Neuroprotective Effect of Reduced Glutathione on Oxaliplatin-Based Chemotherapy in Advanced Colorectal Cancer: A Randomized, Double-Blind, Placebo-Controlled Trial

By Stefano Cascinu, Vincenzo Catalano, Luigi Cordella, Roberto Labianca, Paolo Giordani, Anna Maria Baldelli, Giordano D. Beretta, Emilio Ubiali, and Giuseppina Catalano

Purpose: **We performed a randomized, double-blind, placebo-controlled trial to assess the efficacy of glutathione (GSH) in the prevention of oxaliplatin-induced neurotoxicity.**

Patients and Methods: **Fifty-two patients treated with a bimonthly oxaliplatin-based regimen were randomized to receive GSH (1,500 mg/m^2 over a 15-minute infusion period before oxaliplatin) or normal saline solution. Clinical neurologic evaluation and electrophysiologic investigations were performed at baseline and after four (oxaliplatin dose, 400 mg/m^2), eight (oxaliplatin dose, 800 mg/m^2), and 12 (oxaliplatin dose, 1,200 mg/m^2) cycles of treatment.**

Results: **At the fourth cycle, seven patients showed clinically evident neuropathy in the GSH arm, whereas 11 patients in the placebo arm did. After the eighth cycle, nine of 21 assessable patients in the GSH arm suffered from neurotoxicity compared with 15 of 19 in the placebo arm. With regard to grade 2 to 4 National Cancer Institute common toxicity criteria, 11 patients experienced neuropathy in the placebo arm compared with only two patients in the GSH arm (P = .003). After 12 cycles, grade 2 to 4 neurotoxicity was observed in three patients in the GSH arm and in eight patients in the placebo arm (P = .004). The neurophysiologic investigations (sural sensory nerve conduction) showed a statistically significant reduction of the values in the placebo arm but not in the GSH arm. The response rate was 26.9% in the GSH arm and 23.1% in the placebo arm, showing no reduction in activity of oxaliplatin.**

Conclusion: **This study provides evidence that GSH is a promising drug for the prevention of oxaliplatin-induced neuropathy, and that it does not reduce the clinical activity of oxaliplatin.**

J Clin Oncol 20:3478-3483.

OXALIPLATIN, A new cytotoxic agent from the diaminocyclohexane platinum family, has a spectrum of activity and toxicity different from that of cisplatin and carboplatin, and it has demonstrated a lack of cross-resistance with other platinum compounds.[1] The role of oxaliplatin in colorectal cancer has been well established. In combination with fluorouracil (5FU), it represents an effective first-line therapy, and its addition to 5FU regimens also represents an active salvage therapy.[2-5] Furthermore, a combination of oxaliplatin and 5FU has proven beneficial in enabling surgical removal of hepatic resections in patients with previously unresectable liver metastases.[6] The coming years will probably expand the therapeutic potential of oxaliplatin in several other cancers, such as breast, ovarian, non–small-cell lung, prostate, and stomach cancers.[7-9]

The most common toxicity resulting from oxaliplatin therapy is neurotoxicity. There are two distinct types of neurotoxicity. There are cold-sensitive paresthesias, which are unique among the platinum complexes studied to date. They occur at low total cumulative doses, are always reversible, and do not require discontinuation of therapy. However, there is also a peripheral sensory neuropathy with symptoms similar to those seen with cisplatin. This form of neurotoxicity is the most important for its clinical implications. The risk of developing severe disturbance of neurologic function is related to the cumulative dose, generally becoming a clinical problem when the cumulative dose approximates 800 mg/m^2. It is reversible, but it may last for several months and can even require discontinuation of treatment.[10] The mechanism of neurotoxicity induced by platinum drugs has been proposed to involve the accumulation of platinum within the peripheral nervous system, especially in the dorsal root ganglia.[11] However, unlike the case with cisplatin, for oxaliplatin it seems that the greater retention of platinum is due to a slower clearance rather than a greater accumulation of oxaliplatin.[12] These data suggest that a strategy optimal for reducing the neurotoxicity associated with oxaliplatin may be the use of agents such as glutathione

From the Department of Medical Oncology, Azienda Ospedaliera-Universitaria di Parma, Parma; Division of Medical Oncology, Division of Neurology, Azienda Ospedaliera "Ospedale S. Salvatore," Pesaro; and Division of Medical Oncology, Division of Neurology, Ospedali Riuniti di Bergamo, Bergamo, Italy.

Submitted July 16, 2001; accepted February 20, 2002.

This article was published ahead of print at www.jco.org.

Address reprint requests to Stefano Cascinu, MD, Department of Medical Oncology, Azienda Ospedaliera-Universitaria di Parma, via Gramsci 14, 43100 Parma, Italy; email: cascinu@yahoo.com.

0732-183X/02/2016-3478/$20.00

DOI: 10.1200/JCO.2002.07.061

(GSH), which is able to prevent the initial accumulation of platinum adducts in the dorsal root ganglia.[13]

Clinical trials conducted to assess the neuroprotective efficacy of GSH in patients treated with cisplatin reported a lower incidence of neurotoxicity compared with placebo, without any negative interference in oncolytic activity.[14-17] On the basis of these premises, to assess the efficacy of GSH in preventing oxaliplatin-induced neuropathy, a double-blind, placebo-controlled trial was performed in patients with advanced colorectal cancer. All were treated with the same oxaliplatin-based regimen and were given either GSH or placebo.

PATIENTS AND METHODS

Patients with a histologically verified advanced colorectal carcinoma were eligible for the study. Other eligibility criteria included Eastern Cooperative Oncology Group performance status of 0 to 2 and normal bone marrow function (leukocyte count $>$ 4,000/μL, platelet count $>$ 100,000/μL), liver function (serum bilirubin $<$ 1.5 mg/dL), renal function (creatinine $<$ 1.5 mg/dL), and cardiac function (stable heart rhythm, no active angina, and no clinical evidence of congestive heart failure). Previous chemotherapy with 5FU, adjuvant or not, was allowed. Patients were excluded if they had established clinical neuropathy, diabetes mellitus, alcoholic disease, other neurologic disease, or brain involvement. Patients who received vitamin B_1, B_6, or B_{12} supplements or who followed other vitamin diets were also excluded.

Informed consent was obtained from all participants after the nature of the study had been fully explained. The protocol was approved by the institutional review board.

The chemotherapeutic regimen consisted of oxaliplatin 100 mg/m^2 on day 1, given as a 2-hour infusion in 250 mL of dextrose 5%, concurrent with 6-*S*-stereoisomer of leucovorin 250 mg/m^2 as a 2-hour infusion followed by a 24-hour infusion of 5FU 1,500 mg/m^2/d for 2 consecutive days. Therapy was repeated every 2 weeks. GSH was given at a dose of 1,500 mg/m^2 in 100 mL of normal saline over a 15-minute period immediately before each oxaliplatin administration, while normal saline solution was administered to placebo-randomized patients. Routine antiemetic prophylaxis with dexamethasone 8 mg and 5-hydroxytryptamine-3 receptor antagonist was used for both treatment arms.

Response was evaluated after four cycles of therapy according to the standard World Health Organization criteria.[18] Patients who showed responsive or stable disease received four further cycles of chemotherapy. Toxicity was assessed after every 2-week cycle using the National Cancer Institute's (NCI) common toxicity criteria (CTC).[19] Chemotherapy was delayed until recovery if the neutrophil count decreased to less than 1,500/μL or the platelet count decreased to less than 100,000/μL. 5FU and oxaliplatin doses were reduced when NCI CTC grade 3 diarrhea, dermatitis, or stomatitis occurred. In the case of NCI grade 2 sensory neuropathy, the oxaliplatin dose was reduced to 75% of the previous dose; in the case of NCI grade 3 sensory neuropathy, oxaliplatin was omitted from the regimen until recovery. Patients who experienced NCI CTC grade 4 toxicity, apart from alopecia, were withdrawn from the study.

A complete standardized neurologic examination, including an evaluation of strength and deep tendon reflexes, was performed by the neurologists (L.C. and E.U.) involved in the study. Special care was devoted to the presence of symptoms of peripheral nervous system involvement and to the assessment of position and vibratory sensations. The degree of neurotoxicity was expressed according to the NCI CTC.[19] The neurophysiologic evaluation was based on the bilateral determination with surface electrodes of the sensory nerve conduction in the sural nerves. All neurophysiologic examinations were performed under constant conditions of skin temperature (34°C). The same examiners, blinded with respect to the group to which each patient belonged, always performed the neurologic and electrophysiologic evaluations. All the patients were examined before entry onto the study and after four, eight, and 12 cycles of chemotherapy within 2 weeks of the end of treatment.

The study was defined as a double-blind, randomized, phase III trial in which at least 25 patients were assigned to each of the two treatment arms. The sample size was determined to detect a 40% difference in the occurrence of grade 2 to 4 (NCI CTC) neurotoxicity between the two treatment arms, with alpha and beta errors of 0.05 and 0.1, respectively. Grade 2 to 4 toxicities were chosen because, in our experience, these degrees seem to impair the quality of life of patients.

Using cards from a computer-generated list in sealed envelopes, randomization was performed by a person not involved in the care or evaluation of the patients. The personnel who evaluated the efficacy and tolerability of the treatment did not know the drug administered because administration was performed by other staff members.

Analysis of variance with repeated measures and a supplementary two-sided paired *t* test were used to compare the neurophysiologic results of the two groups after four cycles (oxaliplatin cumulative dose, 400 mg/m^2) and eight cycles (oxaliplatin cumulative dose, 800 mg/m^2) of chemotherapy. A χ^2 test with Yates' correction and the Wilcoxon test were used to assess the difference in terms of clinical neurotoxicity between the two groups, both as overall incidence and as a score.[20] This score was derived from the sum of the degree of the worst neurologic toxicity, according to the NCI scale, for each patient divided by the number of assessable patients for each dose step (400 mg/m^2, 800 mg/m^2, and 1,200 mg/m^2).

RESULTS

Fifty-two patients were entered onto the study: 26 were assigned to the placebo arm and 26 to the GSH arm. The patients' characteristics are listed in Table 1. Twelve patients in the placebo arm and 11 in the GSH arm received a 5FU/leucovorin regimen as adjuvant treatment. Seventeen patients in the placebo arm and 19 in the GSH arm were treated with 5FU and leucovorin as first-line treatment at the time of relapse. At baseline, the distribution of the other clinicopathologic variables was comparable between the two groups, except for a major incidence of women in the GSH arm ($P = .09$). No patient was excluded from the study, and an intention-to-treat analysis was performed.

In the placebo arm, seven patients did not complete the second step of treatment (eight cycles): five showed progressive disease, and two patients complained of persistent grade 3 or 4 neurotoxicity. In the GSH arm, five patients did not complete the treatment: four showed progressive disease, and one refused further therapy without clinical signs of neurotoxicity or disease progression.

In the placebo arm, a total of 172 cycles were administered (median, eight); the median dose-intensity of oxali-

Table 1. Patient Characteristics

	Placebo Arm	GSH Arm
No. of patients	26	26
Age, years		
Median	65	65
Range	50-76	40-77
Sex male/female	19/7	12/14
ECOG performance status		
0	20	17
1	6	9
Primary site		
Colon	15	12
Rectum	11	14
Site of metastases		
Liver	18	16
Abdomen	8	10
Peritoneum	4	3
Lung	10	6
Lymph nodes	3	5
Others	3	1
No. of sites		
1	9	14
> 2	17	12
Previous treatment		
No	9	6
Yes	17	19
Adjuvant therapy		
No	14	15
Yes	12	11

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

platin was 38.8 mg/m^2/wk, and the median cumulative dose of oxaliplatin was 783 mg/m^2. In the GSH arm, a total of 175 cycles was administered (median, eight); the median dose-intensity of oxaliplatin was 39.2 mg/m^2/wk, while the median cumulative dose of oxaliplatin was 782 mg/m^2. The reduced dose-intensity of oxaliplatin was mainly due to neurotoxicity in the placebo arm and to other toxicities in the GSH arm. No statistical difference in number of cycles, dose-intensity, or cumulative dose of oxaliplatin between the two groups was observed. At baseline, no patient suffered from clinical neuropathy in either arm.

At the time of the second neurologic examination (four cycles), seven patients had a clinical neuropathy (grade 1 or 2) in the GSH arm (27%; 95% confidence interval [CI], 9.8% to 44%) compared with 11 patients in the placebo arm (42%; 95% CI, 23% to 61%) (Table 2).

After eight cycles of chemotherapy, nine patients (43%; 95% CI, 22% to 64%) had clinical neuropathy in the GSH arm (score, 0.52) compared with 15 patients (79%; 95% CI, 60% to 80%) in the placebo arm (score, 1.68) ($P = .04$). Remarkably, the incidence of moderate to severe (grade 2 to 4 NCI CTC) clinical neurotoxicity was present in 11 of 19 assessable patients (58%; 95% CI, 35% to 80%) in the placebo arm, compared with only two of 21 assessable patients (9.5%; 95% CI, 0% to 22%) in the GSH arm ($P = .003$). Furthermore, grade 3 or 4 neurotoxicity was not present in the GSH arm, while it was reported in five patients (26%) in the placebo arm ($P = .01$).

Only 18 patients received 12 cycles of treatment, 10 in the GSH arm and eight in the placebo arm. Grade 2 to 4 neurotoxicity was observed in only three patients in the GSH arm and in eight patients in the placebo arm ($P = .004$).

The most frequent neurologic symptoms were distal paresthesia, numbness in the legs, and ataxia, while the physical examinations generally showed decrease or loss of deep tendon reflexes.

The neurophysiologic evaluation showed that no changes in mean latency and sensory amplitude potentials of sural nerves occurred in the GSH and placebo arms after four cycles of chemotherapy. On the contrary, after eight cycles of chemotherapy in the GSH arm, no changes in mean latency and sensory amplitude potentials of the sural nerves had occurred; in the placebo arm, these parameters were significantly affected (Tables 3 and 4). Patients did not continue to receive GSH after oxaliplatin had been stopped, and none of the patients experienced a rebound of their neurologic symptoms.

The other chemotherapy toxicities are reported in Table 5. There were no chemotherapy-related deaths. The main toxicities were neutropenia, diarrhea, stomatitis,

Table 2. Clinical Evaluation of Neurotoxicity

Neurotoxicity NCI NCTC Grade	After 4 Cycles		After 8 Cycles		After 12 Cycles	
	Placebo (n = 26)*	GSH (n = 26)*	Placebo (n = 19)*	GSH (n = 21)*	Placebo (n = 8)*	GSH (n = 10)*
0	15	19	4	12	–	1
1	9	6	4	7	–	6
2	2	1	6	2	2	2
3	–	–	4	–	4	1
4	–	–	1	–	2	–
Score	–	–	1.68	0.52	3	1.3

*Number of assessable patients.

Table 3. Electrophysiologic Results in the Placebo Arm

Sural Nerve	Basal	After 4 Cycles	*P*	After 8 Cycles	*P*
Latency, msec	3.07 ± 0.33	2.90 ± 0.69	NS	3.19 ± 1.70	.03
SAP, μV	10.98 ± 6.92	9.80 ± 5.35	NS	7.20 ± 5.05	.05
CV, m/sec	45.91 ± 4.59	44.03 ± 10.19	NS	39.33 ± 11.66	.01

Abbreviations: SAP, sensory amplitude potential; CV, conduction velocity; NS, not significant.

nausea and vomiting, and transient hepatic failure. They were generally mild, and no statistically significant difference in incidence and severity of toxicities was found between the two groups (Table 5).

No complete response was observed in either arm. A partial response was observed in seven patients (26.9%; 95% CI, 9.8% to 43.9%) in the GSH group and in six patients (23.1%; 95% CI, 6.8% to 39.2%) in the placebo arm, for an overall response rate of 25.0% (95% CI, 13.2% to 36.7%) (Table 6).

After a median overall follow-up period of 11.5 months (range, 3 to 30 months), the median progression-free survival was 7 months (range, 2 to 12 months) for patients in the GSH arm and 7 months (range, 2 to 16 months) for those in the placebo arm. Median survival time was 16 months and 17 months in the GSH and placebo arms, respectively.

DISCUSSION

The mechanism of neurotoxicity induced by platinum drugs has been proposed to involve the accumulation of platinum within the peripheral nerve system.[11,12] The major site of damage seems to be the dorsal root ganglia, which is consistent with the platinum accumulation studies. In fact, biodistribution studies have shown that the platinum concentrations are greater in the dorsal root ganglia followed by the dorsal root and peripheral nerves.[12] Damage to the dorsal root ganglia seems to result in axonopathy of peripheral nerves, especially in the large myelinated fibers responsible for sensory nerve conduction. In a rat model, the sciatic nerves showed marked axonal atrophy and a decrease in the number of large sensory axons, whereas the motor axons remained unaffected.[21]

The neurotoxicity associated with oxaliplatin is similar in nature to that associated with cisplatin. However, unlike the case with cisplatin, the pathologic presence of oxaliplatin in the dorsal root ganglia is due to a relative slower clearance of the drug rather than to an increased accumulation.[13] These data suggest that an optimal strategy for reducing the neurotoxicity associated with oxaliplatin may be the use of agents such as GSH, which may be able to prevent the initial accumulation of platinum adducts in dorsal root ganglia.[13]

A major role of GSH in the prevention of platinum-induced neurotoxicity has been suggested by recent experimental findings. Park et al[22] showed that reactive oxygen species generated by platinum compounds play an important role in platinum-induced neuronal apoptotic cell death via activation of the p53 signaling pathway. Preincubation of nerves from a mouse dorsal root ganglion with *N*-acetylcysteine, a precursor of GSH, blocks or attenuate the accumulation of p53 protein in response to platinum, resulting in a block of platinum-induced apoptosis and in a neuroprotective effect.[22] Finally, preclinical and clinical experiences provided evidence that GSH was effective for the prevention of cisplatin-induced neurotoxicity without reducing the clinical activity of cisplatin.[14-17]

On the basis of these premises, we performed this double-blind, placebo-controlled, randomized trial using the same GSH schedule as reported in our previous work.[16] Our results indicate that GSH can exert a beneficial effect on oxaliplatin neurotoxicity. In fact, we have shown that GSH given concurrently with oxaliplatin is able to reduce the symptoms and signs of neuropathy significantly. In addition, neurophysiologic investigations based on the evaluation of latency and amplitude of the sensory nerve conduction, the most common indexes impaired in platinum neuropathy, supported the neuroprotective effects of GSH.

These findings may have important clinical implications. In fact, in several cases, despite good clinical activity, treatment with oxaliplatin must be discontinued because of the onset of neurotoxicity. The concomitant use of GSH

Table 4. Electrophysiologic Results in the GSH Arm

Sural Nerve	Basal	After 4 Cycles	*P*	After 8 Cycles	*P*
Latency, msec	2.98 ± 0.97	3.17 ± 0.76	NS	3.08 ± 0.99	NS
SAP, μV	9.09 ± 6.34	10.89 ± 7.89	NS	8.71 ± 5.50	NS
CV, m/sec	39.87 ± 13.0	39.48 ± 13.04	NS	39.13 ± 11.63	NS

Abbreviations: SAP, sensory amplitude potential; CV, conduction velocity; NS, not significant.

Table 5. Worst Grade of Toxicity by Each Patient (absolute numbers)

Toxicity (NCI CTC)/Grade	Placebo Arm	GSH Arm
Anemia		
1/2	2	5
3/4	0	0
Neutropenia		
1/2	7	7
3/4	4	1
Thrombocytopenia		
1/2	5	4
3/4	0	0
Nausea		
1/2	9	10
3	0	0
Vomiting		
1/2	7	10
3/4	0	0
Diarrhea		
1/2	6	6
3/4	0	2
Stomatitis		
1/2	6	6
3/4	0	0

Table 6. Tumor Response and Survival

	GSH Arm	Placebo Arm
Patients enrolled, n	26	26
CR	0	0
PR, %	26.9	23.1
SD, %	57.7	53.8
PD, %	15.4	23.1
OR, %	26.9	23.1
95% CI, %	9.8-43.9	6.8-39.2
PFS, months	7+	7
Survival, months	16	17

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OR, overall response; PFS, progressive-free survival.

may allow the administration of an effective treatment for a more prolonged time. In fact, in the placebo arm, none of the patients could receive further oxaliplatin treatment because of the development of neurotoxicity; in the GSH arm, seven patients did not develop any sign of clinical neurotoxicity and could continue on treatment. In the coming years, there will be an expanding use of oxaliplatin in several other cancers as well as in the adjuvant setting, as indicated by two ongoing randomized trials in colon cancer in Europe (Multicenter International Study of Oxaliplatin 5FU-LV in the Adjuvant Treatment of Colon Cancer [MOSAIC] trial) and the United States (National Surgical Adjuvant Breast and Bowel Project C-07), oxaliplatin-induced neuropathy will be a growing, relevant clinical problem.

Regarding toxicity and possible interference with oxaliplatin antitumor activity by GSH, as previously reported in other studies on cisplatin, we did not observe either.

The results we achieved with this double-blind, placebo-controlled trial have provided evidence indicating that GSH is a promising drug for the prevention of oxaliplatin-induced neuropathy. Other attempts to reduce neurotoxicity associated with oxaliplatin included the development of regimens alternating the combination of oxaliplatin/5FU with 5FU alone in order to allow a long-term period of treatment but reducing the total cumulative dose of oxaliplatin, or the use of other possible chemoprotectants, such as gabapentin. Preliminary data with this drug seem to be promising.[23] In seven patients, neuropathy disappeared and did not recur with additional chemotherapeutic courses. However, in some patients, increased doses of gabapentin were needed; so far, a prolonged administration of this drug may be precluded because of its potential side effects. In contrast, the lack of toxicity and interference with oxaliplatin activity, as well as its low economic cost, makes GSH an ideal new drug for the prevention of oxaliplatin-induced neuropathy in colorectal cancer patients.

REFERENCES

1. Misset JL, Bleiberg H, Sutherland W, et al: Oxaliplatin clinical activity: A review. Crit Rev Oncol Hematol 35:75-93, 2000

2. De Gramont A, Figer A, Seymour M, et al: Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18:2938-2947, 2000

3. Giacchetti S, Perpoint B, Zidani R, et al: Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. J Clin Oncol 18:136-142, 2000

4. Brienza S, Bensmaine MA, Souliè P, et al: Oxaliplatin added to 5-fluorouracil-based therapy in the treatment of 5FU-pretreated patients with advanced colorectal carcinoma (ACRC): Results from the European compassionate-use program. Ann Oncol 10:1311-1316, 1999

5. Maindrault-Goebel F, de Gramont A, Louvet C, et al: Evaluation of oxaliplatin dose intensity in bimonthly leucovorin and 48-hour 5-fluorouracil continuous infusion regimens (FOLFOX) in pretreated metastatic colorectal cancer. Ann Oncol 11:1477-1483, 2000

6. Giacchetti S, Itzhaki M, Gruia G, et al: Long-term survival of patients with unresectable colorectal cancer liver metastases following infusional chemotherapy with 5-fluorouracil, leucovorin, oxaliplatin and surgery. Ann Oncol 10:663-669, 1999

7. Piccart MJ, Green JA, Lacave AJ, et al: Oxaliplatin or paclitaxel in patients with platinum-pretreated advanced epithelial ovarian cancer: A randomized phase II study of the European Organization for Research and Treatment of Cancer Gynecology Group. J Clin Oncol 18:1193-1202, 2000

8. Monnet I, Brienza S, Hugret F, et al: Phase II study of oxaliplatin in poor-prognosis non-small cell lung cancer (NSCLC). Eur J Cancer 34:1124-1127, 1998

9. Culy CR, Clemett D, Wiseman LR: Oxaliplatin: A review of its pharmacological properties and clinical efficacy in metastatic colorectal cancer and its potential in other malignancies. Drugs 60:895-924, 2000

10. Extra JM, Marty M, Brienza S, et al: Pharmacokinetics and safety profile of oxaliplatin. Semin Oncol 25:13-22, 1998 (suppl 2)

11. Cavaletti G, Tredici G, Marmiroli P, et al: Morphometric study of the sensory neuron and peripheral nerve changes induced by chronic cisplatin (DDP) administration in rats. Acta Neuropathol 84:364-371, 1992

12. Gregg RW, Molepo JM, Monpetit VJA, et al: Cisplatin neurotoxicity: The relationship between dosage, time, and platinum concentration in neurologic tissues and morphologic evidence of toxicity. J Clin Oncol 10:795-803, 1992

13. Holmes J, Stanko J, Varchenko M, et al: Comparative neurotoxicity of oxaliplatin, cisplatin, and ormaplatin in a Wistar rat model. Toxicol Sci 46:342-351, 1998

14. Hamers FPT, Brakkee JH, Cavaletti G, et al: Reduced glutathione protects against cisplatin-induced neurotoxicity in rats. Cancer Res 53:544-549, 1993

15. Leone R, Fracasso ME, Soresi E, et al: Influence of glutathione administration on the disposition of free and total platinum in patients after administration of cisplatin. Cancer Chemother Pharmacol 29:385-390, 1992

16. Cascinu S, Cordella L, Del Ferro E, et al: Neuroprotective effect of reduced glutathione on cisplatin-based chemotherapy in advanced gastric cancer: A double-blind placebo-controlled trial. J Clin Oncol 13:26-32, 1995

17. Smyth JF, Bowman A, Perren T, et al: Glutathione reduces the toxicity and improves quality of life of women diagnosed with ovarian cancer treated with cisplatin: Results of a double-blind, randomised trial. Ann Oncol 8:569-573, 1997

18. World Health Organization: Handbook for Reporting Results of Cancer Treatment. Geneva, Switzerland, World Health Organization, 1979

19. NCI Common Toxicity Criteria, Version 2.0. Washington, DC, National Institutes of Health, National Cancer Institute, 1998

20. Glantz SA: Primer of Biostatistics (ed 4). New York, NY, McGraw Hill, 1997

21. New P, Barohn R, O'Rourke T, et al: Neuropathy following ormaplatin administration: Human and laboratory studies. Proc Am Soc Clin Oncol 12:88, 1993 (abstr 155)

22. Park SA, Choi KS, Bang JH, et al: Cisplatin-induced apoptotic cell death in mouse hybrid neurons is blocked by antioxidants through suppression of cisplatin-mediated accumulation of p53 but not of FAS/FAS ligand. J Neurochem 75:946-953, 2000

23. Mariani G, Garrone O, Granetto C, et al: Oxaliplatin induced neuropathy: Could gabapentin be the answer? Proc Am Soc Clin Oncol 19:609a, 2000 (abstr 2397)