Nerve Conduction Velocity Study is Effective in Objectively Assessing Oxaliplatin-induced Peripheral Neuropathy

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Abstract

Oxaliplatin is effective in the treatment of metastatic colorectal cancer patients; however, severe neurotoxicity developed frequently. To assess the efficacy of nerve conduction velocity (NCV) study in objectively assessing oxaliplatin-induced peripheral neuropathy, a pilot study was performed. A total of 28 patients with metastatic colorectal cancer treated at Taipei Veterans General Hospital were enrolled. Oxaliplatin (85 mg/m², day 1 and 15), plus weekly bolus 5-fluorouracil (5-FU; 500 mg/m²) and folinic acid (FA; 20 mg/m²) on day 1, 8, and 15 were given every 28 days as first-line treatment. Chemotherapy-associated neurological toxicity and electrophysiological alterations, especially NCV, were assessed. Twenty patients showed a remarkably reduced NCV and the remainders were NCV-normal. After 6 cycles of treatments, a significant correlation was identified in NCV abnormalities and the severity of neurological symptoms (P=0.01), including 16 patients with a reduced NCV accompanied by severe (grade 3 or 4) neuropathy, and 6 patients with a normal NCV without developing severe neurological symptoms. However, there remained 2 patients with a normal NCV who developed severe (grade 3 or 4) neuropathies, and 4 patients who showed a remarkably reduced NCV without or with only mild neurological symptoms. We conclude that nerve conduction studies correlate well with the severity of neurological symptoms and may serve as a useful tool in objectively assessing the severity of oxaliplatin-induced peripheral neuropathy. The addition of a detailed electrophysiological examination to a precise physical examination may be effective in objectively assessing oxaliplatin-induced neuropathy.

Key Words: colorectal carcinoma, nerve conduction velocity, neuropathy, oxaliplatin
INTRODUCTION

Oxaliplatin is effective in the management of metastatic colorectal cancer (mCRC) patients; however, neurotoxicity is the major and dose-limiting toxicity of oxaliplatin and the incidence of oxaliplatin-induced severe neurotoxicity have varied from 12% to 18% in different clinical trials[1-3].

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. And oxaliplatin is the only platinum complex to produce this form of neuropathy[4]. This form of neuropathy usually occurs at low total cumulative doses and could be triggered or exacerbated by exposure to cold. Patients may experience parathesias and dyesthesias 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 days and they generally do not require discontinuation of treatment[4]. The second one is a peripheral sensory neuropathy occurring mainly in the distal extremities with symptoms similar to those caused by cisplatin[5]. Development of this form of neuropathy is correlated with the cumulative dose of oxaliplatin. This form of neuropathy may last for several months, results in a severe disturbance of neurologic function, and has a significant impact on oxaliplatin-containing first-line therapy for a prolonged period[3]. Several neuromodulatory agents, such as calcium-magnesium infusions[6], antiepileptic drugs[7], amifostine[8], glutathione[9], and glutamine[10] have demonstrated some activity in the prophylaxis and treatment of oxaliplatin-induced acute neuropathy. However, large placebo-controlled randomized trials demonstrating a prophylactic or therapeutic effect of these agents on oxaliplatin's cumulative neurotoxicity are still lacking.

The usefulness of nerve conduction studies in objectively assessing chemotherapy-induced peripheral neuropathy is of extreme interest and has been studied previously. Clinically, although sensory nerve conduction may be affected significantly after oxaliplatin-based treatment, the severity of sensory neuropathy does not always correlate to 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 velocity (NCV) were shown to persist[11]. In a study conducted by Cascini, et al., 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[9]. Based on these previous findings, a study was conducted to assess the efficacy of using NCV in objectively assessing oxaliplatin-induced peripheral sensory neuropathy.

MATERIALS AND METHODS

Eligibility Criteria
From September 2004 to December 2005, a total of 28 patients with histologically confirmed adenocarcinoma of the colon or rectum treated at Taipei Veterans General Hospital were enrolled. Eligible patients were required as having metastatic lesions and no previous chemotherapy for metastatic diseases (adjuvant therapy was allowed if more than 6 months had transpired since its completion); ECOG performance status of 0, 1, or 2; normal hematopoietic function as evidenced by white blood cell count \( \geq 3,000/\mu l \) and platelet count \( \geq 100,000/\mu l \); normal liver and renal functions (serum total bilirubin \( <1.5\text{mg/dl} \) and creatinine \( <1.5\text{mg/dl} \)); 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.

**Treatment Plan and Follow-Up**

Patients were treated with oxaliplatin (Sanofi-Aventis, Paris, France) 85 mg/m\(^2\) on day 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 day 1, 8, and 15 every 28 days (per cycle) as first-line setting. To avoid the possible effect on interpretation of neurotoxicity, calcium or magnesium infusion or other medications that have been reported to modulate oxaliplatin-induced peripheral neuropathy were 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)[12]. Electrophysiological examinations including NCV were performed accordingly. Responses to chemotherapy and treatment-related toxicities were evaluated on the basis of standard World Health Organization (WHO) criteria. Treatment was delayed until recovery if grade 3-4 non-neurological toxicity occurred and the doses were modified with 25% reduction 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, vitamin supplements, or prior history of neurotoxic chemotherapy or neuropathy). Symptoms (paresthesias, dysesthesias, numbness, etc.) as well as whether these symptoms interfered with function were assessed separately and were graded according to the NCI-CTC criteria. Complete neurological examinations were performed at baseline and after 2, 4, and 6 cycles of treatment. 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 2, 4, and 6 cycles of treatment. An experienced neurologist evaluated the data to assess possible between-group differences in electrophysiological function. In the
current study, the correlations of abnormalities in NCV and the severity of neurological symptoms was examined with χ² test.

RESULTS
Electrophysiological examinations were performed in 28 patients and the correlations of reduced NCV and the severity of neurological symptoms was examined. The correlations of abnormality in NCV and severity of neurological symptoms of patients received different cycles of oxaliplatin-based chemotherapy were shown in (Table 1). In the current study, the incidence of severe neuropathy (grade 3 or 4) after 2 or 4 cycles of treatment was too low to make any statistical difference. But after 6 cycles treatment, a significant correlation was identified in NCV abnormalities and the severity of neurological symptoms (P=0.01), including 16 patients with a reduced NCV accompanied by severe (grade 3 or 4) neuropathy, and 6 patients with a normal NCV without developing severe neurological symptoms. However, there remained 2 patients with a normal NCV who developed severe (grade 3 or 4) neuropathies, and 4 patients who showed a remarkably reduced NCV without or with only mild neurological symptoms.

DISCUSSION
Approximately 30% of patient experienced dose-limiting neurotoxicity as evidenced by moderate motor and sensory symptoms, even though they are still actively responding to oxaliplatin-based chemotherapy[13]. However, due to this drug’s importance in the treatment of mCRC makes early discontinuation or dose reduction simply due to neurotoxicity undesirable.

Several mechanisms of platinum drug neurotoxicity have been proposed, including the involvement of drug accumulation within the peripheral nervous system, especially in the dorsal root ganglia[14]. The use of glutathione can prevent the initial accumulation of platinum adducts in the dorsal root ganglia and thereby reduce neurotoxicity[13]. Another possible mechanism underlying oxaliplatin-induced neuropathy is that one of oxaliplatin metabolites, such as oxalate, may alter the properties of neuronal voltage-gated sodium channels or slow down the clearance of platinum compounds from the peripheral nervous system[15,16]. Therefore using calcium and magnesium infusions to chelate oxalate may reduce the incidence and intensity of oxaliplatin-induced neuropathies[6]. Prophylactic use of a neurotrophic agent, Xaliproden, has been shown to reduce the risk of grade 3−4 peripheral sensory neurotoxicity by 39% in mCRC patients receiving oxaliplatin[17].

It has been shown that electrophysiological examination is a useful tool in objectively assessing oxaliplatin-induced peripheral sensory neuropathy[18-21]. In a study the damage to the nucleolus of ganglionic sensory neurons of rats treated with various platinum drugs is closely linked to the alteration of sensory NCV[18]. Interestingly, oxaliplatin reduced NCV mainly in peripheral and sensory nerves, without affecting central or motor nerve conductions[24], which was compatible with the clinical manifestations of patients’ who have been treated with oxaliplatin. And the severity of neurological symptoms correlated well with electrophysiological findings[21].
Table 1. The correlation of abnormality in nerve conduction velocity and severity of neurological symptoms of patients received oxaliplatin treatment (n=28).

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<tr>
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<th>Reduced NCV</th>
<th>Normal NCV</th>
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<tr>
<td>After 2 cycles of treatment</td>
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<tr>
<td>Grade 0-2 PSN</td>
<td>2</td>
<td>25</td>
<td>0.78</td>
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<tr>
<td>Grade 3-4 PSN</td>
<td>0</td>
<td>1</td>
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<td>After 4 cycles of treatment</td>
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<tr>
<td>Grade 0-2 PSN</td>
<td>3</td>
<td>23</td>
<td>0.13</td>
</tr>
<tr>
<td>Grade 3-4 PSN</td>
<td>1</td>
<td>1</td>
<td></td>
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<tr>
<td>After 6 cycles of treatment</td>
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<tr>
<td>Grade 0-2 PSN</td>
<td>4</td>
<td>6</td>
<td>0.01</td>
</tr>
<tr>
<td>Grade 3-4 PSN</td>
<td>16</td>
<td>2</td>
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NCV: nerve conduction velocity; PSN: peripheral sensory neuropathy assessment based on NCI-CTC criteria.

Clinically, since the symptoms of peripheral sensory neuropathy are relatively subjective, a precise clinical evaluation including a detailed history-taking as well as physical examination is crucial for detecting the occurrence of peripheral neuropathy during chemotherapy. In fact, the grading systems we commonly used in daily practice and clinical trials for evaluating chemotherapy-induced peripheral neuropathy do not include electrophysiological studies. For example, the grading scales designed by the WHO, ECOG, NCIC-CTC, or an oxaliplatin-specific neuropathy scale designed by MOSAIC trial[1], consist of subjective sensory loss, paresthesias, loss of deep tendon reflexes, constipation, bladder dysfunction, paralysis, etc., without abnormalities in electrophysiological studies.

It is obvious that the evaluation of patients’ neurological symptoms during chemotherapy is very practical and much easier to perform than electrophysiological studies, because the latter is not always available in the general oncological practice. In addition, the findings of nerve conduction studies do not always correlate with the severity of clinical symptoms. For example, it has been shown that the abnormalities of sensory NCV may persist even though the symptoms of oxaliplatin-induced neuropathy have been remarkably reduced after discontinuation of oxaliplatin treatment[11].

Occasionally, the development of severe neurological symptoms after oxaliplatin treatment is not always accompanied with a remarkable change in NCV. In a previous study, we noticed that no significant between-group differences in electrophysiological studies of patients receiving glutamine supplements or not, although patients receiving glutamine supplements during oxaliplatin-treatment period have a lower incidence of grade 3 or 4 neuropathy[10]. In the current study, after 6 cycles of treatments, a significant correlation was identified in NCV abnormalities and the severity of neurological symptoms (P=0.01), including 16 patients with a reduced NCV accompanied by severe (grade 3 or 4) neuropathy, and 6 patients with a normal NCV without developing severe neurological symptoms (Table 1). Although the sensitivity of NCV study in predicting grade 3 or 4 peripheral sensory neuropathy looks quite good (approximately 90%); however, there remained 2 patients with a normal NCV who developed severe neuropathies. Since the sensitivity and specificity of any test, including NCV, have their limit, a detailed his-
tory-taking as well as physical examination remains very important for evaluating the development of neuropathy after oxaliplatin treatment because we believe that it is the “clinical symptoms” of neuropathy that really bothers patients, not “NCV data” themselves.

We conclude that nerve conduction studies correlate well with the severity of neurological symptoms and may serve as a useful tool in objectively assessing the severity of oxaliplatin-induced peripheral neuropathy. The addition of a detailed electrophysiological examination to a precise physical examination may provide more valuable data regarding the characteristics of oxaliplatin-induced peripheral neuropathy.

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REFERENCES


神經傳導速率檢查可用來客觀評估 oxaliplatin 所引發的周邊神經病變

中文摘要

Oxaliplatin 是治療轉移性大腸直腸癌病患有效的藥物，其最為常見的副作用，就是周邊神經病變。在臨床上，我們常用病史詢問及理學檢查等方式來評估化學治療藥物所引發周邊神經病變的嚴重度。於本研究中，我們擬探討神經傳導速率檢查 (NCV) 是否可用來客觀評估 oxaliplatin 所引發的周邊神經病變。共有 28 位轉移性大腸直腸癌病患接受第一線 oxaliplatin 合併 5-FU/leucovorin 治療，其中 20 位病患於治療期間出現神經傳導速率異常的情形。我們發現神經傳導速率的變化，與病患是否在臨床上出現明顯 (第 3 或第 4 級) 周邊神經病變症狀有很好的關連性 (P=0.01)。於本研究中，於 6 個療程的化學治療之後，有 16 位病患出現神經傳導速率異常，同時出現明顯周邊神經病變之症狀，有 6 位病患其神經傳導速率為正常，且在臨床上並未出現明顯周邊神經病變之症狀。然而，我們也發現有 2 位病患其神經傳導速率正常，但在臨床上出現明顯周邊神經病變之症狀。我們的結論是，神經傳導速率之異常與病患出現周邊神經病變之症狀有很好的關連性，該項檢查可以與詳細的病史詢問及理學檢查合併使用，來客觀評估 oxaliplatin 所引發的周邊神經病變。

關鍵字：大腸直腸癌、神經傳導速率、神經病變、oxaliplatin

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