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NCCTG N08CA (Alliance): The use of Glutathione for Prevention of Paclitaxel/Carboplatin Induced Peripheral Neuropathy: A Phase III Randomized, Double-Blind Placebo-Controlled Study

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Abstract

Background—Chemotherapy-induced peripheral neuropathy (CIPN) is a significant side effect of taxane and platinum based chemotherapy. Several studies have supported the potential benefit of glutathione for the prevention of platinum-induced CIPN. The current trial was designed to determine whether glutathione would prevent CIPN as a result of carboplatin/paclitaxel therapy.

Methods—185 patients undergoing treatment with paclitaxel and carboplatin were accrued between 12/04/2009 and 12/19/2011. Patients were randomized to receive either placebo (n=91) or 1.5 g/m^2 glutathione (n=94) over 15 minutes immediately prior to chemotherapy. CIPN was assessed using the EORTC-CIPN20 sensory subscale and the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Results—There were no statistically significant differences between the two study arms with regard to 1) peripheral neurotoxicity, assessed utilizing both EORTC-QLQ-CIPN20 (p=0.21) and CTCAE scales (p=0.449 for grade 2+ neurotoxicity; p=0.039 for time to development of grade 2+ neuropathy, in favor of the placebo); 2) the degree of the paclitaxel acute pain syndrome (p=0.30 for patients who received every 3–4 week paclitaxel vs. p=0.002, in favor of the placebo, for patients who received weekly paclitaxel); 3) the time to disease progression (p=0.63); or 4) apparent toxicities. Subgroup analysis did not reveal any evidence of benefit in any particular subgroup.

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Conclusion—This study does not support the use of glutathione for the prevention of paclitaxel/carboplatin-induced CIPN.

Keywords

glutathione; chemotherapy induced peripheral neuropathy; prevention; paclitaxel; carboplatin

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a significant chemotherapy side effect, which manifests as numbness, tingling and/or pain, generally beginning in the hands and/or feet with proximal progression in a “stocking and glove” type manner[1,2]. It is common with platinum-based agents (e.g., cisplatin, oxaliplatin, and carboplatin), vinca alkaloids, taxanes and other agents[3], with an estimated incidence of 30–40%[2–6]. CIPN can significantly impact patient quality of life; it may lead to dose reductions, dose delays and/or early termination of chemotherapy. Given that there are limited options available to effectively treat CIPN once it is established, efforts have been made to study means to prevent CIPN from developing.

Glutathione is a naturally occurring compound consisting of three amino acids: glutamic acid, cysteine and glycine. Glutathione is an important scavenger molecule, which participates in many detoxification reactions to protect the body from intracellular oxidants such as free radicals and reactive oxygen species. Platinum-induced neurotoxicity is thought to be secondary to the accumulation of platinum within the dorsal root ganglion[7,8]. Glutathione is a non-toxic agent that has been shown to reduce the accumulation of platinum within the dorsal root ganglion[9], supporting that this may provide an underlying mechanism to prevent neurotoxicity.

Multiple previous studies have been performed to investigate the efficacy of glutathione for the prevention of CIPN. One small placebo-controlled randomized trial, involving 33 patients, reported that this regimen was safe; however, there were minimal changes in sensory neuropathy[10]. Another placebo-controlled randomized trial[11], involving 33 patients with relapsed ovarian cancer, reported that higher cisplatin doses could be administered with glutathione. Cascinu et al.[12] performed a double-blind, placebo-controlled, randomized trial evaluating the ability of glutathione to prevent CIPN among a cohort of 50 patients with gastric cancer receiving a cisplatin-based regimen, reporting that there was a decreased incidence of neuropathy in the glutathione arm. Cascinu et al.[13] performed a second small (n=52) randomized, double-blind, placebo-controlled trial to evaluate the efficacy of glutathione for the prevention of oxaliplatin-induced peripheral neuropathy among a cohort of patients with colorectal cancer, which also showed promising- appearing results. Similar findings were observed by Milla et al.[14] (n=27) in patients receiving FOLFOX4. Smyth et al.[15] conducted a randomized, double-blind, placebo-controlled study in 151 patients receiving cisplatin, and reported numerically reduced neurotoxicity among those that received glutathione (p=0.22). Lin et al.[16] reported a small trial consisting of 14 patients receiving adjuvant FOLFOX who were randomized to receive either 1200 mg of oral N-acetylcysteine, a glutathione precursor, or placebo and found a reduced incidence of

oxaliplatin-induced neuropathy among those that received N-acetylcysteine. Further evidence to support the role of glutathione in the reduction of neurotoxicity was reported by Periera et al.,[17] who found that neuronal glutamate toxicity was secondary to the inhibition of cysteine uptake and thus depletion of glutathione stores and resulting oxidative stress/damage.

Pursuant to this extensive body of preliminary data, the current study was developed to evaluate the efficacy of glutathione for preventing CIPN among a cohort of patients receiving paclitaxel/carboplatin chemotherapy.

Patients and Methods

Patients considered for this trial were adults scheduled to undergo treatment with paclitaxel at 150–200 mg/m^2 and carboplatin (CBDCA) at AUC=5–7 every 21 or 28 days for at least 12 weeks. Alternatively, paclitaxel could be prescribed at 80 mg/m^2 weekly for at least 12 weeks, with the same CBDCA dose and schedule. Patients needed an ECOG performance status (PS) of 0–2 and had a life expectancy of at least 6 months. Baseline laboratory values (including white blood cell count [WBC] ≥3.4 ×10^9/L, absolute neutrophil count [ANC] ≥1500/μL, platelets ≥100 ×10^9/L, hemoglobin ≥10.0 g/dL and creatinine ≤1.5 times the upper normal limit) were required. Each participant signed an IRB-approved, protocol-specific informed consent in accordance with United States federal and institutional guidelines.

Patients were excluded from study participation for1) a pre-existing history of peripheral neuropathy greater than grade 1 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 4.0) due to any cause (chemotherapy, diabetes, alcohol, toxin, hereditary, etc.); 2) other medical conditions which would make study participation unreasonably hazardous; 3) prior receipt of paclitaxel and/or carboplatin chemotherapy treatment; or 4) concurrent use of any agents to try to prevent or treat neuropathy including, gabapentin, glutamine, vitamin B6 and vitamin E.

At study baseline and prior to each cycle of chemotherapy, patients were required to undergo a history and physical exam and laboratory evaluation (including complete blood count [CBC], creatinine, aspartate aminotransferase [AST], and bilirubin).

Procedures for measuring CIPN were performed at baseline and one week after each dose of chemotherapy. The EORTC-QLQ-CIPN20, used to measure the primary endpoint in this clinical trial, is a 20-item, CIPN-specific, patient- reported outcome questionnaire that includes three subscales to assess sensory, motor and autonomic symptoms and functioning; each item measured on a 1–4 scale (1 – not at all; 4 – very much). This questionnaire can be completed in five minutes or less and has been well received in previous clinical trials. Additionally, the NCI CTCAE; version 4.0 was utilized to quantify the chronic neurotoxicity associated with chemotherapy, with standardized questions regarding neurotoxic symptoms and examples of answers (Appendix 1), to allow a more accurate classification of patient symptoms as grade 1, 2, 3, or 4.

Paclitaxel-associated acute pain syndrome (P-APS) symptoms were measured by asking patients to keep a daily symptom log on days 2 through 7 following each paclitaxel dose, with a tool used to define this syndrome[18,19].

Functional Assessment of Cancer Therapy for Patients with Ovarian Cancer (FACT-O) assessments were obtained at baseline and one week after each dose of chemotherapy. The FACT-O is a questionnaire utilized to assess quality of life in patients, with particular emphasis on patients with ovarian cancer[20].

Protocol Treatment

Patients received glutathione 1.5g/m^2 or placebo (100 mL of 0.9% NaCl) IV over 15 minutes immediately before chemotherapy. Patients, ideally, were to begin glutathione prior to their first dose of this chemotherapy, but were required to begin prior to their second dose of chemotherapy. Glutathione was obtained from Biomedica Foscarna, a company that makes the product that was used in the positive studies conducted by Cascinu et al.[12,13]. It was reconstituted from glutathione sodium salt (equivalent to 600 mg glutathione) with sterile water.

In the event that a patient developed a CTCAE grade ≥ 3 neurotoxicity, paclitaxel was held until the patient recovered to CTCAE grade ≤2 toxicity, then treatment was resumed at a 10% dose reduction. Modification or discontinuation of CBDCA due to neurotoxicity was at the discretion of the clinician. If CBDCA was discontinued but paclitaxel was continued, the patient continued glutathione/placebo therapy. If a patient developed any clinically significant adverse event (AE) attributed to glutathione/placebo, the glutathione/placebo was stopped. In the event that glutathione/placebo was stopped for an AE, the patient continued to be followed according to protocol criteria. If the patient required additional chemotherapeutic agents due to chemotherapy toxicity and/or disease progression, the patient was taken off study treatment.

Statistical methodology

This clinical trial employed a single-stage parallel group design. The dynamic allocation procedure[21] to balance the marginal distributions of baseline neuropathy, debulked status and cancer type was adopted for randomization.

The primary endpoint was sensory chemotherapy-induced peripheral neuropathy as repeatedly measured by the sensory subscale of the EORTC QLQ-CIPN20 during the first six cycles of chemotherapy. The sensory subscale of EORTC QLQ-CIPN20 was computed by standard scoring algorithm and then converted to 0–100 scale, where higher scores means less symptoms and better quality of life. A repeated measures model was used to compare the primary endpoint between glutathione and placebo arms for the primary statistical analysis. Descriptive statistics such as mean (SD), median (range) and frequency (percentage) were used to summarize all clinical data including the adverse event profile. Two-sample t-tests and Wilcoxon rank-sum tests[22] were used for comparing continuous secondary endpoints, while Kaplan-Meier[23,24] methodology and the log-rank test were adopted for time-to-event secondary endpoints.

Based on a two-sided test of the time-averaged QLQ-CIPN20 sensory subscale scores with an assumption of moderate correlation (rho=0.5), it was calculated that a sample size of 154 patients (77 patients per arm) was required to provide 90% power to detect a difference of 6 points in QLQ-CIPN20 sensory subscale score (SD = 15 points) between the glutathione and placebo arms[25]. This sample size was further inflated by 20% to account for patient ineligibility, cancellation, or major violations.

This trial was monitored at least twice annually by a Data and Safety Monitoring Board, composed of individuals from within and outside the Alliance. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center. Data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chairperson, following Alliance policies. All analyses were based on the study database frozen on January 22, 2013.

Results

Baseline characteristics

This study accrued 195 patients between 12/04/2009 and 12/19/2011 from over 50 individual sites. Baseline patient characteristics, detailed in Table 1, were similar in the two treatment groups. Patient study flow is illustrated in Figure 1.

Neuropathy Data

Paclitaxel acute pain syndrome data—Patient-reported acute pain syndrome data, which have been described as being primarily a manifestation of acute paclitaxel neuropathy[18,19] but have commonly been labeled as paclitaxel-induced arthralgias/myalgias, are illustrated in Figure 2. This figure illustrates that, for 7 days after each chemotherapy dose, there was no significant advantage for glutathione between the two study arms (p=0.30 for the every 3 week subset; p= 0.002 for the weekly subset, in favor of the placebo arm).

Cumulative peripheral neurotoxicity—The presented data regarding peripheral neuropathy include patients receiving weekly and every three week paclitaxel, since the data were quite similar in these two subsets. Peripheral neuropathy data for the two study arms, using the QLQ-CIPN20 sensory neuropathy scale (primary endpoint, Figure 3), illustrate that there were no statistically significant differences in the AUC between the two study arms (p= 0.21). The median follow-up time for these patients was 326 days.

Additionally, no significant benefits for glutathione are illustrated when neurotoxicity was assessed by physicians using the CTCAE scale for determining grade 2+ neurotoxicity (p=0.449) or the time to the development of grade 2+ neurotoxicity (p= 0.039, in favor of placebo arm) (Table 2 and Figure 4).

FACT-O data, evaluating changes from baseline values, did not reveal any substantial difference between the two study arms.

Effect of glutathione on cancer outcome

There were no significant differences between the two study arms with regards to the time to disease progression in the gynecologic patients per CA-125-determined disease progression, defined as an elevation of greater than two times the upper limit of normal on two occasions, separated by at least one week, when the CA-125 level had normalized during, or upon completion of therapy.

Evaluation of glutathione toxicity

There were no statistically significant or clinically apparent toxicity differences between the two study arms with regard to multiple evaluated toxicities (including fatigue, nausea, vomiting, diarrhea, rash, anaphylaxis, anemia and leukopenia).

Sub-group analyses

Sub-group analyses by age, gender, tumor type, and specific paclitaxel regimens, revealed no compelling evidence of benefit in any subgroup.

Discussion

The negative findings from this current trial contrast with the positive pilot findings[10–17] that led to its development. Of the data available to investigate the efficacy of glutathione as a CIPN preventative agent, most of the studies have been conducted in patients receiving either oxaliplatin- or cisplatin-based therapy. In comparing the neurotoxicity of the agents involved in the current trial, carboplatin is the least neurotoxic of the platinum agents and is less neurotoxic than paclitaxel. While the results of this current study support that glutathione is not an effective agent in the prevention of taxane-induced CIPN when given in combination with carboplatin, the current results may not be applicable for cisplatin- or oxaliplatin-induced neurotoxicity.

A recently published study by Smith et al.[26] supports that therapies for chemotherapy-induced neuropathy may be different for different chemotherapy agents. Their manuscript reported data from a randomized, double-blind, placebo-controlled, crossover trial to investigate the efficacy of duloxetine for the treatment of established CIPN among a cohort of patients with either taxane- or oxaliplatin-induced CIPN. These authors found a significant decrease in patient-reported average pain among those that received duloxetine, compared to placebo. However, in a subgroup analysis, it appeared that duloxetine was efficacious in patients with oxaliplatin-induced CIPN but not efficacious in those with taxane-induced CIPN. This may explain the differences between the findings from the present study and what has been previously suggested in other pilot trials looking at oxaliplatin- or cisplatin-based therapies.

Despite substantial efforts, there are no recommended agents for preventing chemotherapy-induced neuropathy at this time. A recent large trial illustrated that intravenous calcium/magnesium was not helpful for oxaliplatin induced neuropathy[27] despite substantial previous enthusiasm for this approach. Similarly, despite pilot reports suggesting the utility of vitamin E, a larger, placebo-controlled, double-blinded randomized trial was not able to

substantiate benefit. Acetyl-L-carnitine, despite preliminary reports and supporting animal tumor data, actually appeared to worsen chemotherapy-induced peripheral neuropathy in patients receiving paclitaxel-based therapy.[28] Two reasonably sized, placebo-controlled, double-blinded clinical trials showed no benefit for an ACTH derivative[29,30] despite four smaller pilot trials suggesting benefit.[31–34]

While this series of negative trials is disappointing, so is the substantial neuropathy caused by commonly-used neurotoxic chemotherapy agents. This calls for ongoing scientific methods to identify ways of utilizing these agents for their anti-tumor activity while preventing unwanted neuropathy.

Along this line, we are excited about the potential utility of minocycline[35–52] and selective serotonin norepinephrine reuptake inhibitors such as venlafaxine[53] and duloxetine.[26] Efforts are ongoing to address the potential utility of these agents. Additionally, work is being done to address the role of genetic factors as a means of identifying which patients are at increased risk for developing chemotherapy-induced peripheral neuropathy.

In conclusion, this study does not support the use of glutathione for the prevention of taxane-induced CIPN. There was no suggestion of glutathione-associated toxicity or interference with antitumor activity. Further inquiries into the efficacy of this drug in patients receiving oxaliplatin- or cisplatin-based therapy would be of interest.

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Appendix I

Neurotoxicity Evaluation

Grade	**I**	**II**	**III**
NCI-CTC AE v4.0	Mild symptoms	Moderate symptoms; limiting instrumental activities of daily living	Severe symptoms; limiting self-care activities of daily living
Questions	**Sample answers for each toxicity grade**		

Grade	I	II	III
Do you have problems tying your shoelaces, buttoning your shirts, fastening buckles or pulling up zippers?	"No, I might feel some tingling in my hands, but I have no problems tying laces, buttoning shirts, fastening buckles or pulling up zippers"	"It is a bit harder than before, but I can still tie laces, button shirts, fasten buckles or pull up zippers"	"I have severe difficulties tying shoe laces, buttoning shirts, fastening buckles or pulling up zippers" or "I cannot tie laces, button shirts, fasten buckles or pull up zippers anymore"
Do you have problems writing?	"No, I might feel some tingling in my hands, but I have no problems writing"	"It is a bit harder than before, but I can still write"	"I have severe difficulties writing" or "I cannot write anymore"
Do you have problems putting on your jewelry or your watch?	"No, I might feel some tingling in my hands, but I have no problems putting on my jewelry or my watch"	"It is a bit harder than before, but I can still put on my jewelry or my watch"	"I have severe difficulties putting on my jewelry or my watch" or "I cannot put on my jewelry or my watch anymore"
Do you have problems walking?	"No, I might feel some tingling in my feet, but I have no problems walking"	"It is a bit harder than before, but I can still walk"	"I have severe difficulties walking" or "I cannot walk anymore"

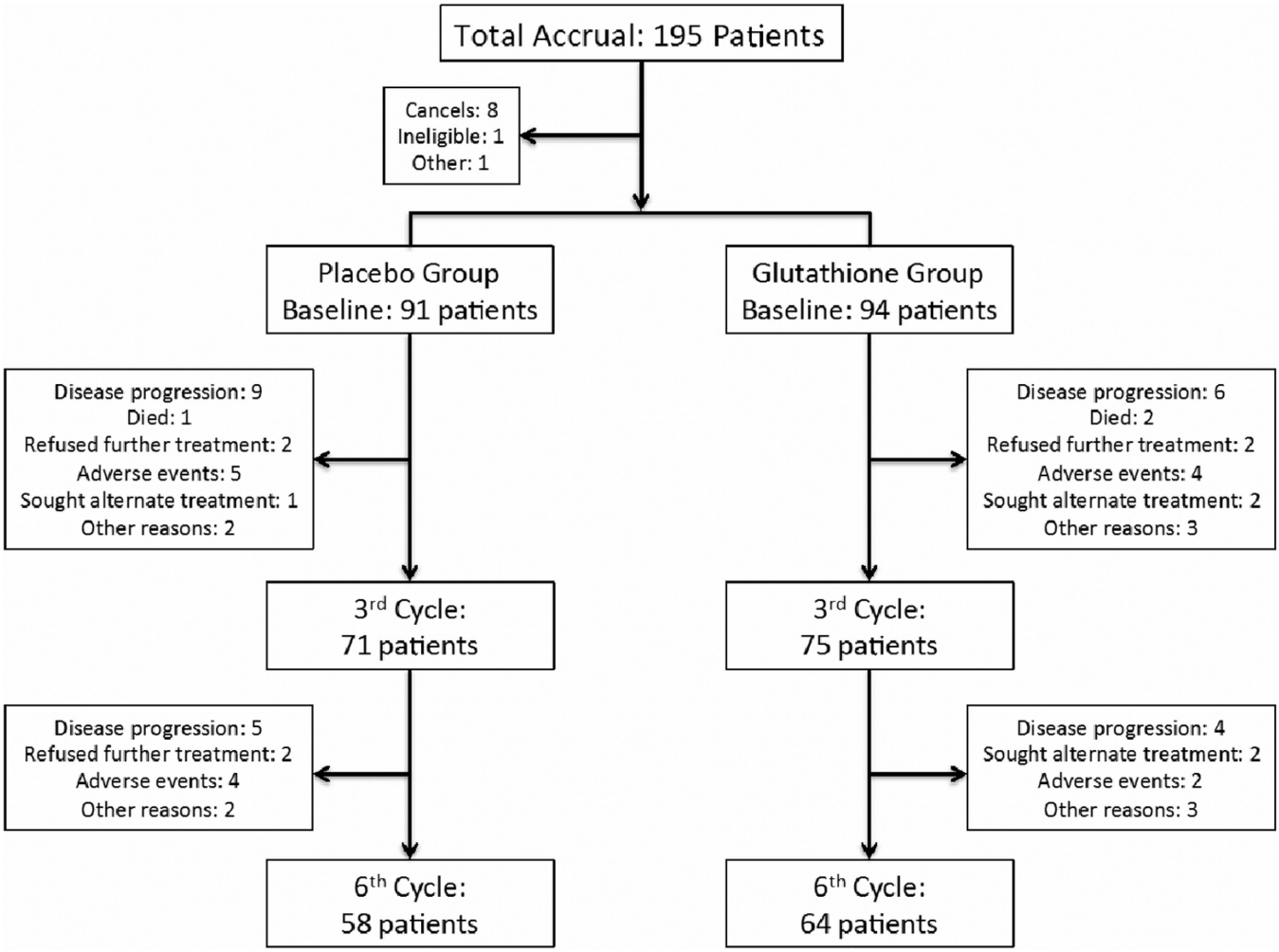
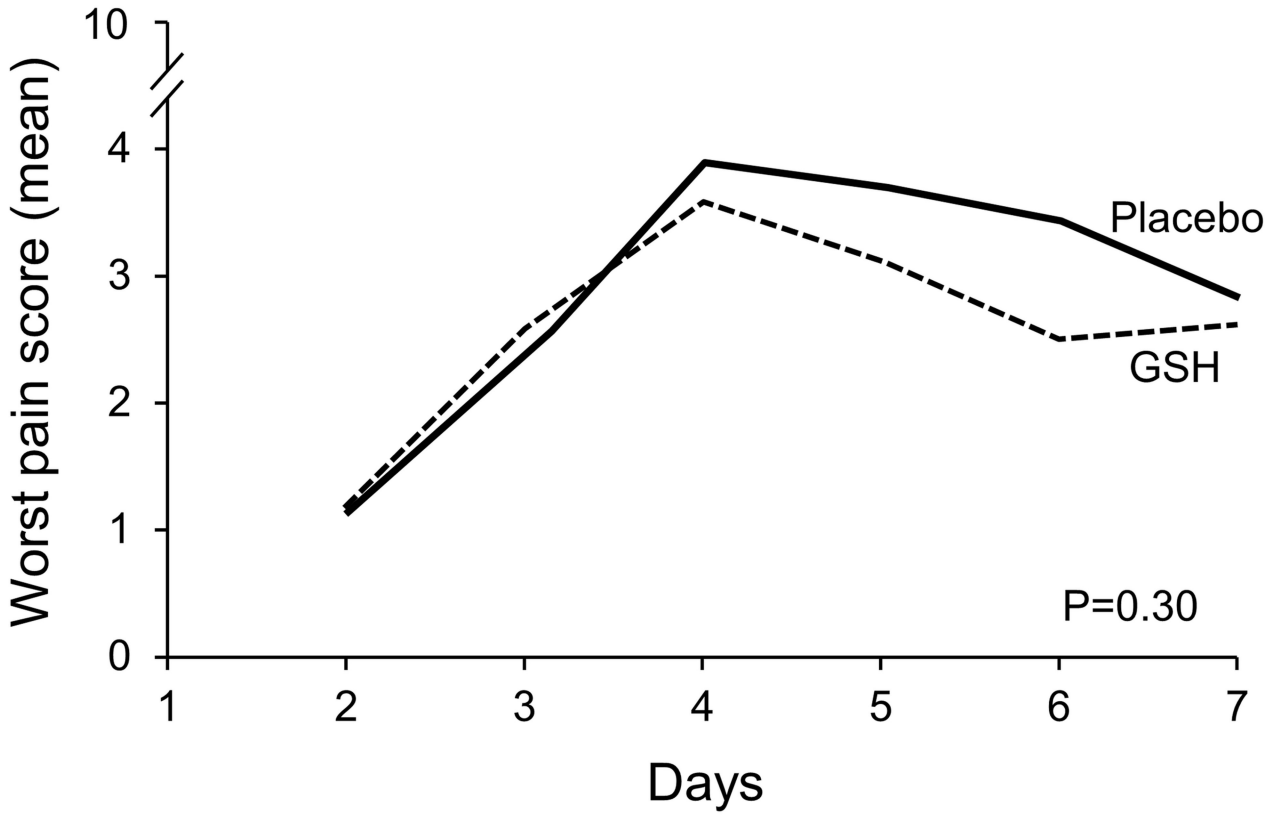


Figure 1.
CONSORT diagram



Placebo	73	73	70	71	72	71
GSH	74	76	73	69	69	72

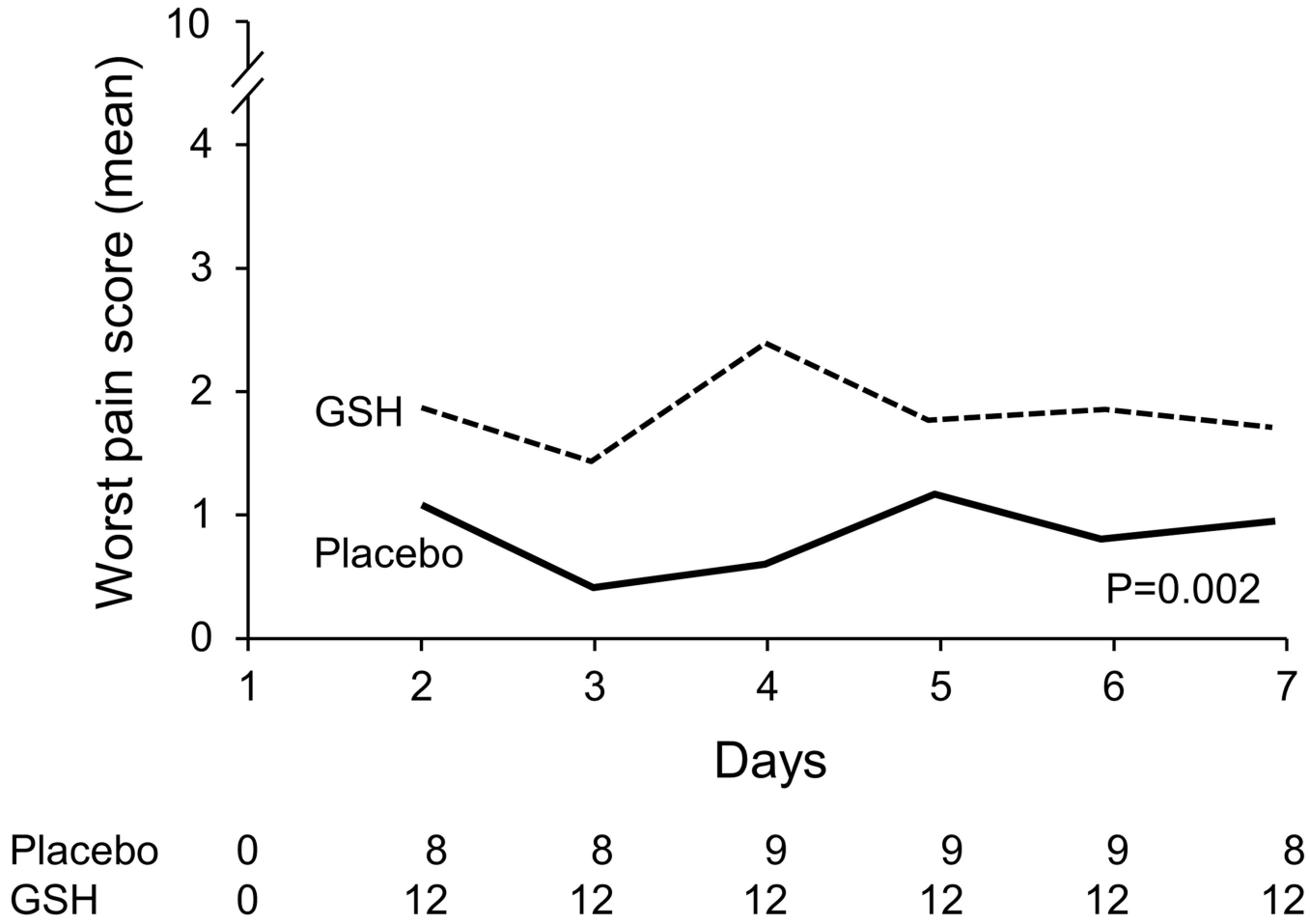


Figure 2.
Worst daily paclitaxel-induced acute pain scores by treatment arm for patients who received every 3–4 week paclitaxel (cycle 1) (A) and weekly paclitaxel (B). Lower scores are better.

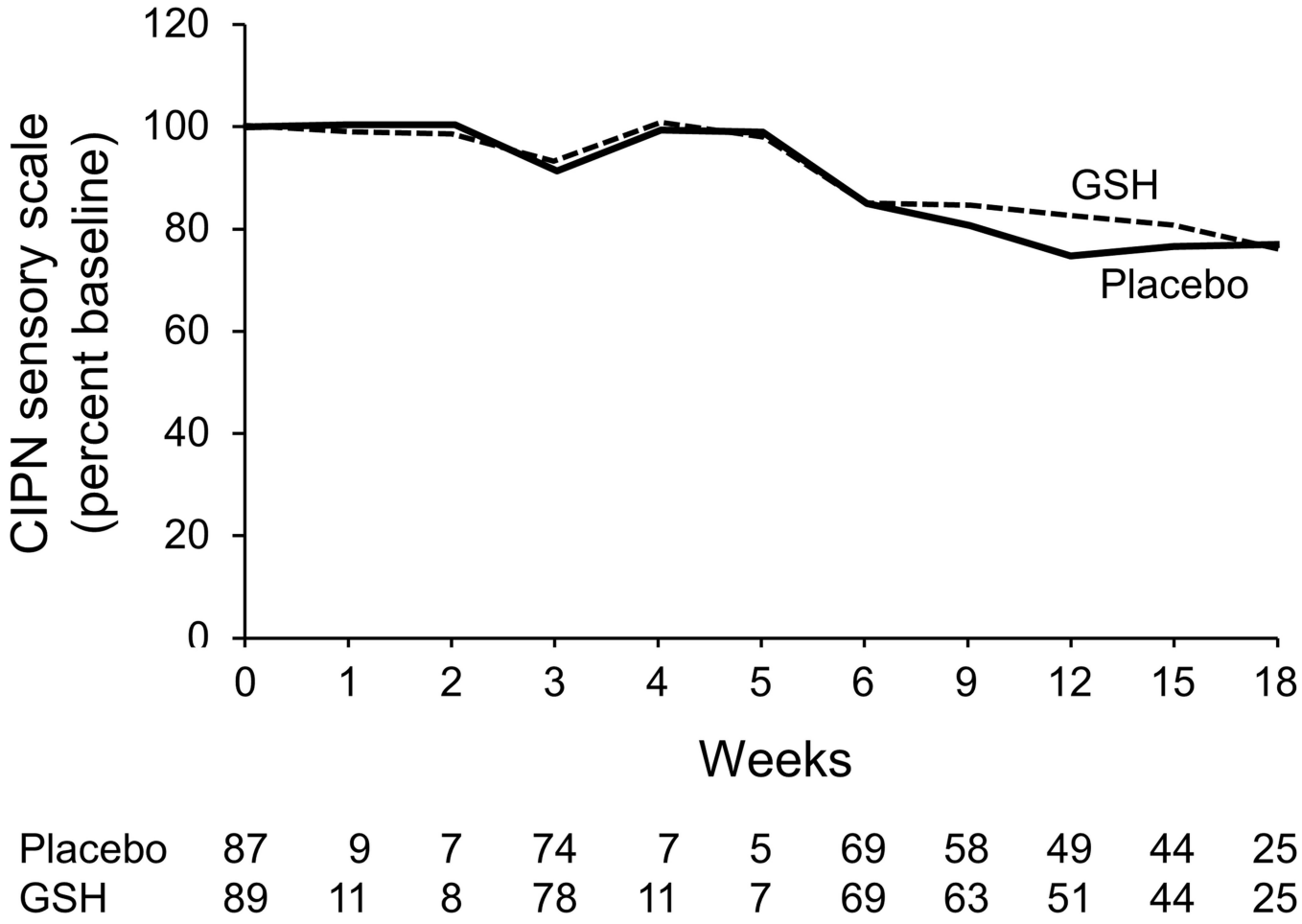


Figure 3.

Percent of baseline neuropathy as measured by the EORTC QLQ-CIPN20 sensory scale. Higher scores are better.

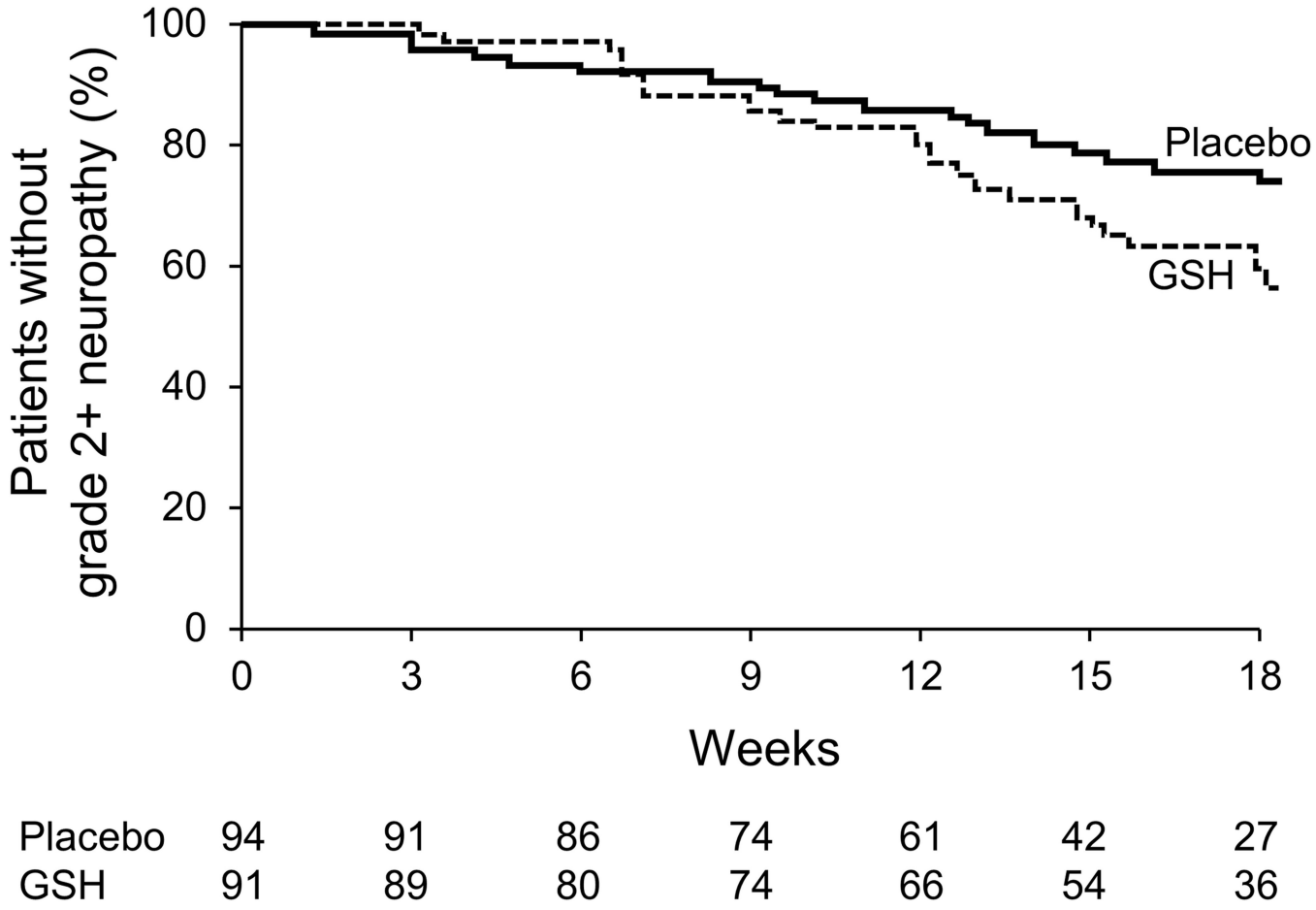


Figure 4.
Time to grade 2+ peripheral neuropathy, as measured by the NCI CTCAE scale

Table 1

Patient Demographics and Clinical Characteristics

	Glutathione (N=94)	Placebo (N=91)	Total (N=185)	p-value
Age				0.41[1]
Median	63.0	63.0	63.0	
Age >50	81 (86%)	79 (87%)	160 (87%)	0.90[2]
Race				0.79[2]
White	88 (94%)	84 (92%)	172 (93%)	
Black or African-American	5 (5%)	5 (6%)	10 (5%)	
Native Hawaiian or Other Pacific Islander	0 (0%)	1 (1%)	1 (1%)	
Asian	1 (1%)	1 (1%)	2 (1%)	
Gender				0.41[2]
Female	74 (79%)	76 (84%)	150 (81%)	
Baseline Neuropathy				0.94[2]
None	83 (88%)	80 (88%)	163 (88%)	
Grade 1	11 (12%)	11 (12%)	22 (12%)	
De-bulked Status[3]				0.69[2]
No gross residual disease	22 (49%)	20 (49%)	42 (49%)	
Optimal[4]	15 (33%)	11 (27%)	26 (30%)	
Sub-optimally de-bulked	8 (18%)	10 (24%)	18 (21%)	
Cancer Type				0.89[2]
Ovarian/fallopian tube/primary peritoneal	45 (48%)	41 (45%)	86 (47%)	
Lung	27 (29%)	26 (29%)	53 (29%)	
Other	22 (23%)	24 (26%)	46 (25%)	
Group				0.30[2]
Weekly	12 (13%)	9 (10%)	21 (11%)	
Every 3 weeks	82 (87%)	80 (88%)	162 (88%)	
Every 4 weeks	0 (0%)	2 (2%)	2 (1%)	
ECOG Performance Score				0.80[2]
0	42 (45%)	39 (43%)	81 (44%)	
1	47 (50%)	45 (50%)	92 (50%)	
2	5 (5%)	7 (8%)	12 (7%)	
Diabetes				0.14[2]
Yes	8 (9%)	14 (16%)	22 (12.0%)	
No	86 (92%)	76 (84%)	162 (88%)	

[1] Kruskal Wallis test,

[2] Chi-Square test,

[3] Applicable only to ovarian/fallopian tube/primary peritoneal,

[4] No residual tumor mass greater than 1 cm.

Table 2

Percentage of patients with grade 2+ and grade 3+ paclitaxel/carboplatin-induced CIPN by CTCAE

	Glutathione (N=94)	Placebo (N=91)	Total (N=185)	p-value
Indicator: Grade 2+ CIPN				0.45[1]
No	58 (62%)	61 (67%)	119 (64%)	
Yes	36 (38%)	30 (33%)	66 (36%)	
Indicator: Grade 3+ CIPN				0.77[1]
No	89 (95%)	87 (96%)	176 (95%)	
Yes	5 (5%)	4 (4%)	9 (5%)	

[1] Chi-Square test