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Clinical Trial Protocol

Efficacy and safety of intravenous administration of high-dose selenium for preventing chemotherapy-induced peripheral neuropathy in platinum-sensitive recurrent ovarian, fallopian or primary peritoneal cancer: study protocol for a phase III, double-blind, randomized study

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ABSTRACT

Background: The second-line chemotherapy using paclitaxel, carboplatin, and bevacizumab for treating platinum-sensitive recurrent ovarian, fallopian or primary peritoneal cancer frequently cause chemotherapy-induced peripheral neuropathy (CIPN), which is significantly associated with deterioration of quality of life. Despite the potential of some agents to prevent and treat CIPN, and there is still a lack of evidence of the effect. Although selenium has been suggested as an antioxidant candidate to prevent CIPN, there are insufficient data regarding its effect due to its low dose by oral administration. Thus, we hypothesized intravenous administration of high-dose selenium (2,000 μg/day) at each cycle of the second-line chemotherapy would prevent and reduce CIPN in patients with platinum-sensitive recurrent ovarian, fallopian or primary peritoneal cancer.
Method: This trial is an investigator-initiated, phase III, double-blinded, randomized controlled trial to evaluate the efficacy and safety of intravenous administration of high-dose selenium (2,000 μg/day) for preventing CIPN in patients with platinum-sensitive recurrent ovarian, fallopian or primary peritoneal cancer who receive paclitaxel, carboplatin, and bevacizumab. A total of 68 patients will be randomly assigned to the experimental and control groups at a 1:1 ratio. As the primary endpoint, the incidence rate of CIPN three months after six cycles of chemotherapy will be compared between the two groups according to the combined criteria of neuropathy using the World Health Organization-CIPN criteria and Common Terminology Criteria for Adverse Events version 5.0. As secondary endpoints, we will compare adverse events, patient-reported quality of life, and requirement of concomitant drugs for reducing CIPN between the two groups.

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Trial Registration
ClinicalTrials.gov Identifier: NCT04201561

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: P.S.J., Y.G.W., L.N., L.S., K.H.S.; Funding acquisition: K.H.S.; Investigation: P.S.J., L.M.; Resources: P.H.; Supervision: L.N., L.S., L.M., K.H.S.; Writing -original draft: P.S.J.; Writing - review & editing: Y.G.W., P.H., L.M., K.H.S.

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Keywords: Selenium; Platinum-Sensitive; Recurrent; Ovarian Cancer; Chemotherapy; Neuropathy

INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common toxicities in taxane- and platinum-based chemotherapy for treating patients with ovarian, fallopian or primary peritoneal cancer [1-3], and up to 76% of the patients suffer from CIPN after the chemotherapy [4]. Moreover, the development of CIPN may lead to a dose reduction of chemotherapeutic agents by 17% [5], and may worsen the quality of life (QoL) of patients [6-11].

In particular, the clinical presentation of CIPN by paclitaxel or carboplatin is shown as symmetrical, glove-stocking distribution, and progressive pattern. Paclitaxel causes sensory and motor neuropathy, while carboplatin is mainly associated with sensory neuropathy [12]. Paclitaxel-induced neuropathy shows significant dose-limiting toxicity, whereas the reversibility of the neuropathy after cessation is not apparent [13,14]. On the other hand, carboplatin-induced neuropathy can develop during or several weeks after the administration and may cause more severe neurotoxicity when combined with other neurotoxic agents [12]. Moreover, bevacizumab used for treating recurrent ovarian, fallopian, or primary peritoneal cancer also causes CIPN [15]. Furthermore, the number of recurrences is associated with a more severe degree of CIPN, and the degree of CIPN remained stable six months after the last chemotherapy [2].

The assessment of CIPN includes clinician-based scales or patient-reported outcome measures because a single modality cannot reflect various aspects of CIPN such as pain, sensory and motor functions, and the degree of activities of daily living [16]. Furthermore, the incidence of CIPN varies widely with regards to the modalities of assessment [17]. Therefore, the evaluation of CIPN should be performed in diversified ways, and the evaluation should be done by combining both subjective and objective evaluation by physicians and patients.

Despite the frequent occurrence of CIPN and related deterioration of QoL in patients with ovarian, fallopian, or primary peritoneal cancer, the effective prevention and treatment strategy of CIPN is not well elucidated. For preventing CIPN, some agents such as magnesium, calcium, anticonvulsants, venlafaxine, vitamin E, and B6 have been evaluated, which still show a lack of evidence [18-22]. Although some drugs such as gabapentin, tricyclic antidepressants, anticonvulsants, non-steroidal anti-inflammatory drugs, and opioids are used to treat CIPN in the clinical setting [23], duloxetine, a serotonin-norepinephrine reuptake inhibitor, is known to be useful among them, however with limited relevant evidence in gynecologic cancer patients [24,25].

On the other hand, there are some shreds of evidence supporting selenium as a candidate for a neuroprotective agent for patients undergoing taxane- and platinum-based chemotherapy. Since CIPN can develop by oxidative stress and relevant mitochondrial dysfunction [26,27], selenium which acts as an antioxidant is expected to have the preventive potential to improve CIPN after taxane- and platinum-based chemotherapy because serum levels of selenium have been reported to decrease significantly in patients with gynecologic cancers [28,29]. A

previous study also supports this hypothesis because selenium supplementation increased the possibility of prevention or reduction of CIPN [18].

However, the effect of selenium for preventing CIPN might be reduced by oral administration of low-dose selenium. Previous studies failed to reveal the effect of selenium on the prevention of CIPN in cancer patients undergoing chemotherapy after oral administration of selenium of 100–800 μg/day [30-34]. In contrast, intravenous administration of high-dose selenium can enhance the effect of selenium with acceptable toxicity because previous studies where intravenous selenium was administered of up to 5,000 μg/day showed few adverse events [35-38]. Nonetheless, the most common grade 3 toxicity at 5,000 μg/day was restlessness and pain [38]. When considering these toxicity results it was decided to administer selenium at a lower dose than 5,000 μg/day since pain can affect the primary outcome of our study. Previously reported selenium-related toxic symptoms were garlic odor, brittle nail and hair, and gastrointestinal discomfort, and all of them were graded as mild according to the National Cancer Institute grading system [35]. Also, intravenous high-dose sodium selenite administration trials on severely ill patients have reported less than 2% of selenium-related toxicity events [39].

Therefore, we hypothesized that intravenous administration of high-dose selenium of 2,000 μg/day before chemotherapy using paclitaxel, carboplatin, and bevacizumab could prevent CIPN with acceptable adverse events for treating platinum-sensitive ovarian, fallopian or primary peritoneal cancer. The Institutional Review Board at Seoul National University Hospital approved this study in November 2019 (No. 1909-077-106), and this study was registered on Clinicaltrials.gov in December 2019 (No. NCT04201561).

PROTOCOL

1. Objective

This phase III, double-blind, the randomized trial aims to evaluate the safety and efficacy of intravenous administration of high-dose selenium for preventing CIPN in patients with platinum-sensitive recurrent ovarian, fallopian or primary peritoneal cancer who receive paclitaxel, carboplatin and bevacizumab.

2. Endpoints

The primary endpoint is to compare the incidence rate of CIPN at three months after six cycles of chemotherapy between the experimental (selenium) and control groups (placebo). The secondary endpoints are to compare adverse events, patient-reported QoL, and requirement of concomitant drugs for reducing CIPN between the two groups. CIPN will be assessed based on the combined criteria of the World Health Organization (WHO)-CIPN criteria and Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (**Table 1**). According to this criterion, the incidence rate of CIPN at three months after six cycles of chemotherapy will be defined as the number of patients who will show grade 1 or higher neuropathy in terms of paresthesia, pain, or motor function divided by the total number of patients in each group [40,41]. Adverse events will be assessed at three weeks after each cycle of chemotherapy and three months after six cycles of chemotherapy according to the CTCAE version 5.0 [41]. Patient-reported QoL will be evaluated at baseline, at least three weeks after three and six cycles of chemotherapy, and at least three months after six cycles of chemotherapy by using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire

Table 1. Evaluation of chemotherapy-induced peripheral neuropathy

Factors	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Paresthesia	No symptom	Presence of paresthesia and/or decreased DTR (no requirement of medication)	Severe paresthesia (improved with medication, tolerable without medication)	Intolerable paresthesia (intolerable without medication)	Life-threatening consequence: urgent intervention indicated (death related to overdose of medication)
Pain	NRS 0	NRS 1–3	NRS 4–6	NRS 7–9	NRS 10
Motor function	No weakness	Normal ADL	Limiting instrumental ADL and/or light muscle weakness	Limiting self-care ADL and/or marked muscle weakness	Life-threatening consequence: urgent intervention indicated

ADL, activity of daily living; DTR, deep tendon reflex; NRS, numerical rating scale.

Table 2. Schematic diagrams for the schedule

Measurement	Screening	1st cycle	2nd cycle	3rd cycle	4th cycle	5th cycle	6th cycle	Follow-up
Informed consent	O							
Review of the inclusion and exclusion criteria	O							
WHO performance status	O	O	O	O	O	O	O	
CIPN assessment	O	O*	O*	O*	O*	O*	O*	O
Electrocardiogram	O	O*	O*	O*	O*	O*	O*	O
Laboratory test†	O	O‡	O‡	O‡	O‡	O‡	O‡	O
Adverse events		O	O	O	O	O	O	O
Quality of life	O§			O‖			O‖	O¶

CIPN, chemotherapy-induced peripheral neuropathy; WHO, World Health Organization.
*Performed three weeks after each cycle of chemotherapy; †Complete blood count, including hematocrit, hemoglobin and platelet, and serum levels of aspartate aminotransferase, alanine aminotransferase, albumin, total bilirubin, and creatinine; ‡Performed within one week before each cycle of chemotherapy; §Quality of life is assessed by EORTC-QLQ-C30, EORTC-CIPN20, before the first cycle of chemotherapy; ‖Quality of life is assessed by EORTC-QLQ-C30, EORTC-CIPN20 at least three weeks after three and six cycles of chemotherapy; ¶Quality of life is assessed by EORTC-QLQ-C30, EORTC-CIPN20 at least three months after six cycles of chemotherapy.

(EORTC QLQ-C30) [42] and the European Organization for Research and Treatment of Cancer Chemotherapy-Induced Peripheral Neuropathy-20 (EORTC CIPN-20) (**Table 2**) [43]. Moreover, the number, dose, and duration of gabapentin, duloxetine, and celecoxib used for treating CIPN as concomitant drugs will be compared between the two groups.

3. Study design

Investigator-initiated, phase III, single-center, double-blinded, randomized controlled trial.

ELIGIBILITY CRITERIA

1. Inclusion criteria

1) Informed consent.
2) Age: 19–80 years old.
3) Epithelial ovarian cancer, fallopian cancer, or primary peritoneal cancer.
4) Complete or partial response after six to nine cycles of chemotherapy using paclitaxel and carboplatin as the first-line treatment according to Response Evaluation Criteria In Solid Tumors (RECIST) or Gynecologic Cancer Intergroup criteria (GCIG) after adjuvant chemotherapy for treating epithelial ovarian cancer [44,45].
5) Disease recurrence at least six months after the first-line chemotherapy.
6) No previous treatment with bevacizumab
7) Plan of the second-line chemotherapy using paclitaxel, carboplatin, and bevacizumab.
8) Eastern Cooperative Oncology Group performance status 0 to 2.
9) No other concurrent disease affecting survival.
10) Normal hematologic, renal, and hepatic functions.

2. Exclusion criteria

1) Pregnancy or breastfeeding.
2) Plan of secondary debulking surgery.
3) Previous treatment with bevacizumab.
4) No plan of the second-line chemotherapy using paclitaxel, carboplatin, and bevacizumab.
5) Other concurrent diseases affecting survival.
6) Underlying diseases such as diabetes, neuropathy, brain, or bone metastasis that can induce neuropathy.
7) Allergy to selenium.
8) Considered to be inappropriate to enroll in a clinical trial at the discretion of the investigator, participation would not be in the best interest of the subject, or that could prevent, limit or confound the assessments

SAMPLE SIZE JUSTIFICATION

In previous studies, the incidence rate of CIPN was 25% when combined with antioxidants [19], whereas it was at least 62.5% without antioxidants three months after chemotherapy using paclitaxel or cisplatin [20]. We expect that 25% of patients will develop CIPN when treated with selenium and chemotherapy, while 62.5% of patients in the control group will develop CIPN. Group sample sizes of 24 in each group are needed to achieve 80% power to detect a difference between the group proportions of −0.37, and the test statistic used is the two-sided Z-Test with unpooled variance, and the significance level of the test is 0.05. However, to evaluate the effect of selenium on the prevention of CIPN, the proportion of patients who can complete six cycles of chemotherapy using paclitaxel, carboplatin, and bevacizumab should be maintained above the lowest proportion. In the Gynecologic Oncology Group (GOG)-213 study, the percentage of patients who completed the planned 4–6 cycles was found to be 85.8% [15]. Therefore, a total of 68 cases, comprising 34 cases per group, is required to evaluate the efficacy of selenium administration, to assume 80% of completion rate for six cycles with consideration of the additional dropout rate of 10%.

RANDOMIZATION

After confirming the eligibility criteria, patients will be randomized into the experimental and control groups as a 1:1 ratio. Randomization table will be produced through a reproducible web-based program and managed by the third-party unblind staff who is an expert in gynecologic oncology (**Fig. 1**).

TREATMENT

1. Experimental group

Before administering the chemotherapeutic agents at each cycle, sodium selenite pentahydrate 2,000 μg/40 mL (Selentab®; Boryung Co., Ltd, Seoul, Korea) will be administered by intravenous infusion over two hours, similar to a previous study every three weeks for six cycles [46]. After that, paclitaxel (175 mg/m^2), carboplatin (area under the curve 5), and bevacizumab (15 mg/kg) will be administered intravenously over 3, 1 and 1.5 hours respectively, for six cycles every three weeks according to GOG-231 protocol [15]. Since the

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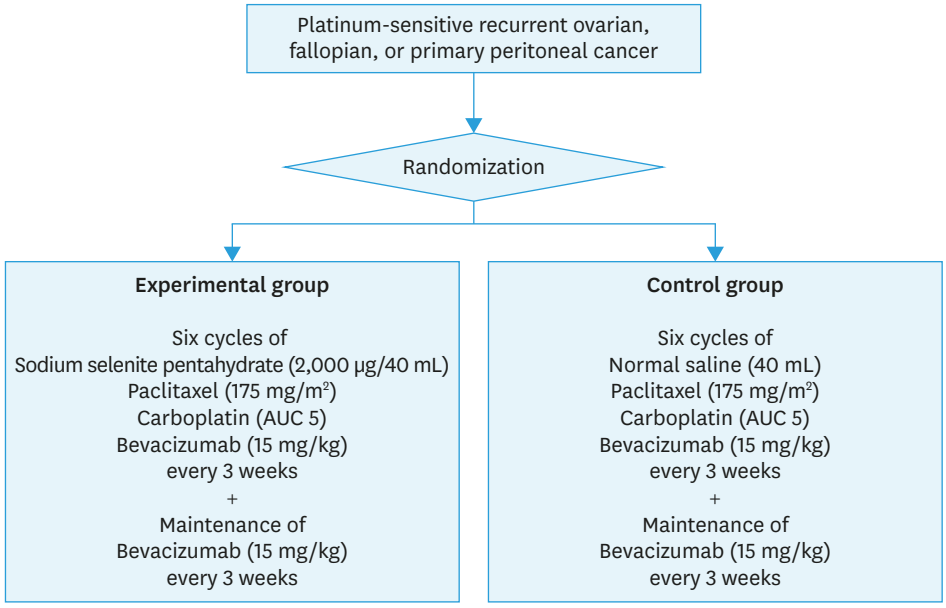

Fig. 1. Schema of this study.
AUC, area under the curve.

elimination half-life of selenium ranges from 17 to 29 hours [38], which is longer than that of paclitaxel (6 to 10 hours) or carboplatin (5 to 6 hours) [47], we decided that the intravenous administration of selenium two hours before chemotherapy might be enough to protect CIPN. After completion of six cycles of chemotherapy using paclitaxel, carboplatin, and bevacizumab, only bevacizumab will be administered as a maintenance therapy every three weeks until relapse, medical necessity or willingness of patients.

2. Control group

Before administering the chemotherapeutic agents at each cycle, normal saline of 40 ml will be administered by intravenous infusion over two hours as a placebo every three weeks for six cycles. After that, paclitaxel (175 mg/m^2), carboplatin (area under the curve 5), and bevacizumab (15 mg/kg) will be administered intravenously over 3, 1 and 1.5 hours respectively for six cycles every three weeks based on GOG-213 protocol [15]. After completion of six cycles of the combination of chemotherapy, only bevacizumab will be administered as a maintenance therapy every three weeks until relapse, medical necessity, or willingness of patients.

MONITORING

Adverse events will be evaluated periodically on the Data Safety and Monitoring Board composed of independent experts without conflict of interest in this study.

STATISTICAL ANALYSIS

Both Intention-To-Treat (ITT) and Per-Protocol (PP) populations will be analyzed. The incidence rate of CIPN three months after six cycles of chemotherapy will be evaluated by

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using the Logistic Regression analysis to analyze the odds ratio. Adverse events and patient-reported QoL will be compared between the two groups by using ordinal logistic regression and generalized estimating equations to see if there are differences between the two groups. The number, dose, and duration of the combined medication will be compared and evaluated using the χ^2 or Fisher's exact test, and the Student-T or Mann-Whitney U test.

DISCUSSION

This is the first study to evaluate the effect of intravenous high-dose selenium administration for the prevention of CIPN. However, few data have shown the effect of selenium on the prevention of CIPN in terms of a well-designed clinical trial. We designed this phase III trial to show the impact of selenium compared to placebo and evaluating CIPN in several aspects. The result of this study will further contribute to conducting a well-designed large-scale trial to evaluate the efficacy of selenium for CIPN prevention.

In addition, previous trials on the prevention of CIPN are known to have shown little positive results. This is because the main outcome of these trials was the various symptoms of neuropathy, subjective evaluation by the clinicians, and subjective evaluation by the patient [48]. Since these limitations also hinder to design a relevant phase II trial, we designed this phase III randomized controlled trial to practically evaluate the preventive effect of selenium on CIPN by hypothesizing the selenium dose and schedule, expected to show little toxicity and maximal effect with the uniform assessment modality for evaluating CIPN. In the future, the results from this study will act as a reference for designing large-scale relevant phase III trials. In addition, the limitation of this clinical trial is that long-term follow-up of CIPN does not occur beyond 3 months after the last chemotherapy. Therefore the long-term effect of selenium should be evaluated in further study.

Furthermore, the cumulative toxicity might increase the incidence of CIPN at the time of enrollment because some degree of patients is known to have persistent neuropathic symptom six months after last chemotherapy. However, chemo-naïve patients might complain neuropathic symptoms, which is not associated with chemotherapy [2], and patients who have undergone chemotherapy will be able to recognize and tell whether the symptoms are neuropathy associated with chemotherapy. In addition, since patients who have previously experienced neuropathy caused by anticancer drugs want to avoid these side effects again, it is considered that the prevention of CIPN for patients receiving second-line treatment would be more meaningful than the first-line treatment.

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