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Oral Glutamine Is Effective for Preventing Oxaliplatin-Induced Neuropathy in Colorectal Cancer Patients

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Key Words. Colorectal carcinoma • Glutamine • Neuropathy • Oxaliplatin

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Identify the clinical features of oxaliplatin-induced neuropathy.
2. Discuss the current approaches for managing chemotherapy-induced neuropathy.
3. Explain the rationale for using glutamine in preventing oxaliplatin-induced neuropathy.

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ABSTRACT

Oxaliplatin is effective in the treatment of metastatic colorectal cancer (MCRC) patients; however, severe neurotoxicity develops frequently. To assess the efficacy of oral glutamine for preventing neuropathy induced by oxaliplatin, a pilot study was performed. A total of 86 patients with MCRC treated at Taipei Veterans General Hospital were enrolled. Oxaliplatin (85 mg/m^2, days 1 and 15) plus weekly bolus 5-fluorouracil (5-FU; 500 mg/m^2) and folinic acid (FA; 20 mg/m^2) on days 1, 8, and 15 were given every 28 days as first-line treatment. Patients were randomized to receive (glutamine group; $n = 42$) or not receive (control group; $n = 44$) glutamine (15 g twice a day for seven consecutive days every 2 weeks starting on the day of oxaliplatin infusion). Efficacy of chemotherapy, neurological toxicity, and electrophysiological alterations were assessed. A lower percentage of grade 1–2 peripheral neuropathy was observed in the glutamine group (16.7% versus 38.6%) after two cycles of treatment, and a significantly lower incidence of grade 3–4 neuropathy was noted in the glutamine group after four cycles (4.8% versus 18.2%) and six cycles (11.9% versus 31.8%). By adding glutamine, interference with activities of daily living was lower (16.7% versus 40.9%), and need for oxaliplatin dose reduction was lower (7.1% versus 27.3%). There were no significant between-group differences in response to chemotherapy (52.4% versus 47.8%), electrophysiological abnormalities, grade 3–4 non-neurological toxicities (26.2% versus 22.8%), or survival. These data indi-

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Received June 23, 2006; accepted for publication January 10, 2007. 1083-7159/2007/$30.00/0 doi: 10.1634/theoncologist.12-3-312

cate that oral glutamine significantly reduces the incidence and severity of peripheral neuropathy of MCRC patients receiving oxaliplatin without affecting response to chemotherapy and survival. ***The Oncologist*** 2007;12:312–319

Disclosure of potential conflicts of interest is found at the end of this article.

INTRODUCTION

Colorectal carcinoma (CRC) is one of the leading causes of cancer-related mortality in Taiwan, and its incidence has increased over the last few decades. Oxaliplatin, a new cytotoxic agent from the diaminocyclohexane platinum family, exerts its cytotoxic effects through the formation of DNA adducts that block both DNA replication and transcription in actively dividing cells [1]. In combination with 5-fluorouracil (5-FU) and folinic acid (FA), oxaliplatin is effective in first-line as well as salvage therapy of metastatic colorectal cancer (MCRC) patients [2, 3]. Furthermore, the combination of oxaliplatin and 5-FU/FA has been proven to be beneficial in enabling surgical removal of previously unresectable liver metastases [4]. In an adjuvant setting for stage II/III CRC patients, oxaliplatin plus 5-FU/FA significantly improved disease-free survival [5].

Neurotoxicity is the principal and dose-limiting toxicity of oxaliplatin and the incidence of oxaliplatin-induced severe neurotoxicity has varied from 12% (Multicenter International Study of Oxaliplatin/5-FU/FA in the Adjuvant Treatment of Colon Cancer, MOSAIC) to 17% (Capecitabine plus Oxaliplatin, XELOX) to 18% (Optimized 5-FU-Oxaliplatin Strategy 1, OPTIMOX1) in different clinical trials [5–7]. Oxaliplatin-induced neuropathy can be divided into two distinct syndromes. The first one is a unique syndrome of acute, transient peripheral nerve hyperexcitability occurring shortly after the infusion of oxaliplatin. Oxaliplatin is the only platinum complex to produce this form of neuropathy [8]. This form of neuropathy usually occurs at low total cumulative doses and could be triggered or exacerbated by exposure to cold. Patients may experience paresthesias and dysesthesias of the hands and feet, as well as larynx and jaw. These symptoms usually occur within hours of exposure and are reversible over the following hours and days; they generally do not require discontinuation of treatment [8]. The second syndrome is a peripheral sensory neuropathy occurring mainly in the distal extremities with symptoms similar to those caused by cisplatin [9]. Development of this form of neuropathy is correlated with the cumulative dose of oxaliplatin. It may last for several months, results in a severe disturbance of neurologic function, and has a significant impact on oxaliplatin treatment [9].

Various strategies have been proposed to prevent or treat oxaliplatin-induced neurotoxicity. The stop-and-go concept uses the predictability and reversibility of neurologic symptoms of oxaliplatin to allow patients to stay on an oxaliplatin-containing first-line therapy for a prolonged period [7]. Several neuromodulatory agents such as calcium-magnesium infusions [10], antiepileptic drugs like carbamazepine and gabapentin [11], amifostine [12], and glutathione [13] have demonstrated some activity in the prophylaxis and treatment of oxaliplatin-induced acute neuropathy. However, randomized trials demonstrating a prophylactic or therapeutic effect of these agents on oxaliplatin's cumulative neurotoxicity are still lacking.

Glutamine, the most abundant amino acid in blood, constitutes 60% of the total free amino acid pool in skeletal muscle [14]. It contains two amine groups per molecule, playing an important role as a nitrogen transporter, and providing precursor nitrogen for the synthesis of purines and pyrimidines [15]. Glutamine becomes a "conditionally" essential amino acid during periods of stress [16]. In patients with malignant diseases, marked glutamine depletion develops over time, and the development of cachexia is accompanied by massive depletion of glutamine in skeletal muscle. This results in a negative impact on the function of host tissues that are dependent upon adequate stores of glutamine for optimal functioning [17]. Furthermore, the extent of normal tissue damage from chemotherapy as well as radiation may be influenced by the presence of adequate tissue glutamine stores [15]. Clinically, a neuroprotective role for glutamine in breast cancer patients receiving high-dose paclitaxel has been identified [18]. These facts support a possible therapeutic role for glutamine in the prevention of damage to normal tissues, including peripheral nerves, during chemotherapy. On the basis of these considerations, a pilot study was conducted in MCRC patients to assess the efficacy of glutamine in preventing oxaliplatin-induced neuropathy. All were treated with the same oxaliplatin-based regimen and were randomized to receive or not receive glutamine.

MATERIALS AND METHODS

Eligibility Criteria

From September 2004 to December 2005, a total of 86 patients with histologically confirmed adenocarcinoma of the colon or rectum treated at Taipei Veterans General Hospital were enrolled. Eligible patients were required to have measurable metastatic lesions and no previous therapy for metastatic diseases (adjuvant therapy was allowed if more than

6 months had transpired since its completion), an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2, normal hematopoietic function as evidenced by white blood cell count $\geq$3,000/μl and platelet count $\geq$100,000/μl, normal liver and renal functions (serum total bilirubin $<$1.5 mg/dl and creatinine $<$1.5 mg/dl), and a life expectancy of more than 3 months. Patients with pre-existing neuropathy, diabetes mellitus, alcoholic disease, or central nervous system metastasis, and patients on vitamin supplement therapy were excluded from this study. An institutional review board had reviewed the treatment protocol and all patients provided written, informed consent before initiation of study-related procedures. Characteristics of enrolled patients are shown in Table 1.

Treatment Plan and Follow-Up

Patients were treated with oxaliplatin (Eloxatin®; Sanofi-Aventis, Paris, France), 85 mg/m^2 on days 1 and 15, plus FA, 20 mg/m^2 over 10–20 minutes, followed by a 500-mg/m^2 bolus dose of 5-FU on days 1, 8, and 15 every 28 days (per cycle). Patients were randomized to receive glutamine (n = 42; glutamine group) or not receive glutamine (n = 44; control group). In the glutamine group, levo-glutamine (Sympt-X®; Baxter Health Care Corporation, Deerfield, IL) was given orally at a dosage of 15 g twice a day for seven consecutive days every 2 weeks starting on the day of oxaliplatin infusion. To avoid the possible effect on interpretation of neurotoxicity, calcium or magnesium infusion was not allowed during oxaliplatin administration. Neurological toxicities were assessed at baseline, and after 2, 4, and 6 cycles of treatment according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) [19]. In some cases, electrophysiological examinations were performed accordingly. Responses to chemotherapy and treatment-related toxicities were evaluated on the basis of standard World Health Organization (WHO) criteria. Interference with activities of daily living (ADL), including transient functional impairment in performing ADL such as manipulating buttons, opening jars, and other measures of fine motor coordination, was evaluated accordingly. Treatment was delayed until recovery if grade 3–4 non-neurological toxicity occurred and the doses were modified with 25% reductions for all three agents in subsequent cycles. In the case of grade 3–4 neuropathies, the oxaliplatin dose was reduced by 25% of the previous dose until recovery; in the case of intolerable neuropathies or persistent functional impairment, oxaliplatin was omitted from the regimen.

Neurologic Evaluation

Patients enrolled in this study were evaluated at baseline (prior to chemotherapy) and after different cycles of treatment. A detailed neurological history was obtained including possible risk factors for the development of peripheral neuropathy (e.g., diabetes mellitus, alcohol abuse, central nervous system diseases, or prior history of neurotoxic chemotherapy or neuropathy). Symptoms (paresthesias, dysesthesias, numbness, etc.) as well as whether symptoms interfered with function were assessed separately and were graded according to the NCI-CTC. Complete neurological examinations were performed at baseline and after two, four, and six cycles of treatment. When possible, electrophysiological examinations, including sensory amplitude potential (SAP), nerve conduction velocity (NCV), compound muscle action potential (CMAP) as well as F wave latency, were performed at baseline and after two, four, and six cycles of treatment. An experienced neurologist evaluated the data to assess possible between-group differences in electrophysiological function.

Statistical Analysis and Survival Curve Plotting

In this study, we primarily focused on oxaliplatin-induced "chronic cumulative neuropathy," because this neuropathy may result in severe disturbance of neurologic function and have a significant impact on oxaliplatin treatment. Because oxaliplatin-induced grade 3, cumulative neuropathy generally develops after 4 months of treatment [7], the estimate of neurotoxicity used to determine sample size was based on toxicity after four cycles of treatment. The sample size ($>$40 patients for each group) was determined based on the hypothesized difference of approximately 35% (control group) versus 10% (glutamine group) in the overall neurotoxicity rate (not including acute, cold-induced neuropathy) when power and alpha levels were set at 80% and 0.05, respectively. The difference in clinicopathological characteristics, including the development of neuropathy, response to chemotherapy, non-neurological toxicity, ADL, as well as survival, between the glutamine group and the control group was analyzed using the χ^2 test. The survival curves of both groups were plotted using the Kaplan–Meier product limit method, and the statistical difference in survival was compared using the log-rank test. All analyses were performed on a microcomputer using the SPSS software package for Windows (SPSS Inc., Chicago, IL). Statistical difference was defined as $p < 0.05$.

Results

Glutamine Supplementation Significantly Reduces the Incidence and Severity of Oxaliplatin-Induced Neuropathy

Statistical analysis revealed that all of the pretreatment parameters were well balanced between the two groups of patients. As shown in Table 1, there were no significant between-group

Table 1. Characteristics of enrolled patients

Characteristic	Glutamine group (%)	Control group (%)	*p*
All patients enrolled	42 (100)	44 (100)	
Age (years)			
≥50	24 (57.1)	28 (63.6)	.66
<50	18 (42.9)	16 (36.4)	
Gender			
Male	27 (64.3)	29 (65.9)	1.00
Female	15 (35.7)	15 (34.1)	
Performance status			
0	23 (54.8)	27 (61.4)	.66
1, 2	19 (45.2)	17 (38.6)	
Location of primary tumor			
Colon	28 (66.7)	29 (65.9)	1.00
Rectum	14 (33.3)	15 (34.1)	
Histological differentiation			
Well/moderately	32 (76.2)	31 (70.5)	.63
Poorly/unknown	10 (23.8)	13 (29.5)	
Sites of distant metastasis			
Liver	16 (38.1)	18 (40.9)	.90
Lung	10 (23.8)	10 (22.7)	
Liver and lung	9 (21.4)	11 (25.0)	
Other sites	7 (16.7)	5 (11.4)	
Serum CEA level (ng/ml)			
≤6	7 (16.7)	6 (13.6)	.77
>6	35 (83.3)	38 (86.4)	

Abbreviation: CEA, carcinoembryonic antigen.

differences in age, gender, performance status, location of primary tumor, histological differentiation, sites of distant metastasis, or serum carcinoembryonic antigen (CEA) levels (χ^2 test). As shown in Table 2, there were significantly fewer neurological symptoms in patients receiving glutamine than in those who did not. After two cycles of treatment, the percentage of grade 1–2 sensory neuropathy was significantly lower in the glutamine group than in the control group (16.7% versus 38.6%; $p = .04$). After four cycles, 11 patients (26.2%) in the glutamine group and 16 patients (36.4%) in the control group experienced grade 1–2 sensory neuropathy. Moreover, the percentage of grade 3–4 sensory neuropathy was lower in the glutamine group after four cycles of treatment (4.8% versus 18.2%; $p = .05$) and remained so after six cycles (11.9% versus 31.8%; $p = .04$). The incidence of acute, transient (cold-induced) peripheral nerve hyperexcitability was remarkably lower with glutamine supplements (33.3% versus 56.8%; $p = .03$) (Table 3). Interference with ADL was significantly less in patients who received glutamine supplements than in those who did not (16.7% versus 40.9%; $p = .02$) (Table 3).

Whether nerve conduction studies are useful in objectively assessing peripheral neuropathy is of extreme interest. In the current study, electrophysiological examinations were carried out in 28 patients who experienced grade 1–4 neurotoxicities (14 in the glutamine group and 14 in the control group). We found that the amplitudes and conduction velocities of peripheral sensory and motor nerves were frequently deteriorated in both groups of patients. However, there was no statistical between-group difference in the incidence of abnormalities concluded from electrophysiological examinations ($p = .68$) (Table 3). Although glutamine supplementation significantly reduced the incidence of "subjective" neuropathy in these patients, it did not exert a protective effect on the deterioration of electrophysiological tests.

Glutamine Supplementation Reduces the Need for Oxaliplatin Dose Reduction without Affecting Response to Chemotherapy and Survival

Because neuropathy is one of the major dose-limiting toxicities of oxaliplatin, and glutamine supplementation might

Table 2. Incidence of oxaliplatin-induced neuropathy in different patient groups

Neurotoxicity	Glutamine group (%)	Control group (%)	*p*
All patients enrolled	42 (100)	44 (100)	
After two cycles			
Grade 0	35 (83.3)	26 (59.1)	.04
Grade 1–2	7 (16.7)	17 (38.6)	
Grade 3–4	0 (0)	1 (2.3)	
After four cycles			
Grade 0	29 (69.0)	20 (45.4)	.05
Grade 1–2	11 (26.2)	16 (36.4)	
Grade 3–4	2 (4.8)	8 (18.2)	
After six cycles			
Grade 0	20 (47.6)	12 (27.3)	.04
Grade 1–2	17 (40.5)	18 (40.9)	
Grade 3–4	5 (11.9)	14 (31.8)	

Neurological toxicity was defined by the National Cancer Institute Common Toxicity Criteria.

Table 3. The outcome of oral glutamine supplementation

Characteristic	Glutamine group (%)	Control group (%)	*p*
Acute, cold-induced neurotoxicity			
Presence	14 (33.3)	25 (56.8)	.03
Absence	28 (66.7)	19 (43.2)	
Activities of daily living			
Interference	7 (16.7)	18 (40.9)	.02
No interference	35 (83.3)	26 (59.1)	
Electrophysiological examination			
Abnormal	9 (21.4)	11 (25.0)	.68
Normal	5 (11.9)	3 (6.8)	
Not examined	28 (66.7)	30 (68.2)	
Oxaliplatin dose reduction			
Needed	3 (7.1)	12 (27.3)	.02
Not needed	39 (92.9)	32 (72.7)	
Survival (months)			
≥12	30 (71.4)	35 (79.5)	.46
<12	12 (28.6)	9 (20.5)	
Grade 3–4 non-neurological toxicity			
Leukopenia	4 (9.5)	5 (11.4)	.76
Thrombocytopenia	5 (11.9)	4 (9.1)	
Elevated liver enzymes	1 (2.4)	1 (2.3)	
Impaired renal function	1 (2.4)	0 (0)	

Non-neurological toxicity assessment was based on standard World Health Organization criteria.

reduce oxaliplatin-induced neuropathy, we proposed that patients receiving glutamine would require fewer oxaliplatin dose reductions. Indeed, the percentage of patients needing oxaliplatin dose reduction was significantly lower in the group receiving glutamine during the treatment periods (7.1% versus 27.3%; $p = .02$). Another important issue was the impact of supplemental glutamine on the response to oxaliplatin-based chemotherapy as well as survival. In the

Table 4. Response to oxaliplatin-based chemotherapy in different patient groups

Response	Glutamine group (%)	Control group (%)	*p*
All patients enrolled	42 (100)	44 (100)	
Complete remission	5 (11.9)	3 (6.8)	.90
Partial remission	17 (40.5)	18 (41.0)	
Overall response	22 (52.4)	21 (47.8)	
Stable disease	12 (28.6)	13 (29.5)	
Progressive disease	8 (19.0)	10 (22.7)	

Response assessment based on World Health Organization criteria.

current study, tumor response was assessed every three cycles of treatment and no patient had progressive disease after three cycles of treatment. However, eight patients (19.0%) in the glutamine group and 10 patients (22.7%) in the control group had progressive disease after six cycles of treatment (Table 4). All patients completed six cycles of treatment and there were no significant between-group differences in the response to chemotherapy (52.4% versus 47.8%; $p = .90$) and in the median survival time (17.3 months versus 18.6 months; $p = .79$) (Table 4 and Fig. 1). Oral glutamine seems not to affect treatment response of oxaliplatin-based chemotherapy or survival for these patients. Moreover, there were no significant between-group differences in non-neurologic toxicities (i.e., grade 3–4 leukopenia, thrombocytopenia, and liver function as well as renal function impairments; $p = .76$).

Discussion

Oxaliplatin has become an integral component of chemotherapeutic regimens for the treatment of MCRC [2–5]. However, up to 30% of patients experience dose-limiting neurotoxicity as evidenced by moderate motor and sensory symptoms, even though they are still actively responding to this drug [20]. This drug's importance in treatment makes early discontinuation or dose reduction due to neurotoxicity undesirable.

The mechanism of platinum drug neurotoxicity may involve drug accumulation within the peripheral nervous system, especially in the dorsal root ganglia [21]. The use of glutathione can prevent the initial accumulation of platinum adducts in the dorsal root ganglia and thereby reduce neurotoxicity [13]. One possible mechanism underlying oxaliplatin-induced neuropathy is that an oxaliplatin metabolite, such as oxalate, may alter the properties of voltage-gated sodium channels or slow down the clearance of platinum compounds from the peripheral nervous system [22, 23]. Therefore, using calcium and magnesium infusions to chelate oxalate may reduce the incidence and intensity of oxaliplatin-induced neuropathies [10]. Prophylactic use of a neurotrophic agent, xaliproden, was recently shown to reduce the risk of grade 3–4 peripheral sensory neurotoxicity by 39% in MCRC patients receiving oxaliplatin [24].

Glutamine is a gluconeogenic nonessential amino acid that is stored primarily in skeletal muscle and liver [14], and is often depleted in stress states, such as malignancy [16]. It serves as the primary carrier of nitrogen and is the main energy source for rapidly proliferating cells. Rapid proliferation of a tumor may deplete glutamine stores and subsequently lead to cancer-related cachexia [17]. Studies have indicated that glutamine supplementation is well tolerated and potentially effective in preventing side effects for patients receiving high-dose chemotherapy and bone marrow transplantation [25]. Supplementation with glutamine can also protect against doxorubicin-induced cardiac toxicity [26] and prevents atrophy of the intestinal mucosa in patients receiving total parenteral nutrition [27]. Preliminary animal studies suggest that glutamine may prevent neurotoxicity caused by vincristine, cisplatin, as well as paclitaxel [28, 29]. Clinically, paclitaxel-induced myalgias and arthralgias have been successfully reduced by glutamine in breast cancer patients [30]. Glutamine supplements may also reduce the severity of peripheral neuropathy in metastatic breast cancer patients receiving high-dose paclitaxel and hematopoietic stem cell transplantation [18]. Interestingly, a byproduct of glutamine metabolism has been identified that protects advanced CRC patients from oxaliplatin-induced neuropathy [13].

In the current study, supplementation with glutamine significantly reduced the incidence and severity of peripheral neuropathy as well as the need for dose reduction of oxaliplatin in these patients (Tables 1 and 3). These properties may increase the therapeutic index of oxaliplatin. The potential role of glutamine as a neuroprotectant may be better understood in the context of the current hypothesis explaining chemotherapy-induced neuropathy. A study of circulating nerve growth factor (NGF) levels in cancer patients treated with neurotoxic chemotherapeutic agents found that peripheral neuropathy worsened as serum levels of NGF declined [31]. Moreover, the administration of

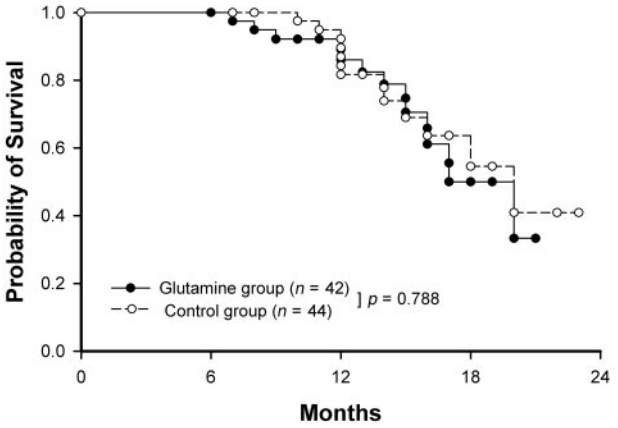

Figure 1. Survival curves of metastatic colorectal cancer patients receiving (filled circle) or not receiving (open circle) glutamine supplementation during oxaliplatin treatments plotted by the Kaplan–Meier method ($p = .788$; log-rank test).

NGF prevents paclitaxel-induced neuropathy in mice [32]. Because glutamine is known to upregulate NGF mRNA in an animal model [33], glutamine supplements may prevent chemotherapy-induced neuropathy via upregulating the NGF level. On the other hand, it has also been hypothesized that high systemic levels of glutamine may downregulate the conversion of glutamine to an excitatory neuropeptide, glutamate, which may also account for the reduced symptoms observed in patients receiving glutamine [34].

The usefulness of nerve conduction studies in objectively assessing peripheral neuropathy remains controversial. Although sensory nerve conduction may be affected significantly after oxaliplatin-based treatment, the severity of clinical sensory neuropathy does not always correlate with findings of nerve conduction studies. For example, it has been reported that the symptoms of oxaliplatin-induced neuropathy could be remarkably reduced after discontinuation of oxaliplatin treatment; however, abnormalities of sensory nerve conduction were shown to persist [35]. In a study conducted by Cascinu et al. [13], sensory nerve conduction was significantly affected by oxaliplatin only in patients receiving placebo, but not in those receiving glutathione, which was consistent with clinical findings. In the current study, we noticed an inconsistency between the electrophysiological findings and the subjective results reported by patients and assessed by physicians. No statistically significant between-group differences were seen in electrophysiological studies of patients receiving glutamine supplements or not ($p = .68$). Because the current study is a non–placebo controlled, unblinded study with a relatively small sample size, patient and physician bias may have played a role in this inconsistency.

A major concern is that glutamine supplements might protect tumor cells from the cytotoxic effects of chemotherapy. However, in the current study, no between-group difference was found in the response to chemotherapy (52.4% versus 47.8%; $p = .90$) or survival ($p = .79$; log-rank test). Although in vitro evidence of the dependence of tumor growth on glutamine has deterred its application in cancer patients [36], several studies have failed to show that supplemental glutamine stimulates tumor growth [37, 38]. In fact, accumulating in vivo evidence suggests that glutamine may actually decrease tumor growth, possibly by upregulating the immune system [37, 39]. The net outcome may improve the therapeutic index of oxaliplatin. The overall lymphocyte response (i.e., entry into the cell cycle and proliferation) has been directly correlated with glutamine concentration of the culture medium [40]. In a breast cancer xenograft model, the supplemental glutamine group had higher natural killer cell activity and nearly one half the tumor volume, compared with the placebo group [41].

In addition to reducing the incidence and severity of peripheral neuropathy, glutamine supplements may also improve ADL (consistent mainly with fine motor coordination) for MCRC patients receiving oxaliplatin. We noticed that 16.7% ($n = 7$) of patients who received glutamine supplementation, compared with 40.9% ($n = 18$) of those who did not ($p = .02$), had difficulty with ADL. Because peripheral neuropathy measurement is not always reproducible, and the level of symptoms or signs on physical examination is not always predictive of ADL disability, performance of ADL is considered a very important indicator of outcome in patients receiving neurotoxic chemotherapeutic agents. In comparison with other neuroprotective agents, the cost of using oral glutamine supplements as a neuroprotective strategy is affordable (about U.S. $150 per month), with an additional advantage of reducing the incidence of gastrointestinal and possibly cardiac side effects induced by chemotherapy [15].

In summary, our data suggest that oral glutamine has a potential neuroprotective effect in MCRC patients treated with oxaliplatin, and may therefore improve the therapeutic index. Larger placebo-controlled, randomized studies are needed to confirm the application of glutamine as a protective agent against oxaliplatin-induced neuropathy.

Acknowledgments

This study was supported by grants V95S5-005 from Taipei Veterans General Hospital and from Taiwan Clinical Oncology Research Foundation to Wang WS.

Disclosure of Potential Conflicts of Interest

The authors indicate no potential conflicts of interest.

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Oncologist 2007;12;312-319
DOI: 10.1634/theoncologist.12-3-312