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Efficacy and safety of intravenous administration of high-dose selenium for preventing chemotherapy-induced peripheral neuropathy in platinum-sensitive recurrent ovarian cancer: a phase 3, double-blind, parallel group, randomized controlled pilot study

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Abstract

Background Chemotherapeutic agents for ovarian cancer commonly cause chemotherapy-induced peripheral neuropathy (CIPN), significantly impairing quality of life (QoL). Selenium, a potent antioxidant, may mitigate toxicity and improve QoL in cancer patients. This study evaluated intravenous high-dose selenium for preventing neuropathic symptoms in platinum-sensitive recurrent ovarian cancer (PSROC).

Methods A phase 3, double-blind, parallel group, randomized controlled pilot trial enrolled 68 patients with PSROC, randomized 1:1 to the experimental (selenium) and control (placebo) groups. Patients received sodium selenite pentahydrate (2000 μg /40 mL) or normal saline intravenously two hours before paclitaxel-carboplatin-bevacizumab infusion for six cycles. The primary endpoint was the incidence of grade 1 or more CIPN at 3 months following six cycles of chemotherapy, comparing the experimental group to the control group. Secondary endpoints included comparisons of grade 1 or more, grade 2 or more CIPN before each cycle, 3 weeks and 3 months after six cycles of chemotherapy, adverse events, QoL, and the need for concomitant medications to manage CIPN, and survival between the two groups.

Results We enrolled sixty-eight patients in the study. The incidence of grade 1 or more CIPN did not differ between the two groups at 3 months post-chemotherapy. However, grade 2 or motor dysfunction incidence was significantly lower in the experimental group before cycle 3 (3.3% vs. 23.3%; $P=0.02$) and before cycle 4 (3.3% vs. 20%; $P=0.04$), particularly in patients ≥ 60 years. QoL showed no statistically significant difference between the two groups. Duloxetine/gabapentin usage and adverse events were comparable between the two groups,

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with no selenium-related toxicity, and there were no differences in progression-free and cancer-specific survivals between the two groups.

Conclusions Intravenous high-dose selenium safely failed to reduce grade 1 or more CIPN, whereas it reduced grade 2 or more motor dysfunction during chemotherapy in patients with PSROC, especially those ≥ 60 years. While the primary endpoint was not met, selenium showed the potential of protective effects against motor neuropathy without safety and survival concerns.

Trial registration ClinicalTrials.gov Identifier: NCT04201561.

Keywords Chemotherapy, Neuropathy, Ovarian cancer, Platinum-sensitive, Recurrent, Selenium

Background

Chemotherapy-induced peripheral neuropathy (CIPN) is a common and debilitating side effect of many chemotherapeutic agents, significantly impacting patients' quality of life and long-term survivorship [1–5]. Studies report that up to 76% of the patients experience CIPN within the first month after chemotherapy, and approximately 30% continue to suffer from symptoms for six months or longer after treatment ends [5]. The prevalence of CIPN varies widely depending on the agent used, ranging from 19% to over 85%. Notably, the highest rates are seen with platinum-based compounds (70–100%) and taxanes (11–87%) [6, 7].

Clinically, CIPN caused by paclitaxel or carboplatin typically presents as a symmetrical, glove-and-stocking distribution neuropathy that progresses over time. Paclitaxel can induce both sensory and motor neuropathies, while carboplatin is primarily associated with sensory neuropathy [8]. Paclitaxel-induced neuropathy shows significant dose-limiting toxicity, and its reversibility after cessation of treatment remains uncertain [9, 10]. Cisplatin, another platinum compound, is known for causing prolonged and sometimes irreversible neuropathy, as platinum accumulates in nerve tissue and remains neurotoxic [11]. Given these challenges, prevention is considered the most effective strategy for managing CIPN.

Despite the high incidence and significant impact of CIPN by taxane- and platinum-based chemotherapy, there are currently no pharmacologic agents recommended by the American Society of Clinical Oncology for its prevention [12]. Various agents—including magnesium, calcium, anticonvulsants, venlafaxine, and antioxidants such as vitamin E and acetyl-L-carnitine—have been investigated, but none have demonstrated conclusive efficacy [13–17]. For symptomatic treatment, medications such as gabapentin, tricyclic antidepressants, anticonvulsants, non-steroidal anti-inflammatory drugs, and opioids are sometimes used, though often with limited success and reluctance [18].

At present, duloxetine, a serotonin-norepinephrine reuptake inhibitor, is the only agent recommended for the treatment of painful CIPN [19]. However, recent preliminary data suggest that duloxetine does not prevent CIPN when compared to placebo [20]. The lack of effective preventive measures underscores the need for new agents and targeted interventions, especially given the complex pathogenesis of CIPN.

Selenium, an essential trace element, acts as a cofactor for selenoproteins like glutathione peroxidases and thioredoxin reductases, which are crucial in reducing reactive oxygen species generated by chemotherapeutic agents. By mitigating oxidative stress-induced neuronal damage and mitochondrial dysfunction [21, 22], selenium has been proposed as a potential neuroprotective agent for patients receiving taxane- and platinum-based chemotherapy [23, 24]. The first preclinical study has shown that oral selenium supplementation can partially protect against cisplatin-induced peripheral nerve damage in an animal model [13]. However, clinical trials using oral selenium (100–800 μg/day) in cancer patients have not demonstrated significant preventive effects against CIPN [25–29]. In contrast, intravenous administration of high-dose selenium (up to 5000 μg/day) has shown potential benefits and acceptable safety profiles in clinical settings such as cardiac surgery, refractory solid tumors, and non-Hodgkin's lymphoma [30–33]. Of note, the most common grade 3 toxicity at 5000 μg/day was restlessness and pain [33]. Therefore, it was decided to administer selenium at a lower dose than 5000 μg/day since pain can affect the primary outcome of our study.

Given these findings, the objective of this study is to evaluate the efficacy and safety of intravenous high-dose selenium (2000 μg/day) administered prior to chemotherapy with paclitaxel, carboplatin, and bevacizumab in preventing CIPN for patients with platinum-sensitive recurrent ovarian cancer (PSROC).

Methods

Study design

This investigator-initiated, phase 3, double-blind, parallel group, randomized controlled pilot trial aimed to evaluate whether intravenous administration of high-dose selenium can prevent CIPN in patients with PSROC undergoing chemotherapy. All participants provided

informed consent prior to enrollment. The study was approved by the Institutional Review Board in November 2019 (No. 1909–077–106) and registered on Clinicaltrials.gov in December 2019 (No. NCT04201561).

Patient characteristics

Patients were recruited from a single center. Eligible criteria were as follows: (1) age between 19 and 80 years; (2) diagnosis of epithelial ovarian cancer with platinum-sensitive recurrence, defined as recurrence occurring at least six months after achieving a complete or partial response to six to nine cycles of first-line chemotherapy with paclitaxel and carboplatin; (3) eligibility for second-line chemotherapy with paclitaxel, carboplatin, and bevacizumab; (4) Eastern Cooperative Oncology Group performance status 0 to 2; (5) no prior treatment with bevacizumab; and (6) normal hematologic, renal, and hepatic organ function. The major exclusion criteria were as follows: (1) patients planned to receive secondary debulking surgery, (2) previous treatment with bevacizumab, (3) underlying disease such as diabetes, brain, or bone metastasis combined with neuropathy, and (4) allergy to selenium. Treatment response was assessed according to the Response Evaluation Criteria in Solid Tumors or Gynecologic Cancer Intergroup criteria [34, 35].

Intervention

Eligible patients were randomized in a 1:1 ratio to either the experimental or control group. Randomization was performed using a reproducible web-based program, and the allocation was managed by third-party unblinded staff (ML). The experimental group received sodium selenite pentahydrate 2000 μg/40 mL (Selentab®; Boryung Co., Ltd, Seoul, Republic of Korea) administered intravenously over two hours prior to chemotherapy. Chemotherapy consisted of paclitaxel (175 mg/m^2), carboplatin (area under the curve 5), and bevacizumab (15 mg/kg), administered intravenously over 3, 1, and 1.5 h, respectively, for six cycles every 3 weeks according to the GOG-213 protocol [36]. The control group received 40 mL of intravenous normal saline as a placebo over 2 h before receiving the same chemotherapy regimen at each cycle. Following completion of six cycles of chemotherapy using paclitaxel, carboplatin, and bevacizumab, maintenance therapy with bevacizumab alone was permitted every 3 weeks until the relapse or as determined by medical necessity or patient preference.

Data collection and assessment tools

The diagnosis of CIPN was based on the presence of symptoms such as symmetrical glove-and-stocking paresthesia or numbness, motor weakness without secondary causes, or loss of deep tendon reflexes attributable to chemotherapy. The severity of CIPN was assessed using a combination of the World Health Organization (WHO) CIPN grading scale [37, 38] and the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 [39] before each cycle, and 3 weeks and 3 months after six cycles of chemotherapy, as previously described (Table 1) [40]. According to these criteria, the incidence rate of CIPN was defined as the proportion of patients exhibiting grade 1 or more neuropathy—manifested as paresthesia, pain, or motor dysfunction—divided by the total number of patients in each group. The NCI-CTCAE and WHO-CIPN criteria have been used in combination in this study to accurately assess the severity of CIPN. In detail, NCI-CTCAE is a clinician-based grading criterion that quantifies the severity of CIPN in both sensory and motor aspects, utilizing a 5-point scale. However, the paresthesia component is only graded from 1 (asymptomatic/mild) to 3 (severe). It also incorporates the severity in limitation of activities of daily living (ADL). For the WHO-CIPN criterion, paresthesia, reflex decrease assessed by deep tendon reflex measurement, pain, as well as the extent of motor loss parameters are included. In this study, DTRs have been assessed by a neurologist (STL), which were graded according to the National Institute of Neurological

Table 1 Evaluation of chemotherapy-induced peripheral neuropathy (WHO-CTCAE criteria)

Factors	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Paresthesia	No symptom	Presence of paresthesia (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 dysfunction	No weakness	Normal ADL and/or decreased DTR	Limiting instrumental ADL and/or light muscle weakness	Limiting self-care ADL and/or marked muscle weakness	Life-threatening consequence: urgent intervention indicated

CTCAE Common Terminology Criteria for Adverse Events, *WHO* World Health Organizatoin, *ADL* activity of daily living, *DTR* deep tendon reflex, *NRS* numerical rating scale

Disorders and Stroke (NINDS) grading system [41]. The grading of deep tendon reflex using this criterion is considered hyporeflexic (1+), when the reflex is decreased, as interpreted as grade 1 in the WHO-CTCAE grade used in our study. All other assessments were graded by an independent researcher, and the most severe parameter was recorded as the final grading.

Adverse events were assessed at 3 weeks after each chemotherapy cycle and at 3 months after completion of six cycles, according to CTCAE version 5.0. Assessments were periodically reviewed by an independent Data Safety and Monitoring Board with no conflicts of interest in the study.

Patient-reported quality of life (QoL) was assessed at baseline, 3 weeks after three and six cycles, and 3 months after six cycles of chemotherapy, using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) [42, 43], and the European Organization for Research and Treatment of Cancer Chemotherapy-Induced Peripheral Neuropathy 20-item scale (EORTC QLQ-CIPN-20) [44]. The CIPN-20 module was utilized to measure the patient-reported symptoms specifically related to CIPN. The QLQ-C30 comprises 15 questions that include five functional scales, three symptom scales, a global health status scale, and six single symptom items. The average of the items that contribute to the scale (raw score) was calculated, and linear transformation was used to standardize the raw score from 0 to 10, according to the EORTC scoring manual [43]. A higher functional scale represents better functioning, whereas a higher symptomatic scale represents worse symptoms. In addition, we calculated the summary score of the EORTC QLQ-C30 from the 13 scales, excluding the financial impact scale and global health scale. For EORTC QLQ-CIPN20 scoring, the same methodology applies with higher scores indicating worse symptoms related to CIPN. This system contains 20 items assessing sensory (9 items), motor (8 items), and autonomic symptoms (3 items). One autonomic item related to male erection was excluded, and one motor item related to driving was excluded in scoring if not applicable. Additionally, the number, dose, and duration of concomitant medications used to manage CIPN—including gabapentin, pregabalin, duloxetine, and analgesics—were compared between the experimental and control groups.

Endpoints

The primary endpoint was the incidence of grade 1 or more CIPN at 3 months following six cycles of chemotherapy, comparing the experimental group to the control group. Secondary endpoints included comparisons of grade 1 or more CIPN before each cycle and 3 weeks after six cycles of chemotherapy, grade 2 or more CIPN before each cycle, 3 weeks and 3 months after six cycles of chemotherapy, adverse events, QoL, and the need for concomitant medications to manage CIPN, and survival between the two groups.

Statistical analysis

The sample size calculation was based on our previously published protocol [38]. Assuming a non-inferiority margin of 37.5%, type-I error probability of 0.05 (two-sided test), 1:1 randomization ratio, and 80% statistical power, 52 patients were required. Accounting for an 85.8% completion rate of six chemotherapy cycles based on the GOG-213 protocol [36], this was adjusted to 62 patients. With an additional 10% dropout rate, the final sample size was 68 patients (34 per group).

Both primary and secondary outcomes were analyzed using the Per-Protocol (PP) population, and the intention-to-treat (ITT) population was used for adverse event analysis. The incidence of grade 1 or more CIPN at 3 months post-chemotherapy was compared between the two groups using chi-square tests for binomial proportions. QoL scores were analyzed using repeated-measures analysis of variance (ANOVA) with Greenhouse–Geisser and Huynh–Feldt adjustments to evaluate group differences, time effects, and group-time interactions.

Subgroup analysis compared CIPN incidence by age (≥ 60 vs. <60 years). Adverse events and toxicities were analyzed using chi-square or Fisher's exact tests for categorical variables, and repeated-measures ANOVA for longitudinal data. Continuous variables were assessed with Student's t-tests or Mann–Whitney U tests, while categorical variables used chi-square or Fisher's exact tests. For survival analysis, progression-free survival (PFS) and cancer-specific survival (CSS) were estimated using the Kaplan–Meier method. Differences between groups were assessed using the log-rank test. All analyses were performed with SPSS for Windows (Version 20.0; IBM Corp., Armonk, NY), with statistical significance defined as $P < 0.05$.

Results

Patient characteristics

The flow chart on patient enrollment and treatment is presented in Fig. 1. A total of 60 patients were included in the PP population. Patient characteristics are summarized in Table 2. Baseline characteristics were comparable between experimental and control groups. Nearly half of the patients were over 60 years of age, and the proportion of patients who had received neoadjuvant chemotherapy was similar in both groups.

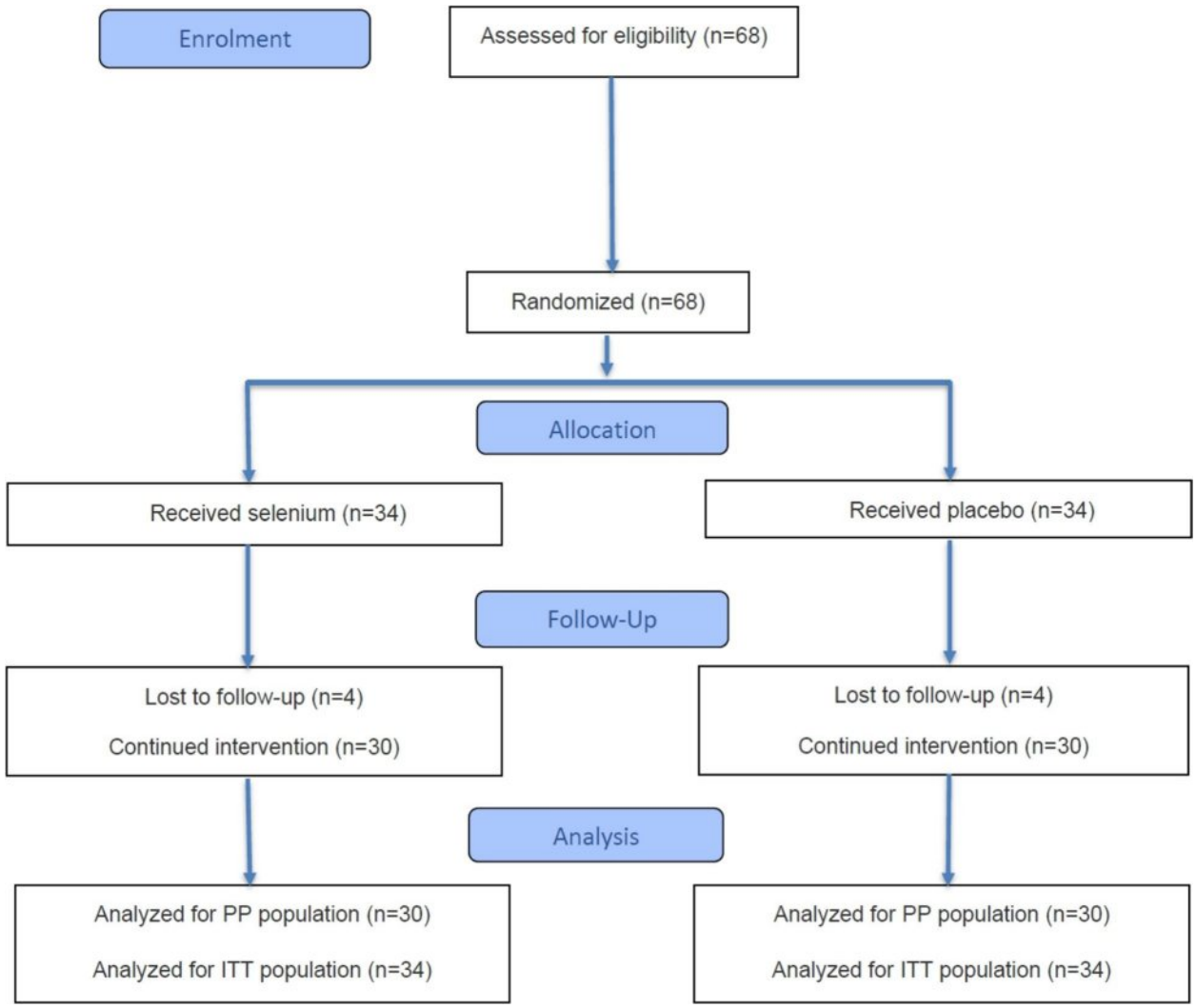

Fig. 1 CONSORT flow diagram (PP, per-protocol; ITT, intention-to-treat)

Primary endpoint

The incidence rate of grade 1 or more CIPN 3 months after six cycles of chemotherapy did not differ significantly between the two groups (Table 3). At 3 months post-chemotherapy, grade 1 or more paresthesia, pain, and motor dysfunction were shown in 19 (73%), 6 (23.1%), and 8 patients (30.7%) in the experimental group, and 24 (79%), 3 (10%), and 9 (30%) in the control group ($P > 0.05$).

Secondary endpoints

The incidence rates of grade 1 or more CIPN before each cycle and 3 months after six cycles of chemotherapy were also not different between the two groups (Table 3). Since grade 1 of CIPN was defined as tolerable without intervention or medication in this study (Table 1), we assessed the incidence rate of grade 2 or more CIPN requiring intervention or medication before each cycle, 3 weeks and 3 months after six cycles of chemotherapy. As a result, a reduction in the incidence of grade 2 or more motor dysfunction was observed before cycle 3 (3.3% vs 23.3%; $P = 0.02$) and before cycle 4 of chemotherapy (3.3% vs 20%, $P = 0.04$) in the experimental group. When stratified into age, a significant decrease in the incidence of motor dysfunction before cycle 3 was observed in patients over 60 years old in the experimental group (5.6% vs 33.3%, $P = 0.04$; Table 4). Moreover, there were no patients with grade 3 or more CIPN in both groups.

No statistically significant difference in the EORTC QLQ-C30 summary score was found between the experimental and control groups over time (Fig. 2, Additional file 1: Table S1). The EORTC QLQ-C30 summary score declined 3 weeks after cycle 6 but increased again 3 months after completion of chemotherapy. No

Table 2 Clinicopathologic characteristics

Characteristics	Placebo ($n=30$, %)	Selenium ($n=30$, %)	*P* value
Age			0.48
≥60	15 (50)	18 (60)	
<60	15 (50)	12 (40)	
Underlying conditions			
Diabetes mellitus	3 (10)	5 (16.7)	0.75
Cardiovascular diseases	8 (26.7)	10 (33.3)	0.45
Thyroid diseases	2 (6.7)	4 (13.3)	0.43
Initial FIGO stage			0.95
1	1 (3.3)	1 (3.3)	
2	2 (6.7)	3 (10)	
3	12 (40)	9 (30)	
4	15 (50)	17 (56.7)	
Histology			0.46
HGSC	22 (73.3)	26 (86.7)	
Endometrioid carcinoma	3 (10)	0 (0)	
Clear cell carcinoma	3 (10)	4 (13.3)	
LGSC	2 (6.7)	0 (0)	
Prior treatment			0.13
Upfront debulking surgery	11 (36.7)	18 (60)	
Neoadjuvant chemotherapy + interval debulking surgery	19 (63.3)	12 (40)	
Prior size of residual tumor			0.07
R0	26 (86.7)	25 (83.3)	
R1	4 (13.3)	3 (10)	
R2	0 (0)	2 (6.7)	
Prior treatment-free interval (mons)	25.4 ± 37.7	17.9 ± 14.1	0.30
Cycles of chemotherapy and bevacizumab	6 (100)	6 (100)	–
Cycles of maintenance bevacizumab	18.0 ± 12.4	15.6 ± 13.6	0.48
Total follow-up (mo)	31.5 ± 11.3	29.8 ± 13.3	0.59

FIGO International Federation of Gynecology and Obstetrics, *HGSC* high-grade serous carcinoma, *LGSC* low-grade serous carcinoma, *R0* no visible tumor, *R1* the size of residual tumor < 1 cm, *R2* the size of residual tumor > 1 cm, *mo* months

difference was found according to age. Similarly, the numerical scores related to sensory and motor function measured by the EORTC QLQ-CIPN20 declined over time after cycle 6 in both groups; however, there were no statistically significant differences in the group-by-time interaction for these scales (Fig. 3, Additional file 2: Table S2).

Both hematologic and non-hematologic toxicities showed no difference in the two groups (Tables 5 and 6). Hypersensitivity reactions were observed only in the control group and were related to chemotherapeutic drugs. Eight patients (23.5%) in the control group and seven patients (20.6%) in the experimental group experienced adverse events during treatment with no significant difference between the two groups ($P=0.31$). The most common adverse event was nonspecific body pain, which was resolved with conservative management. One patient in the control group experienced grade 4 symptomatic hyponatremia, requiring immediate correction and hospitalization. No adverse events were related to selenium toxicity (Table 7).

Adjustment of the dose of chemotherapeutic agents and other concomitant drugs affecting CIPN are shown in Table 8. Approximately 30% of patients in both groups required a dose reduction in chemotherapy. There was no difference in the dosage of duloxetine and gabapentin administered during treatment.

Total mean follow-up months were 31.5 ± 11.3 in the control group and 29.8 ± 13.3 months in the experimental group ($P=0.59$). Median PFS and CSS did not differ significantly between the two groups (Fig. 4).

Discussion

This current study is the first to evaluate the efficacy and safety of high-dose intravenous selenium for the prevention of CIPN in patients with PSROC. Even though the primary endpoint was not met, notable findings emerged. The experimental group demonstrated a significantly lower incidence of motor dysfunction before cycle 3 and before cycle 4 of chemotherapy, with the most pronounced reduction observed in patients over 60 years of age. The QOL scores measured by the EORTC-QLQ30 and EORTC-QLQ-CIPN20 scales did not show any statistically significant difference between the experimental and placebo groups. High-dose intravenous selenium was safely administered, with no serious treatment-related adverse effects reported.

The timing and cumulative dosing of chemotherapeutic agents likely influenced the development and detection of CIPN. Paclitaxel-induced neuropathy typically arises at cumulative doses exceeding 1400 mg/m^2, with sensory symptoms often appearing 2 to 4 weeks after administration and progressing in a glove-and-stocking pattern. Similarly, cisplatin-induced CIPN is associated with cumulative doses of 300–600 mg/m^2 [11, 45]. Given the dosing regimens in this study, it is plausible that sensory neuropathy became more evident after six cycles of taxane and several weeks of platinum therapy. Furthermore, the "coasting phenomenon"—the delayed worsening of neuropathy symptoms after chemotherapy cessation—may have limited the observed preventive effect of selenium at the 3-month assessment [46]. Nonetheless, there was a trend toward a 12% lower incidence of paresthesia in the experimental group at 3 months post-chemotherapy, suggesting a potential benefit that might be more apparent in a larger cohort.

Table 3 Evaluation of grade 1 or more chemotherapy-induced peripheral neuropathy

Parameters	Treatment	Before cycle 1	*P*	Before cycle 2	*P*	Before cycle 3	*P*	Before cycle 4	*P*	Before cycle 5	*P*	Before cycle 6	*P*	3WK	*P*	3MO	*P*
Paresthesia	Placebo	11/0 (36.7/0)	0.79	12/4 (40/13.3)	0.43	15/9 (50/30)	0.54	17/7 (56.7/23.3)	1.00	16/10 (53.3/33.3)	0.73	18/10 (60/33.3)	0.42	19/9 (63.3/30)	0.40	17/7 (56.7/23.3)	0.54
	Selenium	7/3 (23.3/10)		11/8 (36.7/26.7)		11/11 (36.7/36.7)		12/12 (40/40)		9/15 (30/50)		16/9 (53.3/30)		16/6 (61.5/23.1)		16/3 (61.5/11.5)	
< 60 y (*n* = 27, %)	Placebo	4/0 (26.7/0)	0.66	5/1 (33.3/6.7)	0.45	7/3 (46.7/20)	0.71	7/2 (46.7/13.3)	1.00	8/3 (53.3/20)	1.00	11/2 (73.3/13.3)	1.00	11/2 (73.3/13.3)	0.36	10/1 (66.7/6.7)	1.00
	Selenium	1/1 (8.3/8.3)		5/2 (41.7/16.7)		4/3 (33.3/25)		4/4 (33.3/33.3)		4/5 (33.3/41.7)		7/3 (58.3/25)		5/2 (50/20)		6/0 (66.7/0)	
≥ 60 y (*n* = 33, %)	Placebo	7/0 (46.7/0)	0.90	7/3 (46.7/11.1)	1.00	8/6 (40.7/40)	0.61	10/5 (66.7/33.3)	0.49	8/7 (53.3/46.7)	0.23	7/8 (46.7/53.3)	0.23	8/7 (53.3/46.7)	1.00	7/6 (46.7/40)	0.66
	Selenium	6/2 (33.3/11.1)		6/6 (33.3/33.3)		7/8 (38.9/44.4)		8/8 (44.4/44.4)		5/10 (27.8/55.6)		9/6 (50/33.3)		11/4 (68.8/25)		10/3 (58.8/17.6)	
Pain	Placebo	3/0 (10/0)	1.00	4/1 (13.3/3.3)	0.52	5/1 (16.7/3.3)	0.75	5/1 (16.7/3.3)	0.18	3/4 (10/13.3)	0.77	4/3 (13.3/10)	0.75	3/2 (10/6.7)	1.00	2/1 (6.7/3.3)	0.18
	Selenium	2/0 (6.7/0)		4/3 (13.3/10)		4/3 (13.3/10)		7/4 (23.3/13.3)		4/4 (13.3/13.3)		5/1 (16.7/3.3)		3/1 (11.5/3.3)		6/0 (23.1/0)	
< 60 y (*n* = 27, %)	Placebo	0/0 (0)	–	3/0 (20/0)	0.61	2/0 (13.3/0)	0.49	3/0 (20/0)	1.00	2/1 (13.3/6.7)	1.00	2/0 (13.3/0)	1.00	2/0 (13.3/0)	1.00	1/0 (6.7/0)	0.53
	Selenium	0/0 (0)		1/0 (8.3/0)		0/0 (0/0)		2/0 (16.7/0)		2/0 (16.7/0)		2/0 (16.7/0)		1/0 (10/0)		2/0 (22.2/0)	
≥ 60 y (*n* = 33, %)	Placebo	3/0 (20/0)	0.65	1/1 (6.7/6.7)	0.24	3/1 (20/6.7)	0.71	2/1 (14.3/6.7)	0.15	1/3 (6.7/20)	0.72	2/3 (13.3/20)	0.70	1/2 (6.7/13.3)	1.00	1/1 (6.7/6.7)	0.66
	Selenium	2/0 (11.1)		3/3 (16.7/16.7)		4/3 (22.2/16.7)		5/4 (27.8/22.2)		2/4 (11.1/22.2)		3/1 (16.7/5.6)		2/1 (12.5/6.2)		4/0 (23.5/0)	
Motor dysfunction	Placebo	2/0 (6.7/0)	1.00	5/2 (16.7/6.7)	1.00	3/7 (10/23.3)	0.78	5/6 (16.7/20)	0.79	7/4 (23.3/13.3)	0.79	8/6 (26.7/20)	0.60	8/5 (26.7/16.7)	0.33	5/4 (16.7/13.3)	0.95
	Selenium	3/0 (10/0)		6/1 (20/3.3)		8/1 (26.7/3.3)		11/1 (36.7/3.3)		10/2 (33.3/6.7)		8/4 (26.7/13.3)		6/2 (23.1/7.7)		7/1 (26.9/3.8)	
< 60 y (*n* = 27, %)	Placebo	1/0 (6.7/0)	1.00	4/0 (26.7/0)	0.34	2/2 (13.3/13.3)	0.66	4/2 (26.7/13.3)	1.00	5/1 (33.3/6.7)	0.93	5/1 (33.3/6.7)	0.93	4/1 (26.7/6.7)	1.00	2/1 (13.3/6.7)	0.64
	Selenium	0/0 (0/0)		1/0 (8.3/0)		2/0 (16.7/0)		4/0 (33.3/0)		4/1 (33.3/8.3)		4/1 (33.3/8.3)		3/1 (30/10)		3/0 (33.3/0)	
≥ 60 y (*n* = 33, %)	Placebo	1/0 (6.7/0)	0.67	1/2 (6.7/13.3)	0.46	1/5 (6.7/33.3)	1.00	1/4 (6.7/26.7)	0.52	2/3 (13.3/20)	0.74	3/5 (20/33.3)	0.41	4/4 (26.7/26.7)	0.15	3/3 (20/20)	0.71
	Selenium	3/0 (16.7/0)		5/1 (27.8/5.6)		6/1 (33.3/5.6)		7/1 (38.9/5.6)		6/1 (24.2/5.6)		4/3 (22.2/16.7)		3/1 (18.8/6.2)		4/1 (23.5/5.9)	

3WK 3 weeks after chemotherapy, *3MO* 3 months after chemotherapy

Main values are described as No. of patients with grade 1/No. of them with grade 2 neuropathy (%/%)

Table 4 Evaluation of grade 2 chemotherapy-induced peripheral neuropathy

Parameters	Treatment	Before cycle 1	*P*	Before cycle 2	*P*	Before cycle 3	*P*	Before cycle 4	*P*	Before cycle 5	*P*	Before cycle 6	*P*	3WK	*P*	3MO	*P*
Paresthesia	Placebo	0 (0)	0.25	4 (13.3)	0.33	9 (30)	0.58	7 (23.3)	0.17	10 (33.3)	0.19	10 (33.3)	0.78	9 (30)	0.56	7 (23.3)	0.31
	Selenium	3 (10)		8 (26.7)		11 (36.7)		12 (40)		15 (50)		9 (30)		6 (23.1)		3 (11.5)	
< 60 y (*n* = 27, %)	Placebo	0 (0)	0.44	1 (6.7)	0.57	3 (20)	1.00	2 (13.3)	0.36	3 (20)	0.39	2 (13.3)	0.63	2 (13.3)	1.00	1 (6.7)	1.00
	Selenium	1 (8.3)		2 (16.7)		3 (25)		4 (33.3)		5 (41.7)		3 (25)		2 (20)		0 (0)	
≥ 60 y (*n* = 33, %)	Placebo	0 (0)	0.49	3 (11.1)	0.46	6 (40)	1.00	5 (33.3)	0.72	7 (46.7)	0.73	8 (53.3)	0.30	7 (46.7)	0.27	6 (40)	0.24
	Selenium	2 (11.1)		6 (33.3)		8 (44.4)		8 (44.4)		10 (55.6)		6 (33.3)		4 (25)		3 (17.6)	
Pain	Placebo	0 (0)	–	1 (3.3)	0.61	1 (3.3)	0.61	1 (3.3)	0.35	4 (13.3)	1.00	3 (10)	0.61	2 (6.7)	1.00	1 (3.3)	1.00
	Selenium	0 (0)		3 (10)		3 (10)		4 (13.3)		4 (13.3)		1 (3.3)		1 (3.3)		0 (0)	
< 60 y (*n* = 27, %)	Placebo	0 (0)	–	0 (0)	–	0 (0)	–	0 (0)	–	1 (6.7)	1.00	0 (0)	–	0 (0)	–	0 (0)	–
	Selenium	0 (0)		0 (0)		0 (0)		0 (0)		0 (0)		0 (0)		0 (0)		0 (0)	
≥ 60 y (*n* = 33, %)	Placebo	0 (0)	–	1 (6.7)	0.61	1 (6.7)	0.61	1 (6.7)	0.36	3 (20)	1.00	3 (20)	0.31	2 (13.3)	0.60	1 (6.7)	0.47
	Selenium	0 (0)		3 (16.7)		3 (16.7)		4 (22.2)		4 (22.2)		1 (5.6)		1 (6.2)		0 (0)	
Motor dysfunction	Placebo	0 (0)	–	2 (6.7)	1.00	7 (23.3)	**0.02**	6 (20)	**0.04**	4 (13.3)	0.67	6 (20)	0.73	5 (16.7)	0.43	4 (13.3)	0.36
	Selenium	0 (0)		1 (3.3)		1 (3.3)		1 (3.3)		2 (6.7)		4 (13.3)		2 (7.7)		1 (3.8)	
< 60 y (*n* = 27, %)	Placebo	0 (0)	–	0 (0)	–	2 (13.3)	0.49	2 (13.3)	0.49	1 (6.7)	1.00	1 (6.7)	1.00	1 (6.7)	1.00	1 (6.7)	1.00
	Selenium	0 (0)		0 (0)		0 (0)		0 (0)		1 (8.3)		1 (8.3)		1 (10)		0 (0)	
≥ 60 y (*n* = 33, %)	Placebo	0 (0)	–	2 (13.3)	0.58	5 (33.3)	**0.04**	4 (26.7)	0.09	3 (20)	0.31	5 (33.3)	0.42	4(26.7)	0.17	3(20)	0.32
	Selenium	0 (0)		1 (5.6)		1 (5.6)		1 (5.6)		1 (5.6)		3 (16.7)		1 (6.2)		1(5.9)	

3WK 3 weeks after chemotherapy, *3MO* 3 months after chemotherapy

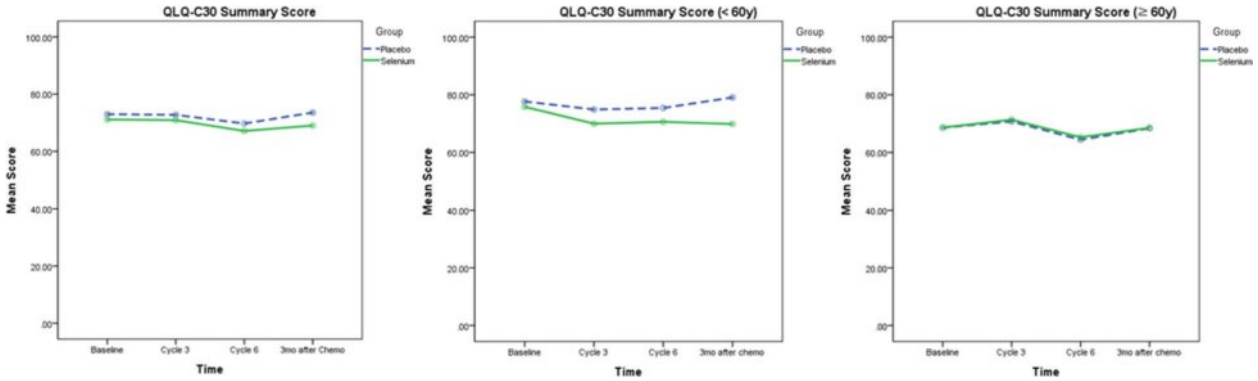

Fig. 2 Change in quality-of-life scores of the EORTC QLQ-C30

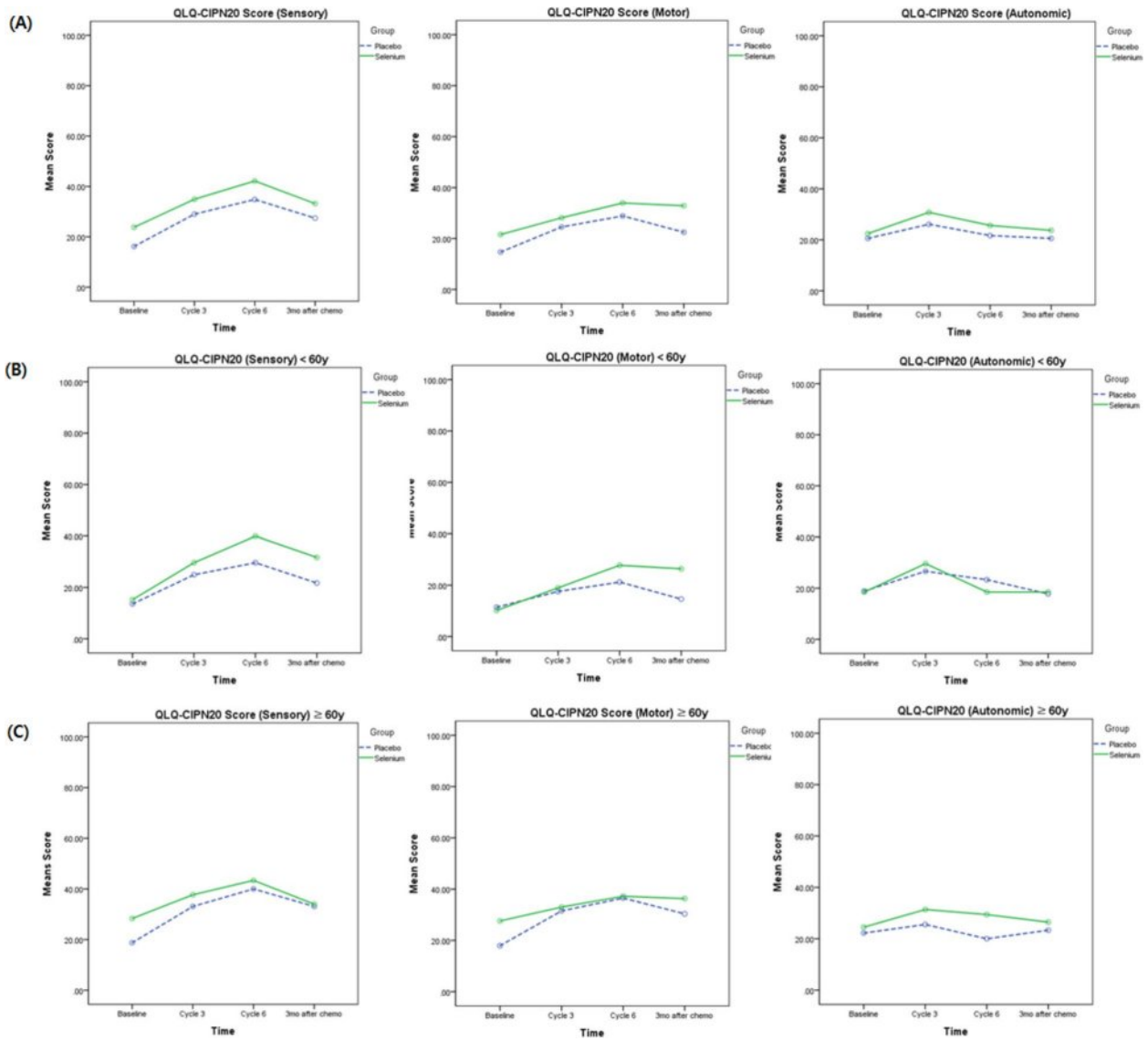

Fig. 3 Changes in quality-of-life scores of the EORTC-CIPN20: **A** all patients; **B** age < 60 years; (C) age ≥ 60 years

Table 5 Repeated measures ANOVA of hematologic toxicities

Factors	Within-times		Between-groups		Interaction	
	F	*P*	*F*	*P*	*F*	*P*
WBC	4.687	0.001	0.413	0.52	0.568	0.71
Hemoglobin	17.912	< 0.001	0.634	0.43	0.865	0.44
ANC	4.445	< 0.001	1.528	0.22	0.422	0.75
Platelet	2.621	0.11	0.000	0.99	0.965	0.34
AST	1.770	0.13	1.811	0.18	2.258	0.05
ALT	6.517	< 0.001	1.614	0.21	1.855	0.13
Bilirubin	0.481	0.54	0.172	0.68	1.334	0.26
Creatinine	2.509	0.04	0.041	0.84	1.859	0.12

ANC absolute neutrophil count, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *WBC* white blood cell

Table 6 Non-hematologic toxicities per treatment cycle with or without selenium

Parameters	Treatment	Cycle 1	*P*	Cycle 2	*P*	Cycle 3	*P*	Cycle 4	*P*	Cycle 5	*P*	Cycle 6	*P*
Electrocardiogram ACV	Placebo	0 (0)	-	1 (3.3)	0.77	0 (0)	0.34	0 (0)	-	1 (3.3)	0.54	1 (3.3)	0.54
	Selenium	0 (0)		2 (6.7)		2 (6.7)		0 (0)		0 (0)		0 (0)	
Nausea	Placebo	1 (3.3)	0.54	1 (3.3)	1.00	0 (0)	0.34	0 (0)	0.54	0 (0)	-	0 (0)	-
	Selenium	0 (0)		1 (3.3)		2 (6.7)		1 (3.3)		0 (0)		0 (0)	
Constipation	Placebo	0 (0)	-	0 (0)	-	0 (0)	-	0 (0)	-	0 (0)	-	0 (0)	-
	Selenium	0 (0)		0 (0)		0 (0)		0 (0)		0 (0)		0 (0)	
Vomiting	Placebo	0 (0)	-	0 (0)	-	0 (0)	-	0 (0)	-	0 (0)	-	0 (0)	-
	Selenium	0 (0)		0 (0)		0 (0)		0 (0)		0 (0)		0 (0)	
Diarrhea	Placebo	0 (0)	-	0 (0)	-	0 (0)	-	0 (0)	-	0 (0)	-	0 (0)	-
	Selenium	0 (0)		0 (0)		0 (0)		0 (0)		0 (0)		0 (0)	
Stomatitis	Placebo	0 (0)	-	0 (0)	-	0 (0)	-	0 (0)	-	0 (0)	-	0 (0)	-
	Selenium	0 (0)		0 (0)		0 (0)		0 (0)		0 (0)		0 (0)	
Hypersensitivity	Placebo	1 (3.3)	0.54	1 (3.3)	0.54	1 (3.3)	0.543	0 (0)	-	1 (3.3)	0.54	3 (10)	0.25
	Selenium	0 (0)		0 (0)		0 (0)		0 (0)		0 (0)		0 (0)	

ACV altered conduction velocity

The observed reduction in grade 2 motor CIPN during chemotherapy may be attributed to the relative resilience of skeletal muscle cells to oxidative stress compared to sensory neurons [47, 48]. Motor cells possess more robust adaptive responses, including activation of antioxidant defense systems such as superoxide dismutase and glutathione peroxidase, which may explain the earlier and more significant reduction in motor symptoms in the experimental group [45]. The combined use of WHO and CTCAE criteria, including assessment of deep tendon reflexes, allowed for a more comprehensive evaluation of motor neuropathy. The effect was especially notable in patients over 60 years, though the underlying mechanism for this age-related difference remains unclear and warrants further investigation. However, it is also necessary to consider that the reduction of grade 2 or more motor CIPN during chemotherapy may be a temporary phenomenon, considering no difference in grade 1 or more CIPN between the two groups.

Antioxidants have been extensively studied for their neuroprotective potential in CIPN [46]. Among them, vitamin E has shown the most promising clinical signals, though results remain inconsistent. Some randomized trials have reported significant reductions in neurotoxicity with vitamin E supplementation [14, 15, 49, 50], while others have not confirmed these findings in double-blind settings. In this context, selenium represents a promising alternative, given its role as a cofactor for antioxidant enzymes and its ability to mitigate oxidative stress and neuronal apoptosis.

The safety profile of high-dose intravenous selenium was reaffirmed in this study. No serious adverse events attributable to selenium were observed, consistent with previous reports in both oncology and cardiac surgery populations [51–53]. While chronic high intake of selenium can cause selenosis, manifesting as dermatologic or gastrointestinal symptoms [54], no such toxicities were documented here. The pharmacokinetic properties of

Table 7 Adverse events

Characteristics	Placebo (*n* = 34, %)	Selenium (*n* = 34, %)	*P* value
AE of any grade	8 (23.5)	7 (20.6)	0.310
Grade 1	1 (12.5)	1 (14.3)	
Grade 2	2 (25.2)	4 (57.1)	
Grade 3	4 (50.0)	2 (28.6)	
Grade 4	1 (12.5)	0 (0)	
Event*			
Skin rash	1 (2.7)	3 (2.0)	
Pain (abdomen/back/epigastric)	0 (0)	5 (12.5)	
Fever	1 (2.7)	3 (7.5)	
Ileus	1 (2.7)	0 (0)	
Peritonitis	1 (2.7)	2 (5.0)	
Hypertension	1 (2.7)	0 (0)	
Urinary tract infection	4 (10.8)	0 (0)	
Hyponatremia	1 (2.7)	0 (0)	
Glaucoma	1 (2.7)	0 (0)	

AE adverse event

* Duplicated events included

intravenous selenium, including a relatively long half-life and rapid tissue distribution, support its use as a neuroprotective agent when administered prior to chemotherapy. However, the potential for delayed-onset CIPN and the "coasting phenomenon" suggest that extended or repeated dosing schedules may be necessary to optimize preventive effects.

This study has several strengths, including its prospective, randomized, double-blind design and the enrollment of a relatively large cohort compared to previous antioxidant trials in CIPN. However, some limitations should be acknowledged. The inclusion of patients previously treated with platinum-based chemotherapy may have influenced baseline neuropathy rates and reduced the observed protective effect of selenium. Variability in baseline QoL scores and the lack of robust reference data for selenium in CIPN prevention also limited the precision of sample size calculations. In addition, there are no universally standardized measurements or outcome measures for CIPN research. Therefore, the assessment methods and primary endpoint vary between studies, which may hinder the interpretation of results. The primary outcome of this study was measured by a combination of two clinician-reported CIPN assessment tools to enhance objectivity. Although CTCAE is the most widely used clinician-based grading tool to assess treatment-related toxicity, there are psychometric limitations for its use in CIPN research. Since it is focused on functional deficits rather than the full subjective patient experience, limited construct validity especially in the sensory domain, lower inter-rater reliability, and sensitivity can miss symptomatic changes and generate inconsistent

Table 8 Total cycles, mean and cumulative doses, does reduction of paclitaxel, carboplatin and bevacizumab, doses of duloxetine and gabapentin and numbers of analgesics before 3 months following six cycles of chemotherapy

Types	Placebo (*n* = 30)	Selenium (*n* = 30)	*P*
Total cycles (mean, SD)			
Paclitaxel	6	6	–
Carboplatin	6	6	–
Bevacizumab	10 ± 0.2	9.8 ± 0.8	0.34
Mean doses per cycle (mg, mean, SD)			
Paclitaxel	266.8 ± 27.4	254.8 ± 37.4	0.16
Carboplatin	481.8 ± 87.9	457.8 ± 108.2	0.35
Bevacizumab	882.0 ± 108.2	865.1 ± 151.2	0.62
Cumulative doses (mg, mean, SD)			
Paclitaxel	1600.6 ± 164.1	1528.6 ± 224.6	0.16
Carboplatin	2890.7 ± 527.3	2747.0 ± 649.4	0.35
Bevacizumab	8790.6 ± 1093.9	8434.7 ± 1753.3	0.35
Dose reduction of paclitaxel (*n*, %)	8 (26.7)	10 (33.3)	0.57
Dose reduction of carboplatin (*n*, %)	9 (30)	10 (33.3)	0.78
Dose of duloxetine (mg/d, mean, SD)	36.7 ± 9.5	22.7 ± 16.8	0.06
Dose of gabapentin (mg/d), mean (SD)	548.9 ± 263.3	672.4 ± 486.7	0.58
No. of analgesics (*n*, %)			1.00
0	14 (46.7)	14 (46.7)	
1	12 (40.0)	12 (40.0)	
2	4 (13.3)	4 (13.3)	

SD standard deviation

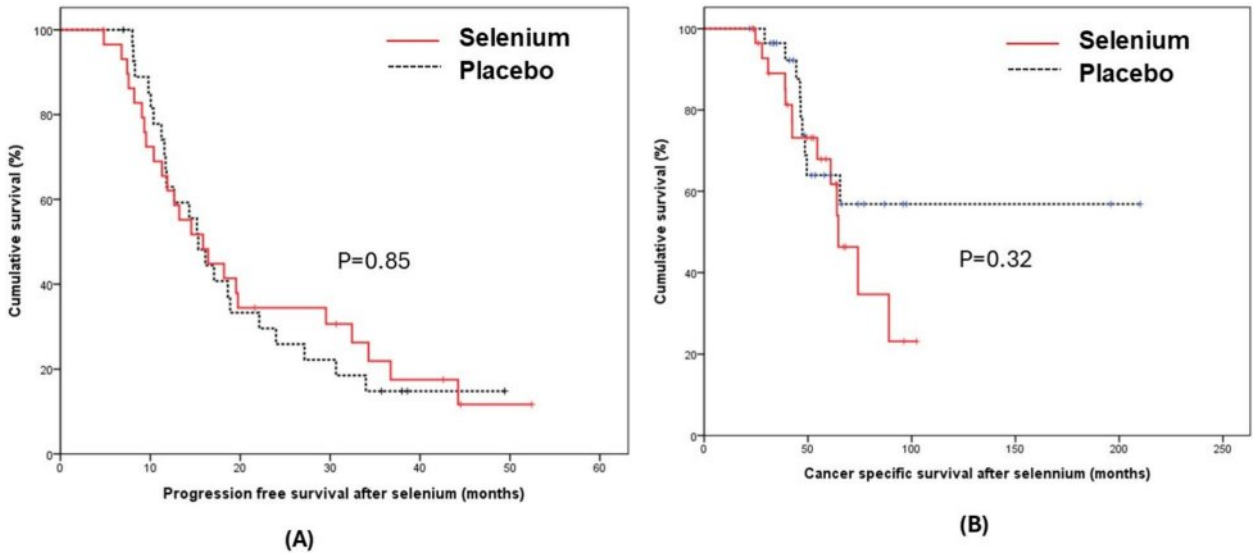

Fig. 4 Comparison of **A** progression-free and **B** cancer-specific survivals

results [55, 56]. Moreover, one of the major limitations of the CTCAE tool is the lack of pain assessment, which is also a significant component of neuropathic symptoms. Therefore, CTCAE and WHO toxicity grading were combined in this study to complement the limitations of each tool. However, this combination assessment tool is exploratory in nature, which needs to be further validated in CIPN research. Since clinician-based grading systems are known to underestimate the incidence of severity of CIPN, the combined CTCAE-WHO assessment may have affected the true incidence of CIPN and treatment effect. As literature using patient-reported outcomes (PROMs) continues to expand, composite measurement of both patient and clinician-assessed valid instruments are suggested for future trial designs [57, 58]. In addition, it is important to consider that symptom-specific modules such as EORTC QLQ-CIPN20 hold validity and interpretability issues for their autonomic subscales, which necessitates caution when used in CIPN research. Despite these challenges, the results of this study may provide valuable insights and a foundation for future research.

Conclusion

In conclusion, high-dose intravenous selenium administered with each chemotherapy cycle was associated with a reduction in grade 2 or more motor neuropathy incidence during treatment and demonstrated an acceptable safety profile in patients with recurrent ovarian cancer. While the primary endpoint was not achieved, the observed trends in motor and sensory neuropathy, particularly among older patients, highlight the need for further investigation. Given the limited options for CIPN prevention and treatment, selenium may represent a promising candidate for future clinical trials aimed at mitigating this debilitating complication. A deeper understanding of the mechanisms underlying CIPN and the role of antioxidants will be essential for the development of effective preventive strategies.

Abbreviations

CIPN	Chemotherapy-induced peripheral neuropathy
QoL	Quality of life
RCT	Randomized controlled trial
CTCAE	Common Terminology Criteria for Adverse Events
WHO	World Health Organization
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC CIPN-20	European Organization for Research and Treatment of Cancer Chemotherapy-Induced Peripheral Neuropathy-20
RECIST	Response Evaluation Criteria in Solid Tumors
GCIG	Gynecologic Cancer InterGroup
GOG	Gynecologic Oncology Group
ADL	Activities of daily living
PP	Per-protocol
ITT	Intention-to-treat
ANOVA	Analysis of variance
PFS	Progression-free survival
ROS	Reactive oxygen species
IU	International unit
µg	Microgram
mg/m^2	Milligrams per square meter
HR	Hazard ratio
AUC	Area under the curve
DTR	Deep tendon reflex
SPSS	Statistical Package for Social Sciences

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-026-04637-x.

Additional file 1. Table S1 – [Results of quality of life questionnaires (EORTC QLQ-C30)].

Additional file 2. Table S2 – [Results of quality of life questionnaires (EORTC QLQ-CIPN20)].

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Authors' contributions
GWY, HSK conceived the study and drafted the original manuscript. GWY, HSK, KHH performed literature search, organized the table, and participated in writing the original manuscript. KHH, ML, STL, SML, HSK reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Institutional Review Board of Seoul National University Hospital in November 2019 (No. 1909-077-106). Written informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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