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Original Article

Low serum magnesium implicated in the acute oxaliplatin-induced peripheral neuropathy

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Abstract: Acute peripheral neuropathy is dose limiting toxicity of oxaliplatin, a wildly used chemotherapeutic drug in colorectal cancer. The present study aimed to identify the relationship between pretreatment serum magnesium concentration and the acute oxaliplatin-induced peripheral neuropathy. We enlisted 318 colorectal cancer patients who received adjuvant or first-line oxaliplatin-based chemotherapy (either FOLFOX6 or XELOX) in this study. Before treatment, serum magnesium concentration was measured. The oxaliplatin-induced peripheral neuropathy was graded by using version 3 of the National Cancer Institute's Common Toxicity Criteria (NCI-CTC v3). The association between serum magnesium concentration and peripheral neuropathy was evaluated. The acute oxaliplatin-induced peripheral neuropathy was diagnosed in 151 of 318 patients (47.5%). Patients with lower serum magnesium concentration (<0.76 mmol/L) had an elevated risk of severe peripheral neuropathy compared to those patients with higher serum magnesium concentration (≥0.76 mmol/L). The hazard ratio was 1.867 (95% confidence interval [CI] 1.151-3.030). This study provides independent support of pretreatment serum magnesium concentration as a novel marker of risk of the acute oxaliplatin-induced peripheral neuropathy.

Keywords: Oxaliplatin, peripheral neuropathy, magnesium

Introduction

Colorectal cancer is the third most common cancer in the worldwide, which is also a significant cause of cancer mortality in China [1]. More than half of the patients were found with wildly invasive local disease and lymph or other organ metastasis at the time of diagnosis. The majority of patients who have undergone surgery or radiotherapy would develop disease relapse [2]. For the advanced colorectal cancer, the chemotherapy is necessary. Oxaliplatin is an effective cytostatic agent for a number of solid tumors, mainly used in first line treatment for colorectal cancer [3, 4]. Oxaliplatin based combination chemotherapy, commonly used in the form of leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX4) or capecitabine and oxaliplatin (XELOX), have showed the efficacy in both the adjuvant and palliative settings. Despite the efficacy of oxaliplatin-based combined chemotherapy, there are drug-related toxicities that lead to serious clinical limitations. Its dose-limiting toxicities are myelosuppression and peripheral neuropathy [5]. Although myelosuppression can be cured successfully, there is no specific preventive management for peripheral neuropathy [6]. It significantly affected the quality of life of patients with cancer and often responsible for the suspension of therapy. The oxaliplatin-induced peripheral neuropathy typically causes sensory symptoms, such as dysphonic syndrome, dysaesthesias, distal paresthesias and mild muscle contrations of hands and feet. Although the exact mechanism have not been well documented, it is clear that oxaliplatin accumulates in the dorsal root ganglia and voltage-dependent Na+ channels are affected [7-9]. Current evidence revealed that the degree of oxaliplatin-induced peripheral neuropathy is mainly dependent on cumulative dose, dose intensity and duration of treatment [10, 11]. There are also various reports suggested that some clinical factors related with oxaliplatin-induced peripheral neuropathy, such as pre-treatment diabetes, body mass index,

patients' age and alcohol consumption [12, 13]. However, despite these risk factors, not all patients receiving the similar cumulative dose of oxaliplatin will develop the similar degree peripheral neuropathy which leads to dose reduction or either treatment suspension. In this way, inter-individual variability is a very important factor in the development of oxaliplatin-induced peripheral neuropathy.

Oxaliplatin-induced peripheral neuropathy presents two distinct types of neurological symptoms. The acute peripheral neuropathy occurs in majority of patients. This symptom characterized by cold-induced paresthesias, pharyngolaryngeal dysesthesias. The chronic type is a pure sensory neuropathy with stocking-and-glove distribution. In clinical practice, more attention was given to the chronic neuropathy more than the acute type, because the cumulative dose of oxaliplatin might be detrimental to patients for a long period. The acute oxaliplatin-induced peripheral neuropathy is transient, often reversible during hours or a few days. The dose of oxaliplatin did not need adjustment or even cessation. However, recent study revealed that the grade of acute nerve dysfunction may relate to the development of chronic neurotoxicity [9]. So in this study, we propose to assess the relationship between clinicopathological variables and the acute oxaliplatin-induced peripheral neuropathy.

Recently, many randomized trials have shown that high dose of intravenous calcium and magnesium could be given before and after oxaliplatin-based chemotherapy to reduce the incidence and severity of oxaliplatin-induced peripheral neuropathy. In 2004, Gamelin et al [14] published results of a retrospective study showing that calcium and magnesium infusion could decrease oxaliplatin-induced peripheral neuropathy. This study enrolled 161 advanced colorectal cancer patients who were randomized assigned into two groups, oxaliplatin-based chemotherapy with or without calcium and magnesium infusion. Oxaliplatin-induced peripheral neuropathy occurred in only 4% of patients in the group of with calcium and magnesium infusion versus 31% of patients who without calcium and magnesium infusion. So it was hypothesized that calcium and magnesium might be involved in the development of oxaliplatin-induced peripheral neuropathy.

Therefore, we describe a retrospective study in order to analyze whether serum calcium and magnesium concentration related with oxaliplatin-induced peripheral neuropathy.

Material and methods

Five hundred and sixty-one patients with colorectal cancer who were newly diagnosed and treated in *The First Hospital of Jiaxing*, Jiaxing, China, between 2010 and 2013. About 318 patients received adjuvant or first-line oxaliplatin-based chemotherapy (either FOLFOX6 or XELOX) were enrolled in this study. All patients had clear histopathological confirmation before treatment. Eligible patients were over 18 years and had life expectancy of more than 9 weeks, Karnofsky performance score ≥70, no previous history of peripheral neuropathy, no chemotherapy and radiotherapy before and adequate hepatic, renal and bone marrow function. Three hundred and eighteen blood samples were obtained before initiation of chemotherapy. All patients provided informed consent prior to undergoing chemotherapy. Detailed information about patient's characteristics and tumor histopathology was collected retrospectively from the medical records.

232 patients received modified FOLFOX-6 regimens every two weeks, oxaliplatin 85 mg/m^2 and L-leucovorin 400 mg/m^2 given intravenously on the first day, followed by 5-fluorouracil 4000 mg/m^2 as an intravenous bolus and then 2400 mg/m^2 as 46 hour infusion. XELOX schedules (86 patients) consisted of OXA 130 mg/m^2 infusion on day 1 plus oral capecitabine for 2 weeks in a 3-week cycle. Dose adjustments of oxaliplatin were done as other studies described [15]. The oxaliplatin dose was reduced by 30% for persisting paresthesias or dysesthesia, and omitted if neurological signs were associated with functional impairment. No prophylactic or symptomatic treatment was administered for neurotoxicity during treatment.

The oxaliplatin-induced peripheral neuropathy was graded by using version 3 of the National Cancer Institute's Common Toxicity Criteria (NCI-CTC v3) [16]. We designed a questionnaire based on NCI-CTC v3. There were eleven most common neurological symptoms related with acute oxaliplatin-induced peripheral neuropathy. The severity of acute neurotoxicity was

Table 1. Patients' characteristics (n=318)

Variables	Case (n, %)
Age (mean ± SD, y)	60.2±8.7
Sex	
Male	198 (62.2)
Female	120 (37.8)
Type of chemotherapy	
FOLFOX 4	232 (73.0)
XELOX	86 (27.0)
Disease setting	
Adjuvant	246 (77.4)
Palliative	72 (22.6)
Median cumulative doses of oxaliplatin	1066 (800-1988)
Smoking status	
Never	92 (28.9)
Ever/current	226 (71.1)
Alcohol status	
Never	166 (52.2)
Ever/current	152 (47.8)
Serum calcium concentration	
Mean ± SD, mmol/L	2.37±0.24
≤2.50 mmol/L	208 (65.4)
>2.50 mmol/L	110 (34.6)
Serum magnesium concentration	
Mean ± SD, mmol/L	0.90±0.07
<0.76 mmol/L	116 (36.5)
0.76-0.84 mmol/L	150 (47.2)
>0.84 mmol/L	52 (16.4)

graded as 0 (no toxicity), 1 (1-2 symptoms), 2 (3-4 symptoms), 3 (5-8 symptoms) and 4 (9-11 symptoms) [17]. All the neurological assessment performed at the initiation of the treatment and repeated 6 courses (oxaliplatin planned dose, 510 mg/m^2) and 12 courses (oxaliplatin planned dose, 1020 mg/m^2) of the FOLFOX6 schedule and after 4 courses (oxaliplatin dose, 520 mg/m^2) and 8 courses (oxaliplatin dose, 1040 mg/m^2) of the XELOX schedule [16].

Statistical analysis

Serum calcium and magnesium concentration was analyzed as a continuous variable and a categorical variable after grouping by normal levels and high levels. The association between clinicopathological variables and severity of acute oxaliplatin-induced peripheral neuropathy was evaluated using unconditional logistic regression analysis. All tests were two-sides, and significance was set at P<0.05. All statistical calculations were performed with SPSS 17.0 for Windows (Chicago, IL).

Results

A total of 318 colorectal cancer patients were enrolled in this study. The demographics and clinical characteristics of the patients are summarized in **Table 1** (The detail information can be found in Supplementary Data). The study population had a median age of 60.5 years (range: 38-79 years). A total of 226 patients (71.1%) had experience of smoking, and 152 (47.8%) of drinking alcohol. Acute oxaliplatin-induced peripheral neuropathy was occurred in 151 of 318 patients (47.5%). The severity of the acute oxaliplatin-induced peripheral neuropathy was graded as grade 1 in 50 patients (15.7%), grade 2 in 48 patients (15.1%) and grade 3 in 53 patients (16.7%). No patients experienced grade 4 peripheral neuropathy.

The median of serum calcium and magnesium concentration in all patients were 2.33 mmol/L (range: 1.78-3.98 mmol/L) and 0.81 mmol/L (range: 0.69-1.15 mmol/L). A total of 110 patients (34.6%) had high serum calcium concentration and 208 patients (65.4%) had lower concentration. Serum magnesium concentration was divided into three levels according to the previous study [18]: lowest group, <0.76 mmol/L; middle group, 0.76 to 0.84 mmol/L; highest group, 0.84 mmol/L. A total of 116 patients (36.5%) were in the lowest group of magnesium concentration, 150 patients (47.2%) in the middle group and 52 patients (16.4%) were in the highest group.

The median number of symptoms was four symptoms (range: 1-8 symptoms). The acute oxaliplatin-induced peripheral neuropathy was diagnosed in 151 of 318 patients (47.5%). The acute oxaliplatin-induced peripheral neuropathy was graded as 1 in 50 patients (15.7%), grade 2 in 48 patients (15.1%), and grade 3 in 53 patients (16.7%). None was diagnosed as grade 4.

Then, the acute oxaliplatin-induced peripheral neuropathy with grade 0 and grade 1 was

Table 2. Association of clinicopathological variables and Oxaliplatin induced peripheral neurotoxicity

Variables	Peripheral neurotoxicity		OR (95% CI)	P
	Grade 0-1 (n, %)	Grade 2-3 (n, %)		
SEX				
Female	164 (66.4)	83 (33.6)	1 (Ref)	0.190
Male	53 (74.6)	18 (25.4)	0.671 (0.370-1.218)	
Age				
<65	152 (68.5)	70 (31.5)	1 (Ref)	0.894
≥65	65 (67.7)	31 (32.3)	1.036 (0.620-1.730)	
Chemotherapy				
FOLFOX4	155 (68.8)	77 (33.2)	1 (Ref)	0.369
XELOX	62 (72.1)	24 (27.9)	0.779 (0.452-1.343)	
Cumulative dose of Oxaliplatin				
<1036 mg	147 (73.9)	52 (26.1)	1 (Ref)	0.006
≥1036 mg	70 (58.8)	49 (41.2)	1.979 (1.221-3.208)	
Smoking status				
Never	67 (72.8)	25 (27.2)	1 (Ref)	0.554
Ever/current	150 (66.4)	76 (33.6)	1.185 (0.675-2.082)	
Alcohol status				
Never	121 (72.9)	45 (27.1)	1 (Ref)	0.112
Ever/current	96 (63.2)	56 (36.8)	1.498 (0.910-2.465)	
Serum calcium concentration				
≤2.50 mmol/L	140 (67.3)	68 (32.7)	1 (Ref)	0.624
>2.50 mmol/L	77 (70.8)	33 (30.0)	0.882 (0.535-1.455)	
Serum magnesium concentration				
≥0.76 mmol/L	148 (73.3)	54 (26.7)	1 (Ref)	0.012
<0.76 mmol/L	69 (59.5)	47 (40.5)	1.867 (1.151-3.030)	
BMI				
≤21.3	112 (71.3)	45 (28.7)	1 (Ref)	0.153
>21.3	105 (65.2)	56 (34.8)	0.753 (0.469-1.210)	
Hemoglobin				
≤13.0	120 (72.3)	46 (27.7)	1 (Ref)	0.106
>13.0	97 (63.8)	55 (36.2)	0.676 (0.421-1.086)	

regard as a mild group, and grade 2 and grade 3 were regarded as severe group. The univariate logistic regression analysis (**Table 2**) indicated that serum magnesium concentration was an independent predictor for the acute oxaliplatin-induced peripheral neuropathy. Patients with lower serum magnesium concentration (<0.76 mmol/L) had an elevated risk of severe peripheral neuropathy compared to those patients with higher serum magnesium concentration (≥0.76 mmol/L). The hazard ratio was 1.867 (95% confidence interval [CI] 1.151-3.030). The severity of the acute oxaliplatin-induced peripheral neuropathy was also related with the cumulative dose of oxaliplatin (hazard ratio: 1.979, 95% CI: 1.221-3.208). Association between the peripheral neuropathy and sex, age, chemotherapy regimen, smoke and drinking failed to reach significance. Furthermore, serum calcium concentration was not related with the severity of the acute oxaliplatin-induced peripheral neuropathy (P>0.05).

Discussion

Oxaliplatin is commonly used as the standard therapy in adjuvant and palliative chemotherapy. However, the toxicity of oxaliplatin is often reported. The oxaliplatin induced peripheral neuropathy can decrease not only the quality of life of patients but also cause dose reduction and even treatment suspension. In this study,

we have found that pre-treatment serum magnesium concentration linked with the oxaliplatin-induced peripheral neuropathy. Serum magnesium concentration might serve as a marker to predict the subgroups of patients at high risk of acute peripheral neuropathy that could receive alternative chemothepeutic regimens.

It is commonly accepted that the acute oxaliplatin-induced peripheral neuropathy is caused by a dysfunction of nodal axonal voltage-gated channels, probably the calcium-dependent channels. This effect is mainly caused by the oxalate chelating effect on both Ca2+ and Mg2+ which could interfere with channel kinetics and reduce the overall Na+ current. Sensory axonal is damaged with reducing amplitude of the sensory nerve action potentials in the patients received oxalipaltin-base chemotherapy [19, 20]. Repetitive compound muscle action potentials and neuromyotonic discharges were observed in the first 24-48 hour following oxaliplatin infusion, and all these abnormalities could be resolve during 3 weeks [21].

Magnesium, modulates vasomotor tone, peripheral blood flow and blood pressure, exerts several beneficial effects on vascular endothelium and function [22]. Amighi J et al suggested that low serum magnesium concentration may be association with neurological disease [18]. The study performed by Feng P et al revealed that low serum magnesium level was associated with increased risk of short-term acute ischemic stroke [23]. In our present study, lower serum magnesium concentration was related with higher risk of the acute oxaliplatin-induced peripheral neuropathy. The mechanisms by which lower serum magnesium concentration may increase risk of peripheral neuropathy in the patients with colorectal cancer have not been well elucidated. First of all, lower level of serum magnesium may accelerate neurological events by promoting inflammation and oxidative modification. Magnesium deficiency may increases circulating levels of cytokines, which triggers oxidative response in endothelial cells [24]. Secondly, serum magnesium concentration was inversely related with von Willebrand factor. In previous study' report, elevated von Willebrand factor was associated with deteriorating nerve function [25]. Furthermore, serum magnesium could bind to adenosine triphosphate, which expression would be decreased after nerve injury [26].

To date, the excellent strategies to minimize the acute oxaliplatin-induced peripheral neuropathy is lacking. The supplement calcium/magnesium infusions might be effective in reducing some forms of neurotoxicity [15]. However, there are still not clearly data from powered prospective randomized clinical studies that the relationship between Ca/Mg infusions and the antitumor efficacy.

In summary, it is important to identify patients at high risk of developing the acute oxaliplatin-induced peripheral neuropathy. Pretreatment serum magnesium concentration is likely to be a predicting factor for the neurological events. Lower serum magnesium concentration was associated with higher risk of the acute oxaliplatin-induced peripheral neuropathy. However, more and larger prospective studies are still needed to confirm this result.

Disclosure of conflict of interest

None.

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