading to dropout, 33 patients will be enrolled in each group, resulting in a total of 66 patients in the study.

3. Results

The results have yet to be obtained because this trial has not been finished.

4. Discussion

PTX is a crucial cytotoxic anticancer agent and a component of the standard treatment regimens for various malignant tumors, including inoperable advanced or recurrent NSCLC and cancers of unknown primary origin. However, PTX-induced CIPN represents a significant adverse event that can impede the continuation of chemotherapy and lead to a decline in the QOL. No drugs have been shown to be effective for CIPN prevention. If the prophylactic effect of GJG against

CIPN is proven by the results of this trial, it could contribute to the continuation of chemotherapy and maintenance of patients' QOL.

5. Conclusions

The OLCSG2101 is the prospective, randomized, multicenter, phase II trial to evaluate the prophylactic effect of GJG against CIPN. We believe that better CIPN management will lead to a safe continuation of chemotherapy. As this is a Phase II trial, if GJG shows promising preventive effects on CIPN, there is potential to verify its efficacy in a Phase III trial.

Conflict of interest

The authors have no conflicts of interest.

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Author Contributions

NN, YK, and GM participated in the trial design and setup. IO participated in the sample size calculation. All authors contributed to the protocol description.

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Table 1. Eligibility criteria of the OLCSG2101 study

Inclusion criteria:
(1) Age over 20 years old
(2) Eastern Cooperative Oncology Group (ECOG) performance status 0–1
(3) Patients who have been pathologically diagnosed with malignant tumors and are scheduled to undergo at least four cycles of chemotherapy, including carboplatin (CBDCA) and paclitaxel (PTX), with PTX administered at a dose of 150 mg/m^2 or higher every 3–4 weeks, are eligible. Chemotherapy regimens that include angiogenesis inhibitors such as bevacizumab and immune checkpoint inhibitors such as atezolizumab, pembrolizumab, and nivolumab are allowed.
(4) Adequate organ function as defined by the following: leukocyte count ≧3,000/μL, absolute neutrophil count ≧1,500/μL, platelet count ≧100,000/μL, hemoglobin level ≧9 g/dL, total bilirubin level ≦1.5 mg/dL, aspartate aminotransferase and alanine transaminase levels ≦100 IU/L, serum creatinine ≦2.0 mg/dL
(5) The objectives and contents of this study have been explained to the patient, and written consent has been obtained from the patient themselves.
Exclusion criteria:
(1) There is a history of treatment with taxane-based anticancer agents, such as paclitaxel (PTX), albumin-bound PTX, docetaxel, or cabazitaxel.

(2) There is a history of CIPN
(3) If the patient is currently taking duloxetine, pregabalin, mirogabalin, gabapentin, mecobalamin, vaccinia virus-inoculated rabbit skin inflammatory extract, tricyclic antidepressants, or goshajinkigan (GJG), including over-the-counter versions.
(4) If the patient has evident peripheral neuropathy, including symptoms such as numbness or sensory abnormalities, regardless of the cause (including orthopedic diseases, diabetes, or neuropathy resulting from previous treatments).
(5) If the patient has difficulty taking goshajinkigan (GJG) orally.
(6) Pregnant or breast-feeding women
(7) If the principal investigator or co-investigator deems the patient unsuitable for participation in the study for any other reason.

Figure Legend

Fig. 1. Overview of the study design.