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Oral Alpha-Lipoic Acid to Prevent Chemotherapy-Induced Peripheral Neuropathy: A Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Objectives—Chemotherapy-induced peripheral neuropathy is frequently a dose-limiting factor in cancer treatment and may cause pain and irreversible function loss in cancer survivors. We

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tested whether alpha-lipoic acid (ALA) could decrease the severity of peripheral neuropathy symptoms in patients undergoing platinum-based chemotherapy.

Methods—Cancer patients 18 years or older were randomly selected to receive either 600 mg ALA or a placebo three times a day orally for 24 weeks while receiving chemotherapy regimens including cisplatin or oxaliplatin. Neuropathy was measured by the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) scale and the NCI Common Toxicity Criteria for Adverse Events neurotoxicity grades. Results from timed functional tests and the Brief Pain Inventory (BPI) were secondary endpoints.

Results—70 of 243 (29%) patients completed the study (24 weeks). Both the ALA and the placebo arms had a comparable drop-out rate. No statistically significant differences were found between the ALA and the placebo groups for FACT/GOG-Ntx scores, BPI scores, and patients' functional outcomes..

Conclusion—This strategy of oral ALA administration was ineffective at preventing neurotoxicity caused by oxaliplatin or cisplatin. High attrition rates due to poor patient compliance and manner of dosage administration in this trial demonstrated a lack of feasibility for this intervention. Future studies to explore ALA as a neuroprotective agent should take heed of the barriers confronted in this study.

Keywords

Chemotherapy-induced peripheral neuropathy; sensory neuropathy toxicity; Alpha-lipoic acid

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) caused by platinum is common and can severely compromise the quality of life of cancer survivors [1]. Dose-limiting neurotoxicity is a major side effect of platinum-based treatments, frequently leading to a negative prognosis for patients [2,3]. The incidence and severity of CIPN vary, depending – among other factors – upon the treatment drug used [4], its cumulative dose [5], patients' prior comorbid condition, if any [6], and/or whether the patient is on concurrent therapy [7].

For patients receiving cisplatin, neuropathy is generally most likely to occur at cumulative doses exceeding 300 mg/m² [8]. Oxaliplatin-induced neurotoxicity consists of a rapid-onset acute sensory neuropathy and/or a late-onset cumulative sensory neuropathy that commonly occurs after several cycles of therapy. The late-onset neuropathy is dependent upon the cumulative dose of oxaliplatin received and essentially affects all patients who receive cumulative doses greater than or equal to 540 mg/m² [9–11].

In the acute phase of oxaliplatin-induced peripheral neuropathy, the most prevalent neurological symptoms experienced by patients are cold sensitivity (85%), and tingling and numbness in the hands (67% and 55%, respectively) [12]. In the chronic phase, the most prevalent symptoms include tingling (29%), numbness (17%) and aching or burning pain (13%).[13]. Patients frequently continue to have persistent symptoms 2 years after treatment [14,15]. Oxaliplatin-treated patients additionally experience several symptoms that significantly limit their physical abilities and diminish their overall quality of life [1,16]. In

particular, some of the symptoms frequently reported by patients during or post-treatment include muscular and skeletal problems, difficulty walking [17], depression, and insomnia [12]. Current pharmacological treatments that are prescribed to address these conditions (such as antidepressants and amifostine) have demonstrated limited efficacy and themselves frequently induce additional undesirable adverse effects [16]. Consequently, there has been significant interest in the investigation of neutraceuticals that may be preventative or neuro-protective against CIPN, and that may serve as adjuvants in cancer treatment. Recent reviews have examined the potential use of several agents such as vitamin E, acetyl-L-carnitine, glutamine, glutathione, calcium, magnesium, alpha-lipoic acid, and N-acetylcysteine, among others [16,18]. No agent, however, has reliably demonstrated sufficient or significant benefit such that it may be prescribed for the prophylaxis of CIPN [18,16,19].

Alpha-lipoic acid (ALA) is a physiologic antioxidant that has been examined quite extensively as a treatment for diabetic neuropathy, but its use as a potential prophylactic against CIPN in patients with cancer has not been exhaustively investigated. ALA has been shown to be effective in the treatment of distal sensory motor neuropathy [20], as well as in the modulation of peripheral neuropathy and pain reduction in diabetic patients. [21]. The mechanism of neurotoxicity induced by platinum drugs in cancer patients has been proposed to involve the oxidation of accumulated platinum derivatives in the dorsal root ganglia [22]. ALA's neuroprotective mechanism is related to the reduction of oxidative stress from free-radical formation; thus, the systemic oxidation of platinum derivatives resulting from chemotherapy may be modulated by ALA's antioxidant effects [23]. Indeed, ALA was found to be effective in a small open-label pilot study when co-administered with oxaliplatin [24]. The treatment combination used in this pilot study (600 mg ALA given intravenously once a week for 3–5 weeks followed by 600mg three times daily orally) showed a trend toward a reduction in the severity of oxaliplatin induced CIPN in 8 out of 15 patients [24].

In light of the paucity of effective pharmacological or non-pharmacological agents against CIPN, substantial evidence of its effectiveness in diabetic peripheral neuropathy, and promising results from the above pilot ALA trial, we conducted this current randomized trial to further investigate the potential efficacy of ALA in preventing or reducing CIPN in cancer patients being treated with cisplatin or oxaliplatin. Additionally, we sought to examine if ALA may have ancillary positive effects on patients' pain levels and functional performance.

Methods

Study Site and Participants

This study was conducted at The University of Texas MD Anderson Cancer Center and at participating MD Anderson Cancer Center Community Clinical Oncology Program (CCOP) Research Base sites. It was approved by the Institutional Review Boards of all participating institutions. All patients provided written informed consent.

Cancer patients 18 years or older and scheduled to receive chemotherapy with cisplatin or oxaliplatin were eligible for the study. Inclusion criteria required patients to be in a normal state of arousal per treating physician(s); have moderately normal liver and renal function as

determined by serum bilirubin < 2 mg/d and creatinine < 2 mg/dL, or calculated creatinine clearance > 45 mL/min. Women of child-bearing age were required to be on acceptable forms of contraception. Excluded patients were those exposed to carboplatin, vincristine, paclitaxel or docetaxel within the past 6 months, or expecting to be exposed to these agents in the next 12 months; those with a history of clinical neuropathy, diabetes mellitus (oral/insulin-dependent), chronic alcoholism, central nervous system disease, those pregnant, and those on an oral dose of 100 IU of Vitamin E daily. Participants on any medication that might modify peripheral neuropathy were prohibited from modifying their medication dosage starting 2 weeks prior to the study and during the course of the trial.

Study Design

This study was a randomized, double-blind, placebo-controlled trial using 1800 mg of ALA daily or placebo in patients who received platinum-based chemotherapy. The study plan involved the assignment of approximately 122 eligible patients to each of the 2 treatment groups in order to detect a one half standard deviation difference in the main outcome, i.e., the FACT/GOG-Ntx scores of the 2 groups at 24 weeks with a significance level of 0.05 and 90% power.

Prior to randomization, patients in each group were stratified into three sets according to their prior exposure to platinum. The first set comprised patients with no prior platinum exposure; the second, of those whose prior exposure was < 399 mg/m² cisplatin or < 750 mg/m² oxaliplatin, and the third, of those whose prior exposure was > 400 mg/m² cisplatin or > 750 mg/m² oxaliplatin. Once stratified, patients in each set were randomly assigned to receive ALA (two 300-mg ALA sustained-release tablets by mouth three times daily) or matching placebo (three times daily orally on an empty stomach at least 1 hour before or 2 hours after meals). This process ensured that prior platinum exposure was not a confounding factor between the two study arms. The ALA dose was selected based on its prior successful use in previous trials [25,26]. Oral ALA was obtained from Jarrow Formulas, Los Angeles, California. Patients received ALA or a placebo continuously for 24 weeks, except during the period 2 days before to 4 days after delivery of each dose of platinum in order to avoid the possibility of its potential interference with the antitumor effects of the platinum. Clinical assessments to measure symptoms of neuropathy were planned at baseline, and then at 24, 36, and 48 weeks of treatment.

Measures

Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) Version 4—Patients' subjectively experienced neuropathic symptoms were assessed using the FACT/GOG-Ntx, version 4 [27,28]. The 11-item FACT/GOG-Ntx subscale was developed specifically to assess neurotoxic effects of chemotherapy and has been shown to have good psychometric properties [29]. Patients reported their symptoms on a scale of 0 (not at all) to 4 (very much). Overall scores were calculated based on the approach described in the FACT manual [30], with low scores indicating no neuropathy. A difference of 4 points on the FACT/GOG-Ntx scale indicates a minimal clinically important change [31].

Functional Tests—Three functional tests, selected for their ease and speed of administration, were administered to test patients' physical limitations imposed by neuropathy: Time to button a 6-hole shirt (patients put on a 6-hole button shirt and are timed on the number of seconds needed to button the 6 buttons as fast as they can); 50-foot walk at fastest speed (patients are timed as they walk 25 feet, turn around, and walk back to the start as fast as they can [32]); and coin test (patients sit at a table and are timed while they pick up four coins, one at a time, in any order, and place the coins in a cup).

Brief Pain Inventory (BPI) Partial Form—The BPI Partial Form is a valid, 3-item questionnaire that assesses subjectively experienced pain symptoms [33,34]. The first two questions ask patients to rate their worst and average pain on a scale of 0 (no pain) to 10 (pain as bad as you can imagine); the third question (using an interference scale) asks patients to describe pain interference during the past 24 hours on a 0 (does not interfere) to 10 (completely interferes) scale. Previous research indicates that asking patients to rate their pain at its "worst in the last 24 hours" is both practical and valid for assessing a pain-reduction treatment effect [34].

All patients completed a daily medication log that was reviewed at each assessment point. Additionally, pills were counted at each assessment to measure adherence. Those patients who had taken less than 80% of the assigned pills at the end of the study were considered noncompliant and excluded from analysis. Adverse events were graded with a numerical score based on the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE, version 3.0) [35]. Tumor response data were collected from treating physicians. Patients receiving adjuvant therapy were not formally followed for response.

Statistical Analysis

The primary analysis for this trial consisted of an analysis of covariance based on intent-to-treat, excluding only those patients who died during follow-up or who chose to withdraw from the study. Group differences were tested in FACT/GOG-Ntx scores at 24 weeks using each patient's initial score as a covariate. Pain scores from the BPI for "average pain," "worst pain," and the "pain interference scale" and scores from the 3 timed functional tests were analyzed using analyses of covariance in order to determine if there were significant differences in clinical improvement between groups. The 24 week time point was used as a starting point for evaluation as it was not expected that differences between the groups would occur before this time point. If attrition was minimal at 24 weeks, group differences in FACT-GOG-Ntx, BPI, and functional test scores were expected to be analyzed at 36 and 48 weeks utilizing an analysis of variance as described for the primary analysis. Specific statistical tests involved the comparison of patient characteristics between the ALA and placebo groups at baseline using the chi-squared test; comparison of scores obtained from each of the measures at 24 weeks using the Wilcoxon two-sample test for non-normal data; comparison of tumor response at 24 weeks using the chi-squared test, and finally, a comparison of drop-out rate between the 2 treatment arms using the Fisher Exact test.

Results

Two hundred forty three eligible patients were enrolled in the study; of these 122 were randomized to the ALA arm, and 121 to the placebo arm. 28% of patients in the ALA arm ($n=34$), and 30% of patients in the placebo arm ($n=36$) completed the study at 24 weeks. The remaining patients in each arm dropped out of the study prior to 24 weeks; the main reasons for discontinuation were withdrawal of consent and patient non-compliance (Figure 1).

Table 1 presents patient characteristics at baseline in each study arm. There were no statistically significant differences between patients in the 2 study arms for each of the variables listed (all $P > .05$).

Due to high attrition, we were able to evaluate data for all 3 measures primarily at the 24 week time point (Table 2). Patients' subjective report of neuropathy symptoms was similar in both the treatment and the placebo arms ($P > .05$). Four patients in the ALA arm had received cisplatin, whereas all remaining patients in both arms had received oxaliplatin. For this reason, we conducted additional analyses by comparing patient-reported neuropathy scores between the 2 groups by excluding the 4 patients that had received cisplatin, but found differences between the 2 groups to still be non-significant. While our data indicated that neuropathy scores rose significantly from baseline for both groups at 24 weeks ($P < .001$ for each group), we did not observe a statistically significant ameliorating effect from the ALA in the treatment arm.

Patients' worst pain, average pain, and pain interference scores obtained from the BPI were not significantly different between the treatment and placebo groups (Table 2, All $P > .05$). Similarly, scores from the 3 functional tests did not indicate any statistically significant differences between the 2 groups, and were generally comparable.

Adverse event data indicated that neurotoxicity levels were nearly identical between the 2 arms; several other reported adverse events were common side effects of chemotherapy (Table 3).

Finally, although not a main outcome of our study, we also compared best tumor response between the 2 groups at 24 weeks utilizing standard tumor response classification criteria (Complete Response/Partial Response/Stable Disease/Disease Progression; patients receiving adjuvant therapy were excluded). Nineteen patients in the ALA group exhibited Stable Disease relative to 12 in the placebo group, and 5 patients in the ALA group exhibited Complete Response, relative to 4 in the placebo group (data not shown). There were, however, no statistically significant differences between the 2 groups for the outcomes related to treatment response (All $P > .05$).

Discussion

Chemotherapy induced peripheral neuropathy (CIPN) is a debilitating and dose-limiting side effect of commonly used chemotherapeutic agents that frequently results in compromising the efficacy of cancer therapy [1–3]. There has thus been a need for the investigation of agents that may ameliorate or modulate neurotoxic symptoms induced by cancer therapies.

In this trial, we investigated ALA to determine if its use may decrease the severity of peripheral neuropathy after patients' exposure to 24 weeks of chemotherapy with cisplatin or oxaliplatin.

The chemotherapy dose received by each group in our trial was in excess of 750 mg/m², a dose known to result in clinically significant neuropathic symptoms [9,10] [11]. Although both the ALA and the placebo groups exhibited worsening neuropathic symptoms at 24 weeks relative to baseline levels, the overall patient-reported neuropathy scores between the 2 groups were not significantly different. The secondary endpoints of our study (patients' pain levels and performance on functional tests) similarly did not show a statistically significant difference between the 2 treatment groups at the 24 week assessment. We were unable to evaluate data at the anticipated 36 and 48 week time points due to the high attrition rate in both study groups at or before 24 weeks.

The most severe challenge experienced in this randomized trial was that of patient withdrawal from the study and treatment non-compliance, so much so that only 28% of patients in the ALA arm, and 30% in the placebo arm were available for assessment at the 24 week time point. We were therefore unable to take the trial to its completion and obtain complete clinical assessments for the planned number of patients at all time points (24, 36, and 48 weeks), which would have provided the data essential to determining the effect of ALA in the treatment arm with the sample size or statistical power originally intended for the study. Thus, notwithstanding the lack of statistically significant differences in patients' neuropathy scores between the ALA and placebo arms at 24 weeks, ALA's overall efficacy, or its lack thereof, as a potential neuroprotective agent against CIPN could not be conclusively determined from this trial. Our data indicate that drop out was largely unrelated to toxicities prior to the 24 week time point (adverse events were comparable between the ALA and placebo arms prior to 24 weeks, and patients reported primarily grade 1 or 2 toxicity at previous observational points; data not shown). We did determine, however, that this dose and schedule of ALA, framed for the purpose of prevention of CIPN, was not feasible for this patient population over a prolonged timeframe where patients were expected to take this medication.

The most important reason that data obtained at 24 weeks did not show a therapeutic effect from ALA on patients' neuropathy scores in the treatment arm was the high rate of attrition and subsequent loss of power to detect any potential differences between the ALA and placebo groups. We believe that a major factor that led to high rates of attrition and non-compliance in our study was both the frequency and dose size of the ALA. While adherence to medication regimens in cancer patients is generally good [36–38], it is largely correlated with patients' perception of the risk-benefit ratio associated with compliance. In the case of a prevention trial (as the current one) in which the patient is blinded to whether he/she is receiving a drug or a placebo, the perceived benefit is relatively abstract in comparison to studies in which an agent may be taken to obtain relief for a specific symptom. Our results indicate that given the 24 week duration of this study, the burden of taking an experimental agent or a placebo as a prophylactic against impending neuropathy symptoms (for a prolonged period) far exceeded the anticipated perceived benefit for most patients. In a previous successful trial that examined the effect of ALA on neuropathic symptoms in

advanced colorectal cancer patients, 600 mg of the ALA was administered intravenously once a week for 3–5 weeks from onset of therapy followed by 600mg 3 times a day orally [24]. It is therefore reasonable to conclude that patients might prefer a once a week intravenous method of dose administration relative to taking pills of a substantial size 3 times a day for a prolonged duration. An important lesson thus to be derived from the current trial is that the manner of dose administration in a prevention trial is crucial; it must necessarily be both acceptable to the patient and conducive to high compliance.

Another point of note with respect to the lack of effect obtained from the ALA in the treatment arm at 24 weeks may be related to the fact that in this trial, ALA administration was discontinued 2 days prior to, and 4 days after, the administration of oxaliplatin due to concern regarding ALA's antitumor activity (Newman R et al, Nerium Biotechnology, Inc. San Antonio, TX 78230, personal communication). Platinum-based neuropathy has previously been linked to increased oxidative stress, DNA damage, mitochondrial dysfunction, and neuronal apoptosis of the dorsal root ganglia. [5,39]. It is conceivable that considerable or irreversible damage to the dorsal root ganglia may occur concurrently with oxaliplatin administration, or in the period immediately after its administration. In the previous trial undertaken by Gedlicka et al, ALA was co-administered with oxaliplatin, and this treatment combination showed a trend toward a reduction in the severity of oxaliplatin-induced CIPN in the majority of patients [24]. Future trials should thus carefully evaluate the potential benefits of co-administration of ALA with oxaliplatin against the withholding of ALA in the peri-oxaliplatin administration period. The tradeoff that must be weighed is the potential risk that ALA will protect the tumor (and reduce the treatment effect of chemotherapy).

A limitation of our study additionally pertains to the evaluation of patients' neuropathic symptoms using a subjective, patient-reported outcome (PRO) measure. While PRO's are the instrument of choice for several cancer treatment-related symptoms, a systematic review of studies evaluating oxaliplatin-induced peripheral nerve damage indicates that the assessment of CIPN should optimally be based on neurologic clinical examination and quantitative methods such as nerve conduction studies rather than on subjective measures [7]. Future trials should thus consider incorporating these more objective methods for accurate CIPN assessment, although such approaches clearly introduce practical barriers to patient enrollment and retention in the busy outpatient oncology setting.

Finally, while we evaluated patients' pain levels (average and worst), functional performance, and tumor outcomes in both treatment groups, these were not the primary outcomes of our study, and given high attrition in our study at or before 24 weeks, data from our trial (though presented) are inconclusive with respect to these outcomes.

Management of CIPN continues to remain an important challenge for both cancer patients and clinicians, and current standard of care includes dose reduction and/or discontinuation of chemotherapy treatment. Recent systematic reviews have summarized the potential use of several neutraceuticals as adjuvants in cancer treatments [16,18]; yet due to scarcity of conclusive evidence, no agent is currently recommended for the treatment or prophylaxis of CIPN. Agents that have shown some promise without compromising the anti-tumor effects

of cancer therapy include Vitamin E [14–18], N-acetyl cysteine [21,16], Acetyl-L-Carnitine [31,32,16], and ALA, among a few others [20,16]. As with our trial, the majority of these agents require further investigation. The critical lesson of note from the current trial is that even a well-designed and carefully planned randomized trial may fail to retain patients to the study's completion if the method of agent administration is cumbersome or distasteful to the patient, notwithstanding its promising potential benefits. Given previous evidence of ALA's neuroprotective properties obtained through epidemiologic trials in patients with diabetic peripheral neuropathy [20,21]; key biologic mechanisms common to diabetic neuropathy and platinum-induced neuropathy (such as free-radical induced oxidative damage)[22], and the inconclusive nature of our trial, future investigation of ALA as a potential prophylactic against CIPN should not be dismissed if innovative approaches and trial designs can be identified and pursued.

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References

1. Tofthagen C. Patient perceptions associated with chemotherapy-induced peripheral neuropathy. *Clin J Oncol Nurs*. 2010; 14(3):E22–28. DOI: 10.1188/10.CJON.E22-E28 [PubMed: 20529785]
2. Hausheer FH, Schilsky RL, Bain S, Berghorn EJ, Lieberman F. Diagnosis, management, and evaluation of chemotherapy-induced peripheral neuropathy. *Semin Oncol*. 2006; 33(1):15–49. S0093-7754(05)00493-8 [pii]. DOI: 10.1053/j.seminoncol.2005.12.010
3. Verstappen CC, Heimans JJ, Hoekman K, Postma TJ. Neurotoxic complications of chemotherapy in patients with cancer: clinical signs and optimal management. *Drugs*. 2003; 63(15):1549–1563. 63153 [pii]. [PubMed: 12887262]
4. Park SB, Krishnan AV, Lin CS, Goldstein D, Friedlander M, Kiernan MC. Mechanisms underlying chemotherapy-induced neurotoxicity and the potential for neuroprotective strategies. *Curr Med Chem*. 2008; 15(29):3081–3094. [PubMed: 19075655]
5. Krishnan AV, Goldstein D, Friedlander M, Kiernan MC. Oxaliplatin-induced neurotoxicity and the development of neuropathy. *Muscle Nerve*. 2005; 32(1):51–60. DOI: 10.1002/mus.20340 [PubMed: 15880395]
6. Uwah AN, Ackler J, Leighton JC, Pomerantz S, Tester W. The effect of diabetes on oxaliplatin-induced peripheral neuropathy. *Clin Colorectal Cancer*. 2012; 11(4):275–279. DOI: 10.1016/j.clcc.2012.05.002 [PubMed: 22682776]
7. Argyriou AA, Polychronopoulos P, Koutras A, Xiros N, Petsas T, Argyriou K, Kalofonos HP, Chroni E. Clinical and electrophysiological features of peripheral neuropathy induced by administration of cisplatin plus paclitaxel-based chemotherapy. *Eur J Cancer Care (Engl)*. 2007; 16(3):231–237. DOI: 10.1111/j.1365-2354.2006.00718.x [PubMed: 17508942]
8. Cersosimo RJ. Cisplatin neurotoxicity. *Cancer Treat Rev*. 1989; 16(4):195–211. [PubMed: 2561592]
9. Extra JM, Marty M, Brienza S, Misset JL. Pharmacokinetics and safety profile of oxaliplatin. *Semin Oncol*. 1998; 25(2 Suppl 5):13–22.
10. Eng C. Toxic effects and their management: daily clinical challenges in the treatment of colorectal cancer. *Nat Rev Clin Oncol*. 2009; 6(4):207–218. nrclinonc.2009.16 [pii] . DOI: 10.1038/nrclinonc.2009.16 [PubMed: 1933227]
11. de Gramont A, Figuer A, Seymour M, Homerin M, Hmissi A, Cassidy J, Boni C, Cortes-Funes H, Cervantes A, Freyer G, Papamichael D, Le Bail N, Louvet C, Hendler D, de Braud F, Wilson C, Morvan F, Bonetti A. Leucovorin and fluorouracil with or without oxaliplatin as first-line

- treatment in advanced colorectal cancer. *J Clin Oncol.* 2000; 18(16):2938–2947. [PubMed: 10944126]
12. Toftthagen C, McAllister RD, McMillan SC. Peripheral neuropathy in patients with colorectal cancer receiving oxaliplatin. *Clinical journal of oncology nursing.* 2011; 15(2):182–188. DOI: 10.1188/11.cjon.182-188 [PubMed: 21444285]
 13. Mols F, Beijers T, Lemmens V, van den Hurk CJ, Vreugdenhil G, van de Poll-Franse LV. Chemotherapy-Induced Neuropathy and Its Association With Quality of Life Among 2- to 11-Year Colorectal Cancer Survivors: Results From the Population-Based PROFILES Registry. *J Clin Oncol.* 2013; 31(21):2699–2707. DOI: 10.1200/jco.2013.49.1514 [PubMed: 23775951]
 14. Land SR, Kopec JA, Cecchini RS, Ganz PA, Wieand HS, Colangelo LH, Murphy K, Kuebler JP, Seay TE, Needles BM, Bearden JD, Colman LK, Lanier KS, Pajon ER, Cella D, Smith RE, O'Connell MJ, Costantino JP, Wolmark N. Neurotoxicity from oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: NSABP C-07. *J Clin Oncol.* 2007; 25(16):2205–2211. DOI: 10.1200/JCO.2006.08.6652 [PubMed: 17470850]
 15. Pietrangeli A, Leandri M, Terzoli E, Jandolo B, Garufi C. Persistence of high-dose oxaliplatin-induced neuropathy at long-term follow-up. *Eur Neurol.* 2006; 56(1):13–16. DOI: 10.1159/000094376 [PubMed: 16825773]
 16. Schloss JM, Colosimo M, Airey C, Masci PP, Linnane AW, Vitetta L. Nutraceuticals and chemotherapy induced peripheral neuropathy (CIPN): A systematic review. *Clin Nutr.* 2013; doi: 10.1016/j.clnu.2013.04.007
 17. Kopec JA, Land SR, Cecchini R, Ganz P, Cella D, Costantino J, Wieand HS, Smith RE, Kuebler JP, Wolmark N. Validation of a self-reported neurotoxicity scale in patients with operable colon cancer receiving oxaliplatin. *The Journal of Supportive Oncology.* 2006; 4(8):W1–W7.
 18. Wolf S, Barton D, Kottschade L, Grothey A, Loprinzi C. Chemotherapy-induced peripheral neuropathy: prevention and treatment strategies. *Eur J Cancer.* 2008; 44(11):1507–1515. DOI: 10.1016/j.ejca.2008.04.018 [PubMed: 18571399]
 19. Albers JW, Chaudhry V, Cavaletti G, Donehower RC. Interventions for preventing neuropathy caused by cisplatin and related compounds. *Cochrane Database Syst Rev.* 2011; (2):CD005228.doi: 10.1002/14651858.CD005228.pub3 [PubMed: 21328275]
 20. Ibrahimspasic K. Alpha lipoic acid and glycaemic control in diabetic neuropathies at type 2 diabetes treatment. *Med Arh.* 2013; 67(1):7–9.
 21. Snedecor SJ, Sudharshan L, Cappelleri JC, Sadosky A, Mehta S, Botteman M. Systematic Review and Meta-Analysis of Pharmacological Therapies for Painful Diabetic Peripheral Neuropathy. *Pain Pract.* 2013; doi: 10.1111/papr.12054
 22. Roelofs RI, Hrushesky W, Rogin J, Rosenberg L. Peripheral sensory neuropathy and cisplatin chemotherapy. *Neurology.* 1984; 34(7):934–938. [PubMed: 6330613]
 23. Evans P, Halliwell B. Free radicals and hearing. Cause, consequence, and criteria. *Ann N Y Acad Sci.* 1999; 884:19–40. [PubMed: 10842581]
 24. Gedlicka C, Scheithauer W, Schull B, Kornek GV. Effective treatment of oxaliplatin-induced cumulative polyneuropathy with alpha-lipoic acid. *J Clin Oncol.* 2002; 20(15):3359–3361. [PubMed: 12149316]
 25. Ruhnau KJ, Meissner HP, Finn JR, Reljanovic M, Lobisch M, Schutte K, Nehrdich D, Tritschler HJ, Mehnert H, Ziegler D. Effects of 3-week oral treatment with the antioxidant thioctic acid (alpha-lipoic acid) in symptomatic diabetic polyneuropathy. *Diabetic medicine: a journal of the British Diabetic Association.* 1999; 16(12):1040–1043. [PubMed: 10656234]
 26. Ziegler D, Reljanovic M, Mehnert H, Gries FA. Alpha-lipoic acid in the treatment of diabetic polyneuropathy in Germany: current evidence from clinical trials. *Experimental and clinical endocrinology & diabetes: official journal, German Society of Endocrinology [and] German Diabetes Association.* 1999; 107(7):421–430. DOI: 10.1055/s-0029-1212132
 27. Huang HQ, Brady MF, Cella D, Fleming G. Validation and reduction of FACT/GOG-Ntx subscale for platinum/paclitaxel-induced neurologic symptoms: a gynecologic oncology group study. *Int J Gynecol Cancer.* 2007; 17(2):387–393. IJG794 [pii] . DOI: 10.1111/j.1525-1438.2007.00794.x [PubMed: 17362317]

28. Cella D, Peterman A, Hudgens S, Webster K, Socinski MA. Measuring the side effects of taxane therapy in oncology: the functional assesment of cancer therapy-taxane (FACT-taxane). *Cancer*. 2003; 98(4):822–831. DOI: 10.1002/cncr.11578 [PubMed: 12910528]
29. Calhoun EA, Welshman EE, Chang CH, Lurain JR, Fishman DA, Hunt TL, Cella D. Psychometric evaluation of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (Fact/GOG-Ntx) questionnaire for patients receiving systemic chemotherapy. *Int J Gynecol Cancer*. 2003; 13(6):741–748. 13603 [pii]. [PubMed: 14675309]
30. Cella, D. FACIT manual: manual of the functional assessment of chronic illness therapy (FACIT) measurement system. Center on Outcomes, Research and Education; 1997.
31. (CDC) CfDcAP. Cancer survivors--United States, 2007. *MMWR Morb Mortal Wkly Rep*. 2011; 60(9):269–272. [PubMed: 21389929]
32. Simmonds MJ. Physical function in patients with cancer: psychometric characteristics and clinical usefulness of a physical performance test battery. *J Pain Symptom Manage*. 2002; 24(4):404–414. S088539240200502X [pii]. [PubMed: 12505209]
33. Cleeland C. Research in cancer pain. What we know and what we need to know. *Cancer*. 1991; 67(3 Suppl):823–827. [PubMed: 1986852]
34. Atkinson TM, Mendoza TR, Sit L, Passik S, Scher HI, Cleeland C, Basch E. The Brief Pain Inventory and its “pain at its worst in the last 24 hours” item: clinical trial endpoint considerations. *Pain medicine (Malden, Mass)*. 2010; 11(3):337–346. DOI: 10.1111/j.1526-4637.2009.00774.x
35. Program CTE. Common Terminology Criteria for Adverse Events v3.0 (CTCAE). 2006. [Accessed 2003]
36. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005; 353(5):487–497. 353/5/487 [pii]. DOI: 10.1056/NEJMr050100 [PubMed: 16079372]
37. Haynes RB, McDonald HP, Garg AX. Helping patients follow prescribed treatment: clinical applications. *JAMA*. 2002; 288(22):2880–2883. jsr20017 [pii]. [PubMed: 12472330]
38. Waterhouse DM, Calzone KA, Mele C, Brenner DE. Adherence to oral tamoxifen: a comparison of patient self-report, pill counts, and microelectronic monitoring. *J Clin Oncol*. 1993; 11(6):1189–1197. [PubMed: 8501505]
39. Joseph EK, Chen X, Bogen O, Levine JD. Oxaliplatin acts on IB4-positive nociceptors to induce an oxidative stress-dependent acute painful peripheral neuropathy. *J Pain*. 2008; 9(5):463–472. DOI: 10.1016/j.jpain.2008.01.335 [PubMed: 18359667]

Figure 1.
Flow of Participants through the Study

Table 1

Baseline Characteristics of Patients in the Study Groups

	ALA (n = 122)	Placebo (n = 121)
Mean age (years) ± SD	55±11	57±12
	n (%)	n (%)
Male	66 (54)	63 (52)
Plan to receive adjuvant chemotherapy	47 (39)	47 (39)
Prior platinum exposure		
None	112 (93)	112 (95)
Cisplatin <399 mg/m ² or Oxaliplatin <750 mg/m ²	3 (2)	2 (2)
Cisplatin >400 mg/m ² or Oxaliplatin >750 mg/m ²	6 (5)	4 (3)
Prior surgery (yes)	91 (82)	80 (78)
Prior radiation (yes)	21 (19)	22 (20)
Tumor location		
Gastrointestinal	87 (74)	89 (77)
Lung	14 (12)	13 (11)
Genitourinary	7 (6)	7 (6)
Other	9 (8)	6 (5)

Abbreviations: ALA, Alpha-lipoic acid; SD, Standard deviation.

^aThere were no statistically significant differences between the two groups for all items (All $P>.05$)

Table 2

Comparison of Patient-reported Neurological Symptoms, Pain Scores, and Results from Functional Tests at Baseline and at 24±4 Weeks between the ALA and Placebo Groups

	Mean ± Standard Deviation			
	ALA-Baseline	ALA-24±4 weeks	Placebo-Baseline	Placebo-24±4 weeks
Platinum received				
Cisplatin, mg/m²		291±127 (n = 4)		
Oxaliplatin, mg/m²		798±464 (n =29)		1019±572 (n = 31)
FACT/GOG-NTX score ^a	3.7±5.1	9.6±7.6	3.0±4.1	9.7±8.1
BPI score ^b				
Pain worst	1.8±3.1	2.4±3.4	2.2±3.0	1.9±2.9
Pain average	1.7±2.3	1.9±2.4	1.8±1.7	1.3±1.6
Pain interference with:				
General activity	1.5±2.8	1.8±2.4	1.5±2.1	1.4±2.2
Mood	1.2±2.3	1.5±2.4	1.8±2.4	1.3±2.2
Walking ability	1.3±2.7	1.9±2.7	1.4±2.1	1.6±2.4
Normal work	1.6±2.8	2.1±2.7	2.4±3.2	1.7±2.7
Relations with others	0.5±1.2	1.0±1.7	1.6±2.6	1.2±2.4
Sleep	1.8±2.8	1.6±2.5	2.5±2.9	1.5±2.7
Enjoyment of life	1.0±2.1	1.6±2.6	2.7±3.4	1.6±2.8
Functional Tests ^c				
Six-hole button test	28±16	32±19	33±33	29±15
50-foot walk test	17±14	17±11	20±27	15±6
Coins test	6±4	6±2	6±3	6±2

Abbreviations: ALA, Alpha-Lipoic Acid; FACT/GOG-Ntx, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity Scale, Version 4; BPI, Brief Pain Inventory.

^aThere were no statistically significant differences between the two groups ($P > .05$). A difference of 4 points on the total FACT/GOG-Ntx score indicates a minimal clinically important change.

^bRatings in the past 24 hours on a scale of 0 (no pain) to 10 (pain as bad as you can imagine); Difference between groups for pain scores, All $P > .05$.

^cTime in seconds; Difference between groups on functional tests, All $P > .05$.

Table 3

Number of Patients with Adverse Events According to National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE Version 3.0) at 24±4 Weeks in the Study Groups

Adverse Events	ALA (n = 34)	Placebo (n = 36)
Anemia		
* Grade 1/2	16	10
Grade 3/4	0	2
Neutropenia		
Grade 1/2	11	7
Grade 3/4	6	2
Thrombocytopenia		
Grade 1/2	12	12
Grade 3/4	2	0
Nausea		
Grade 1/2	17	16
Grade 3/4	0	2
Vomiting		
Grade 1/2	3	5
Grade 3/4	0	0
Diarrhea		
Grade 1/2	14	11
Grade 3/4	1	1
Stomatitis		
Grade 1/2	0	0
Grade 3/4	0	1
DVT/PE	1	2
Neurotoxicity		
Grade 1/2	27	27
Grade 3/4	3	5

Abbreviations: ALA, Alpha-lipoic acid; DVT/PE, Deep venous thrombosis/pulmonary embolism.

* Grade indicates severity of the adverse event (AE) (Grade 1= Mild AE; Grade 5=Death related to AE). There were no statistically significant differences between the two groups (All $P > .05$)