Amitriptyline in the Prevention of Chemotherapy-induced Neuropathic Symptoms

ANNA-LIISA KAUTIO[1,2], MAIJA HAANPÄÄ[3], ARTO LEMINEN[4], EIJA KALSO[3,5], HANNU KAUTIAINEN[6,7] and TIINA SAARTO[1]

[1]*Department of Oncology,* [3]*Pain Clinic, Department of Anaesthesiology and Intensive Care, and* [4]*Department of Obstetrics and Gynaecology, Helsinki University Central Hospital, FIN-00029 HUS, Helsinki;* [2]*Department of Oncology, Tampere University Hospital, FIN-33521 Tampere;* [5]*Institute of Clinical Medicine, University of Helsinki;* [6]*Central Finland Central Hospital, Unit of Family Practice, Jyväskylä;* [7]*ORTON, Rehabilitation Unit, Helsinki, Finland*

Abstract. *Background: Neuropathy is a common adverse effect of chemotherapy. The tricyclic antidepressant, amitriptyline, is a gold standard in the treatment of neuropathic pain. This double-blind, randomized placebo-controlled trial assessed the efficacy of amitriptyline to prevent chemotherapy-induced neuropathic symptoms. Patients and Methods: Patients without previous neuropathy, who started chemotherapy with vinca alcaloids, platina derivatives or taxanes, were randomized to receive amitriptyline (target dose, 100 mg daily) or placebo for the duration of their chemotherapy. Chemotherapy-induced neuropathic symptoms were evaluated with a patient diary and after every third chemotherapy cycle with clinical examination. The diary data were transformed to a neuropathy score. A total of 114 patients fulfilling the inclusion criteria were randomly assigned to the treatment or control arm. Results: There was no difference in the appearance of chemotherapy-induced neuropathic symptoms between the groups. In general, the intensity of neuropathic symptoms was mild. Conclusion: Amitriptyline does not prevent chemotherapy-induced neuropathy.*

Chemotherapy is one of the most effective therapies of cancer, however, it can cause many adverse effects. Most of these adverse effects are reversible, but some, such as neurotoxicity can be permanent. The most neurotoxic chemotherapeutic agents are vinca alkaloids, cisplatin and its derivatives, and taxanes (1, 2). The incidence of neurotoxicity varies depending on the cumulative dose and it is higher when neurotoxic agents are used in combination (3). Very little is known about the mechanism of chemotherapy-induced neuropathy. The most typical clinical presentation of peripheral neuropathy is symmetric sensory and motor impairment, which causes paraesthesia, numbness, pain, muscle weakness and peripheral motor dysfunction.

Chemotherapy-induced neuropathy is usually reversible if chemotherapy is discontinued or the dose is reduced, but recovery may take from months to years. However, chemotherapy-induced neurotoxicity may be the dose-limiting adverse effect and thus indirectly influence survival.

There is no consistent evidence from double-blind randomized controlled trials (RCTs) of the efficacy of any drug to prevent chemotherapy-induced peripheral neuropathy (4-6).

Amitriptyline is a gold standard in the treatment of neuropathic pain (7). Its efficacy in preventing chronic neuropathic pain has been studied in one RCT of post-herpetic neuralgia (8). The aim of the current study was to show whether amitriptyline has efficacy in preventing chemotherapy-induced neuropathic symptoms (CINS) compared with placebo.

Patients and Methods

This double-blind, randomized, placebo-controlled parallel group study was performed between February 2003 and May 2006 in cancer patients treated at the Departments of Oncology and Gynaecology of the Helsinki University Central Hospital. Cancer patients aged 20-75 years who were starting their first neurotoxic chemotherapy with vinca alcaloids, platinum derivatives or taxanes were included. Patients were excluded if they had other possible causes of neuropathy (*i.e.* diabetes, thyroid dysfunction, B_{12} vitamin deficiency or alcohol abuse), concomitant medication for neuropathic

Correspondence to: Tiina Saarto, MD, Ph.D., Helsinki University Central Hospital, Department of Oncology, P.O.Box 180, 00029 HUS, Finland. Tel:+358 504270256, +358 405717538, Fax:+358 947174247, e-mail: tiina.saarto@hus.fi

Key Words: Amitriptyline, antidepressants, chemotherapy-induced neuropathy, neoplasms, neurotoxicity, prevention.

symptoms or contraindications for amitriptyline. At the screening visit, laboratory tests were taken to exclude other causes of neuropathy or contraindications to amitriptyline (serum creatinine, transaminases, glucose, free T4, thyroid-stimulating hormone (TSH), vitamin B_{12} and electrocardiogram). A blood sample for the measurement of amitriptyline and nortriptyline concentrations was taken at week 8. The protocol was approved by the Ethics Committee of the Helsinki University Central Hospital and written informed consent was obtained from all participants.

Randomization and dosing of study medication. A computer-generated randomization schedule was used to allocate the patients to either the amitriptyline or the placebo group. The randomization was stratified according to the chemotherapy group and the diagnosis. The hospital pharmacy performed the randomization and provided identical capsules of either placebo or amitriptyline 25 mg. The treatment was started with one 25 mg drug capsule or placebo per day. Dose elevation was 25 mg per week up to the target maximum dose of 100 mg/day if tolerated. In the case of intolerable adverse effects, dose escalation was terminated and the dose was reduced by 25 mg, if necessary. The treatment was continued until the end of the neurotoxic chemotherapy. Both patients and clinicians were blinded during the whole treatment period.

Follow-up visits. The baseline visit was before commencement of chemotherapy, or if that was not possible, with the shortest possible delay after the first dose of chemotherapy. The follow-up visits were performed every two months. The patients were asked about their neuropathic symptoms and side-effects of the study medication on the visits. Additionally, a neurological examination was performed. The severity of sensory and motor neuropathy was scored according to the National Cancer Institute Common Toxicity Criteria NCI-CTC (9). Quality of life (QoL) was assessed with the EORTC-C30 quality of life questionnaire (10) for cancer patients on the visits. The patients graded neuropathic symptoms by visual analogue scale (VAS) in a diary twice a week during the whole study period to report the intensity of their neuropathic symptoms. During the visits they assessed sensory and motor symptoms, and side-effects of the study medication on a four-point verbal scale (none, mild, moderate, severe). The primary end point was the appearance or progression of neuropathic symptoms based on the diary data. The secondary end-points were the severity of sensory or motor neuropathy assessed with the NCI-CTC score and QoL.

Statistical analyses. Analyses were performed on the intent-to-treat (ITT) population, defined as all randomized patients who returned their diaries at the follow-up visits. The last-observation-carried-forward (LOCF) approach was used for missing data. Statistical comparison between groups was made by using either *t*-test or Chi-square test. The appearance and progression of neuropathic symptoms was assessed with neuropathy score: the sum of the intensity of the different symptoms (no=0, mild=1, moderate=2, severe=3) divided by ten, the score having a theoretical range from 0 (no symptoms) to 3 (all ten symptoms graded as severe). The area under the curve (AUC) for neuropathy score was calculated with the trapezoidal method.

Permutation test was used to test differences between groups for side effects and bootstrap-based multiplicity adjustment was applied to correct levels of significance for multiple testing. Quality of life data were analyzed using generalizing estimating equations (GEE) models with the exchangeable correlation structure. Correlation coefficients were calculated by the Spearman method.

The planned study size was 250 patients. This study was designed to have 125 patients in each arm to provide 80% power (α error, 0.05) to detect a 20% change in symptom score, which was regarded as a clinically significant change. According to the original protocol, interim analyses were carried out when 120 patients had been randomized. Because of the negative results in the interim analyses, recruitment was cancelled after 123 patients had been randomized.

Table I. *Pretreatment patient characteristics*.

	All patients	Amitriptyline group	Placebo group
Number	114	58	56
Age (years, mean, range)	56 (25-75)	55 (25-74)	57 (26-75)
Gender			
Male	32 (28%)	19 (33%)	13 (23%)
Female	82 (72%)	39 (67%)	43 (77%)
Diagnosis			
Ovarian cancer	50 (44%)	23 (40%)	27 (48%)
Lymphoma	18 (16%)	9 (16%)	9 (16%)
Colorectal cancer	15 (13%)	9 (16%)	6 (11%)
Breast cancer	8 (7%)	5 (9%)	3 (5%)
Uterine cancer	7 (6%)	4 (7%)	3 (5%)
Chemotherapy			
Vinca alkaloids	24 (21%)	12 (25%)	12 (21%)
Platinum derivatives	26 (23%)	16 (28%)	10 (18%)
Taxanes	7 (6%)	4 (7%)	3 (5%)
Combination	57 (50%)	26 (45%)	31 (55%)
Current chemotherapy			
Adjuvant	50 (44%)	24 (41%)	26 (46%)
1st-line chemotherapy	54 (47%)	26 (45%)	28 (50%)
2nd-line chemotherapy.	10 (9%)	8 (14%)	2 (4%)

Results

After randomization of 123 patients, 5 patients were excluded from the study because of diseases confusing the assessment of neuropathic symptoms. An additional 4 patients were excluded because of multiple lines of chemotherapy. Fifteen patients did not return the diaries (4 on amitriptyline and 11 on placebo). Thus, data of 99 patients (54 on amitriptyline and 45 on placebo) were available in the final analyses. Pre-treatment characteristics were well balanced between the groups (Table I).

The median follow-up time was 21 weeks for the amitriptyline group and 19 weeks for the placebo group. Eight patients (3 on amitriptyline and 5 on placebo) withdrew their consent after 1 to 47 weeks (median, 7 weeks): two patients on amitriptyline because of side-effects (dry mouth), one patient on amitriptyline because she suspected she was receiving placebo and one patient on placebo because of fear of interactions of the study drug. Four patients did not report the reason for their consent withdrawal.

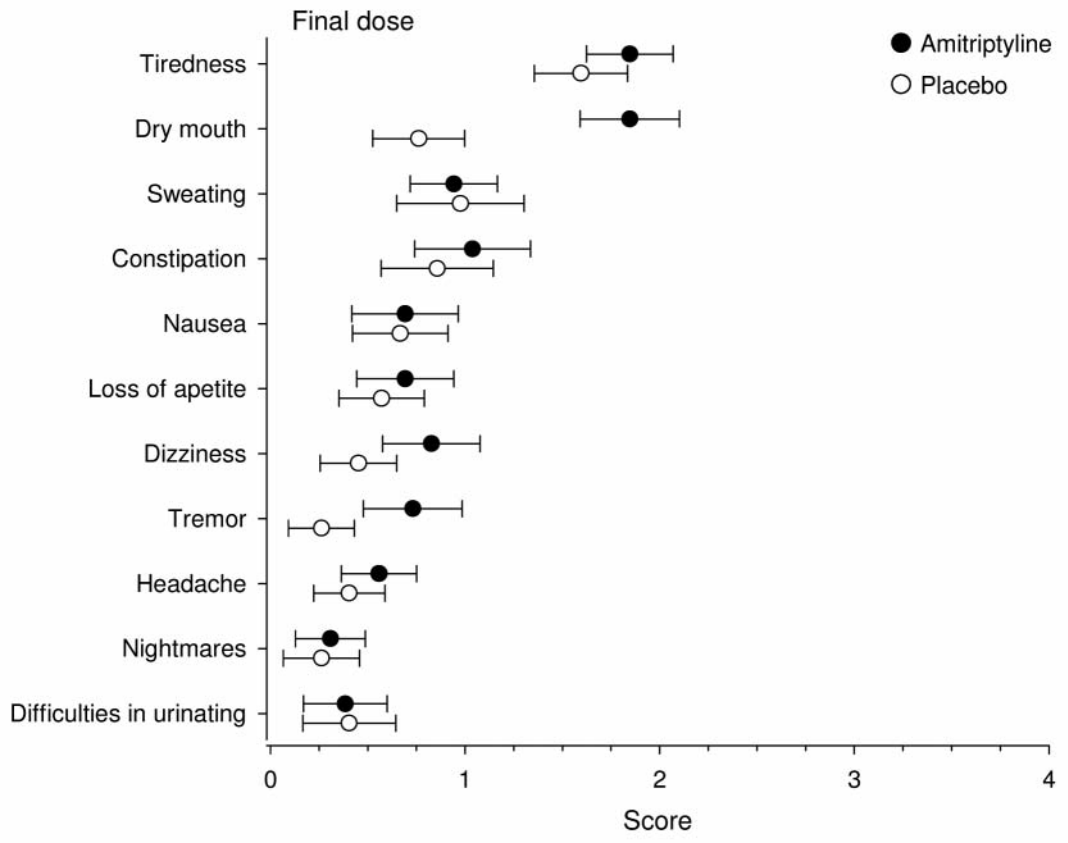

Figure 1. *Side-effects of the study medication with the stable dose.*

Chemotherapy was given as planned in 74 patients (74%), the dose was reduced or treatment was delayed in 15 patients (15%) and terminated in 4 (4%) due to reasons other than neuropathy. In 7 patients (7%) neuropathy caused dose reduction (3 on placebo and 1 on amitriptyline) or treatment termination (1 on placebo and 2 on amitriptyline).

Amitriptyline dose and side-effects. In general, amitriptyline 100 mg per day was well tolerated. Forty out of 54 patients were on the target dose. The daily dose was reduced to 25 mg in one patient and to 50 mg in 13 patients. The most common reason for dose reduction was tiredness (n=11). Dry mouth, visual disturbances and constipation caused dose reduction in one patient each. The concentration of amitriptyline ranged from below 100 nmol/l to 827 nmol/l (median 206 nmol/l), of nortriptyline from below 100 nmol/l to 433 nmol/l (median 124 nmol/l) and the total combined concentration of amitriptyline and nortriptyline from below 100 nmol/l to 1068 nmol/l (median 317 nmol/l). In the placebo group the dose was reduced to 50 mg in 4 patients out of 45 because of palpitation, dizziness, dry mouth and tiredness in one patient each. The severity of the side-effects in the amitriptyline and placebo groups is presented at the stable dose in Figure 1. Dry mouth was more severe in the amitriptyline group both at the titration phase ($p<0.001$) and stable dose phase ($p<0.001$). Tremor was more severe in the amitriptyline group at the stable dose phase ($p=0.034$). There was no significant association between the severity of the side-effects and the drug concentration.

Appearance of neuropathic symptoms. Results of the neuropathy score are presented in Figure 2. The intensity of neuropathy was in general mild. There was no significant difference between the amitriptyline and placebo groups.

Severity of sensory and motor neuropathy assessed with NCI-CTC score. Results of NCI-CTC scoring are presented in Table II. In line with results of the neuropathic score, there was no significant difference in NCI-CTC scoring between the amitriptyline and placebo groups. After 3, 6 and 9 cycles, sensory neuropathy was seen in 59 out of 97 patients (61%), 44/79 (57%) and 31/41 (76%), respectively, and motor neuropathy in 25/97 (26%), 29/80 (36 %) and 9/41 (22%). The intensity of neuropathy was mild, grade 1, in the majority of the cases.

Table II. *NCI-CTC grading on visits 1-4 (number of patients).*

Neuropathy	Group	Baseline (visit 1) Grade				Visit 2 Grade				Visit 3 Grade				Visit 4 Grade			
		0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3
Sensory	AMI	51	3	0	0	23	27	2	2	19	17	6	1	7	6	5	3
	PL	41	4	0	0	15	27	1	0	16	11	8	1	3	10	3	4
	Sum	92	7	0	0	38	54	3	2	35	28	14	2	10	16	8	7
Motor	AMI	47	4	3	0	42	7	3	2	30	12	2	0	18	2	0	1
	PL	42	2	1	0	30	10	3	0	21	13	2	0	14	5	1	0
	Sum	89	6	4	0	72	17	6	2	51	25	4	0	32	7	1	1

Visit 2: median time 9 weeks; visit 3: median time 18 weeks; visit 4: median time 27 weeks. AMI, amitriptyline group, PL, placebo group.

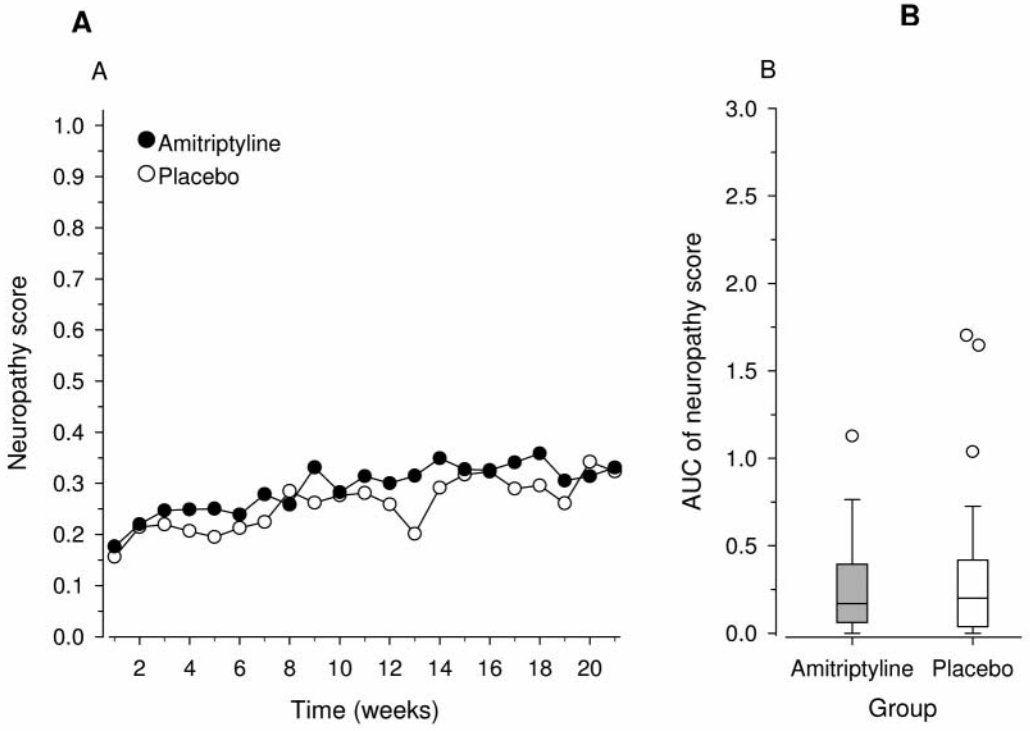

Figure 2. *Neuropathy score in the amitriptyline and placebo groups (A) and area under the curve (AUC) of the neuropathy score (B).*

Quality of life. There was no significant difference in the EORTC-C30 results between the amitriptyline and placebo groups at the follow-up visits.

Discussion

To our knowledge, this study is the first prospective RCT of the efficacy of amitriptyline in prevention of CINS. The present study failed to demonstrate any effect of amitriptyline in prevention of CINS.

The treatment and prevention of chemotherapy-induced neuropathy has been challenging. Our finding is in line with previous studies of prevention of chemotherapy-induced neuropathy. Gabapentin, another first-line drug for neuropathic pain, was studied in 81 patients who started treatment with oxaliplatin (11). No difference was found in the severity or duration of neurotoxicity between the groups. No improvement in the ability to deliver the chemotherapy was found. The daily dose of gabapentin ranged between 300-1800 mg. However, the dose was lower than 900 mg daily in 61% of the patients, which might, at least partly, explain the negative results. Likewise, carbamazepine has failed to show any efficacy over placebo in preventing CINS (12). In the present study, the dose of amitriptyline was rather high; most

patients took 100 mg amitriptyline daily. In studies on painful neuropathy, the dose of amitriptyline has been increased to 75-150 mg, 100 mg being the most common daily dose (6), as in the present study. However, amitriptyline has been shown to prevent post-herpetic neuralgia even when used at as low a dose as 25 mg daily (8). The results of some other drugs tested in the prevention of chemotherapy induced neuropathy such as amifostine, diethyldithiocarbamate (DDTC), glutathione, leukaemia inhibitory factor, *N*-acetylcysteine, nimodipine, hexapeptide analogue Or-2766, and vitamin E have been inconsistent (5). As yet, no neuroprotective drugs are recommended for routine use to prevent CINS in clinical practice so far (13). Both tricyclic antidepressants and anticonvulsants, which are the first-line and most extensively studied drugs for painful diabetic neuropathy and post-herpetic neuralgia (7, 14) have failed to relieve CINS in patients with established symptoms in RCTs (15-18).

In addition to CINS, symptoms of HIV-induced neuropathy seem to be refractory to the standard pharmacotherapy of neuropathic pain (7). Two large placebo-controlled studies (395 patients) failed to demonstrate any efficacy of tricyclic antidepressants on HIV-related neuropathy (19, 20). Thus, mechanisms leading to neuropathic symptoms may be, at least partly, different in neuropathies from various aetiologies. An other plausible explanation could be the different symptom profile. The most prominent symptoms of chemotherapy-induced neuropathy are paraesthesia, dysaesthesia and numbness, which may be less responsive to pharmacotherapy than neuropathic pain dominating in other neuropathies.

Even though the results of our study are in line with the previous literature, there are some limitations in the present study. In general, neuropathy was only mild. One plausible explanation for that could be the age limit of 75 years and exclusion of all patients with other possible risk factors of neuropathy such as diabetes, vitamin B_{12} deficiency, excessive alcohol consumption and hypothyroidism, which might enhance the severity of the neuropathic symptoms. In addition, the majority of the patients only had a few cycles of neurotoxic chemotherapy. In general, measuring neurotoxicity of chemotherapy is difficult as paraestesiae are the leading symptom instead of pain. Sensory paraesthesiae seldom disturb patients very significantly and the subjective inconvenience is often rated as mild. We assume that our method to assess CINS is a sensitive one, as patients rated their symptoms by themselves in a diary twice a week without any interference. Hence, even a slight effect of the study drug should have been noticed thus we are convinced of the negative result of our study.

In summary, the negative finding of amitriptyline in the prevention of CINS is in line with the previous studies of prevention and treatment of CINS. Differences in the mechanisms leading to neuropathic symptoms in various conditions may explain why chemotherapy-induced neuropathy is difficult to prevent and relieve once established. A better understanding of the pathophysiological mechanisms is crucial in the search for new agents for both prevention and treatment of CINS.

Acknowledgements

The study received financial support from a grant by the Finnish Cancer Society and research funds of the Helsinki University Central Hospital (T10200066).

References

1 Quasthoff S and Hartung HP: Chemotherapy-induced peripheral neuropathy. J Neurol *249*: 9-17, 2002.
2 Ocean AJ and Vahdat LT: Chemotherapy-induced peripheral neuropathy: pathogenesis and emerging therapies. Support Care Cancer *12*: 619-625, 2004.
3 Winton T, Livingston R, Johnson D, Rigas J, Johnston M, Butts C, Cormier Y, Goss G, Inculet R, Vallieres E, Fry W, Bethune D, Ayoub J, Ding K, Seymour L, Graham B, Tsao MS, Gandara D, Kesler K, Demmy T and Shepherd F: Vinorelbine plus cisplatin *vs*. observation in resected non-small cell lung cancer. N Engl J Med *352*: 2589-2597, 2005.
4 Albers J, Chaudhry V, Cavaletti G and Donehower R: Interventions for preventing neuropathy caused by cisplatin and related compounds. Cochrane Database Syst Rev *24(1)*: CD005228, 2007.
5 Walker M and Ni O: Neuroprotection during chemotherapy. A systematic review. Am J Clin Oncol *30*: 82-92, 2007.
6 Wolf S, Barton D, Kottschade L, Grothey A and Loprinzi C: Chemotherapy-induced peripheral neuropathy: Prevention and treatment strategies. Eur J Cancer *44*: 1507-1515, 2008.
7 Saarto T and Wiffen PJ: Antidepressants for neuropathic pain. Cochrane Database Syst Rev *20(3)*: CD005454, 2005.
8 Bowsher D: The effect of pre-emptive treatment of postherpetic neuralgia with amitriptyline: a randomized, double-blind, placebo-controlled trial. J Pain Symptom Manage *13*: 327-331, 1997.
9 Postma TJ and Heimans JJ: Grading chemotherapy-induced peripheral neuropathy. Ann Oncol *11*: 509-13, 2000.
10 Ford ME. Havstad SL and Kart CS: Assessing the reliability of the EORTC QLQ-C30 in a sample of older African-American and Caucasian adults. Quality of Life Res *10(6)*: 533-41, 2001.
11 Mitchell PL, Goldstein D, Michael M, Beale P, Friedlander M, Zalcberg J, White S, Thomson JA and Clarke S: Addition of gabapentin to a modified FOLFOX regimen does not reduce oxaliplatin-induced neurotoxicity. Clin Colorectal Cancer *6*: 146-151, 2006.
12 von Delius S, Eckel F, Wagenpfeil S , Mayr M, Stock K, Kullmann F, Obermeier F, Erdmann J, Schmelz R, Quasthoff S, Adelsberger H, Bredenkamp R, Schmid RM and Lersch C: Carbamazepine for prevention of oxaliplatin-related neurotoxicity in patients with advanced colorectal cancer: final results of a randomised, controlled, multicenter phase II study. Invest New Drugs *25*: 173-80, 2007.
13 Hensley ML, Hagerty KL, Kewalramani T, Green DM, Meropol NJ, Wasserman TH, Cohen GI, Emami B, Gradishar WJ, Mitchell RB, Thigpen JT, Trotti A 3rd, von Hoff D and Schuchter LM: American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. J Clin Oncol *27(1)*: 127-45, 2009.

14 Attal N, Cruccu G, Haanpää M, Hansson P, Jensen TS, Nurmikko T, Sampaio C, Sindrup S, Wiffen P and EFNS Task Force: EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol *13*: 1153-69, 2006.

15 Kautio A, Haanpää M, Saarto T and Kalso E: Amitriptylin in the treatment of chemotherapy incuded neuropathic symptoms. J Pain Symptom Manage *35*: 31-39, 2008.

16 Hammack JE, Michalak JC, Loprinzi CL, Sloan JA, Novotny PJ, Soori GS, Tirona MT, Row-land KM Jr, Stella PJ and Johnson JA: Phase III evaluation of nortriptyline for alleviation of symptoms of *cis*-platinum-induced peripheral neuropathy. Pain *98*: 195-203, 2002.

17 Rao RD, Michalak JC, Sloan JA, Loprinzi CL, Soori GS, Nikcevich DA, Warner DO, Novotny P, Kutteh LA and Wong GY; North Central Cancer Treatment Group: Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy. Cancer *110*: 21110-2118, 2007.

18 Rao RD, Flynn PJ, Sloan JA, Wong GY, Novotny P, Johnson DB, Gross HM, Renno SI, Nashawaty M and Loprinzi CL: Efficay of lamotrigine in the management of chemotherapy-induced peripheral neuropathy. Cancer *112*: 2802-2808, 2008.

19 Kieburtz K, Simpson D, Yiannoutsos C Max MB, Hall CD, Ellis RJ, Marra CM, McKendall R, Singer E, Dal Pan GJ, Clifford DB, Tucker T and Cohen B: A randomized trial of amitriptyline and mexiletine for painful neuropathy in HIV infection. AIDS Clinical Trial Group 242 Protocol Team. Neurology *51*: 1682-1688, 1998.

20 Shlay JC, Chaloner K, Max MB, Flaws B, Reichelderfer P, Wentworth D, Hillman S, Brizz B and Cohn DL: Acupuncture and amitriptyline for pain due to HIV-related peripheral neuropathy: a randomized controlled trial. Terry Beirn Community Programs for Clinical Research on AIDS. JAMA *280*: 1590-1595, 1998.

Received February 23, 2009
Revised April 10, 2009
Accepted May 4, 2009