RESEARCH ARTICLE

Effects of Analgecine on Oxaliplatin-Induced Neurotoxicity in Patients with Gastrointestinal Cancer

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Abstract

Background: As the third generation of platinum-based antineoplastic agent aginst gastrointestinal cancer, oxaliplatin is considered to be associated with severe sensory neurotoxicity. Acorrding to previous studies, vitaminE, intravenous Ca/Mg and glutamine may partly reduce the incidence and severity of oxaliplatin-induced neurotoxicity. The aim of this study was to investigate the safety and efficacy of analgecine for preventing oxaliplatin-induced neurotoxicity in the patients with gastrointestinal tumors. Method: In this study, patients undergoing oxaliplatin-based chemotherapy were assigned to analgecine (experimental) group or control group. Analgecine 6ml was administered once a day for seven days from the day of oxaliplatin treatment. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; version 3) was used to evaluate oxaliplatin-induced neurotoxicity. The incidence rates and grade of neurotoxicity of patients were assessed before and during (after four and eight cycles) treatment. Results: Totally, 82 patients were enrolled in this study, 42 in experimental group and 40 in control group. The occurrence of each grade neurotoxicity in the experimental group was significantly lower than that in control group. The overall occurrence rate was 31% vs 55% (*P*=0.043) after 4 cycles and 52% vs 75% (*P*=0.050) after 8 cycles. Conclusion: Analgecine appears could be effective in reducing oxaliplatin-induced neurotoxicity and be applicated for patients with gastrointestinal tumors who would be treated with oxaliplatin-based chemotherapy.

Keywords: Analgecine - oxaliplatin-induced neurotoxicity

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Introduction

The incidence and mortality rates of gastrointestinal carcinoma, including gastric and colorectal cancers, are still high in china. Among there, colorectal cancer is the third most commonly cancer in males and the second in females, with over 1.2 million new cancer cases and 608, 700 deaths estimated to occurred in 2008 (Wu et al., 2014). Gastric cancer is also a leading cause of cancer-related deaths, with the highest incidence in Korea, Japan and China (Liu et al., 2014). Regarding about that, oxaliplatin-based chemotherapy is a crucial regimens in both adjuvant and palliative settings for patients with gastrointestinal cancer, e.g., FOLFOX (Wang et al., 2007; Axel et al., 2010). Neurotoxicity is the main dose-limiting side effect of oxaliplatin-based chemotherapy, in case of grade III-IV neurotoxicity, dose reductions and interruption of treatment should be considered. It was reported that oxaliplatin-induced peripheral neurotoxicity is varying from 82% to 98%, and severe events occur in 10% to 20% of patients (Toru et al., 2013). The neurotoxicity of oxaliplatin is demonstrated in two distinct forms: acute and chronic. The formor includes transient symptoms, e.g., cold related paresthesia, dysesthsia or jaw stiffness, and muscle cramps. The latter causes numbness and tingling, affacting hands and feet, and vibration sensation (Axel et al., 2010; Cath et al., 2013). Various kinds of regimens have been tested to control the neurotoxicity of oxaliplatin, e.g., vitaminE, intravenous Ca/Mg and GM1 (Ganglioside-monosialic acid) (Lisa et al., 2011; Axel et al., 2010; Zhu et al., 2013). However, the treatment effect of these regimens were dissatisfied. Therefore, there is an urgent need to develope new medications to relieve oxaliplatin-induced neurotoxicity.

Analgecine (Extracts from Rabbit Skin Inflamed by Vaccinia Virus for Injection) is a biological agent with neurotropism. It has shown therapeutic effects for the control of neuropathic pain, especially in patients with diabetes mellitus, by playing an important role in improving peripheral circulation, anti-allergic reaction, and repairing cellular damage (Li et al., 2009). The possible mechnism of analgecine is considered as follows: first, directly affact hypothalamus to regulate the activities of neuroendocrine and cellular automaticity, consequently relieve the symptomes of numbness; second, improving peripheral circulation by regulating autonomic nerves, thus recovering peripheral circulation disorders (Li et al., 2009; Fu et al., 2010). The aim of this study was to assess the safety and efficacy of analgecine in controlling the oxaliplatin-induced neurotoxicity.

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Materials and Methods

Eligiblility criteria

Patients were eligible in this clinical trial if they had histologically or cytologically confirmed gastrointestinal tumors and were scheduled to receive oxaliplatin-based adjuvant or palliative chemotherapy in Jiangsu Cancer Hospital and Research Institute. All eligible patients were required to have a good performance status (ECOG 0-2), life expectancy 6months, routine blood test performed 0 to 3 days before chemotherapy and normal hematopoietic function as evidenced by white blood cell count 3000/ul and platelet count 100000/ul, normal hepatic function test (aspartate aminotransaminase and alanine aminotransferase less than 1.5 times of the upper limit of normal values), renal function test (serum total bilirubin<1.5mg/dl and creatinine<1.5mg/dl). Exclusion criteria included history of alcoholic intoxication, diabetes, central nervous system metastasis, preexisting neuropathy from any case, had received pior treatment with neurotoxic chemotherapy or radiation therapy, and patients who were pregnant or nursing.

Neurotoxicity Evaluation

The incidence rates of neurotoxicity in this study were assessed at baseline and respectively after four and eight cycles of treatment, the grade of neurotoxicity was determined according to The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; version 3), which describe the four grades as follows: grade 1, loss of deep tendon reflxes or paresthesia, including tingling, but not interfering with function; grade 2, objective sensory alteration or paresthesia, including tingling, interfering with function, but not interfering with activities of daily living (ADL); grade 3, sensory alteration or paresthesia interfering with ADL; and grade4, permanent sensory losses that are disabling (Toru et al., 2013).

Statistical analysis

All dates in this study were processed using the Stata.11 software. The rates of neurotoxicity were calculated for each grade and compared between experimental and control group. The difference in the grades of neurotoxicity between two groups was compared using Chi-square test and $P<0.05$ defined as statistically significant.

Table 1. Patients Characteristics

Characteristics	Experimental group N=42 (%)	Control group N=40 (%)	*P* Value
Age			
50	29 (72%)	28 (77%)	0.817
50	13 (28%)	12 (23%)	
Gender			
Male	14 (38%)	13 (27%)	1.021
Female	28 (62%)	27 (73%)	
Performance status			
0	23 (56%)	24 (67%)	0.727
1,2	19 (44%)	16 (33%)	
Primary tumor			
Gastric timor	15 (31%)	12 (23%)	0.378
Colorectal tumor	27 (69%)	28 (77%)	
Tumor stage			
Locally advanced	14 (28%)	15 (40%)	0.550
Metastatic	28 (72%)	25 (60%)	

Results

In this study, 82 patients with gastrointestinal cancer enrolled from Jiangsu Cancer Hospital &Research Institute and divided into two groups, the experimental group (N=42), and the control group group (N=40).

As showed in Table 1, there were no significant difference between two groups in age, gender, performance status, primary tumor and tumor stage (Chi-square test). In our study, the incidence rates and grading scales of neurotoxicity in two groups were compared by Chi-square test. As showed in Table 2, after four cycles of treatment, the ocurrance rates of grade 1, 2, 3, 4 neurotoxicity were16.7%, 9.5% , 4.8% , 0, in experimental group respectively, while those in control group were25%, 15%, 12.5%, 0.5%, respectively. The overall incidence of occurance of neurotoxicity in experimental group (31%) was significantly lower than that in control group (55%), (p=0.043). Moreover, after eight cycles of treatment, the incidence rates of grade1 neurotoxicity in experimental and control group was 28.6% versus 25%, that of grade 2 was 16.7% versus 20%, which of grade 3 was 9.5% versus 17.5%, and grade 4 was 2.3% versus 12.5%, respectively. Totally, 52% patients in experimental group experienced neurotoxicity while that in control group was 75%, (52%versus75%, $P=0.050$). The proportion of patients who received analgecine experienced sighificant lower neurotoxicity than those who did not.

Discussion

Oxaliplatin is one of the crucial components of chemotherapeutic regimens in the treatment of patients with gastrointestinal cancer. However, the marjority

Table 2. The Occurrence and Grade of Neurotoxicity Between Experimental Group and Control Group after Four, Eight Cycles

Group	N	0 (%)	I (%)	II (%)	III (%)	IV (%)	ocurrance rate	*P* value
After four weeks								0.043
Control group	40	18 (45)	10 (25)	5 (15)	5 (12.5)	2 (0.5)	55%	
Experimental group	42	29 (69)	7 (16.7)	4 (9.5)	2 (4.8)	0 (0)	31%	
After eight weeks								0.050
Control group	40	10 (25)	10 (25)	8 (20)	7 (17.5)	5 (12.5)	75%	
Experimental group	42	18 (42.9)	12 (28.6)	7 (16.7)	4 (9.5)	1 (2.3)	52%	

of patients receiving oxaliplatin-based chemotherapy developing different grades of neurotoxicity, which can seriously affact the quality of life, even leads to dose-reduction or interruption of chemotherapy regimens, consequently limiting treatment effect.

Analgecine is a kind of purified non-protein physiologically substances obtained by inflammation and immune reaction, which has a wide spectrum of pharmacologic actions (Liu et al., 2005). Analgecine exerts its neuroprotective function by affacting hypothalamus to regulate the activities of neuroendocrine as well as cellular automaticity, and through regulating autonomic nervous, consequently improving peripheral circulation. Clinical trials and animal studies have indicated that analgecine supplementation has remarkable efficacy in controlling chronic pain, nerve damage, numbness and other symptoms of nervous system (Fu et al., 2010; Li et al., 2009). Analgecine supplementation may relieve neurologic symptoms of diabetic peripheral neuropathy, which may also exert its curative effect in ameliorating the postherpetic neuralgia and relieving facial neuritis in combination with glucocorticoid (Liu et al., 2009; Li et al., 2011). Many other neuroprotective agents have been proved to be effective in reducing the neurotoxicity induced by oxaliplatin-based chemotherapy. Ca/Mg infusion has been supposed to have remit oxaliplatin associated neurotoxicity (Axel et al., 2010). However, there are still controversies in this field among oncologists. The CONcePT trial, which assigned patients to receive Ca/Mg infusion prior or after oxaliplatin, seemed active against acute neurotoxicity at first. Unfortunately, this trial was prematurely aborted because of a low tumor response rate in the Ca/Mg arm. However, another French NEUROXA study demonstrated equivalent antitumor activity in patients receiving Ca/Mg and those receiving placebo (Game et al., 2005). In another prospective randomized, double-blind, placebo-controlled study, the antidepressant drug venlafaxine, has been reported to remarkably reduce the symptoms of oxaliplatin-induced neuropathy. Unfortunately, the occurance of grade 1-2 vomitting was observed more frequently in patients who recived venlafaxine (Toru et al., 2013; Dura et al., 2012). Compared with venlafaxine, analgecine has reassured security. Because analgecine is a kind of non-protein physiologically substances exerted from rabbit skin inflamed by vaccinia virus for injection, only working for the injuried body and having no adverse effects on normal physiological function. According to the testified studies, the security of analgecine has no between-group differences compared with the placebos (Liu et al., 2009). What's more, analgecine is a kind of easily administered agents which is more convenient for the patients, with another additional advantage of the cost of analgecine is affordable for the marjority of patients.

In our study, the overall incidence rate of neurotoxicity in experimental group was 31% after 4 cycles and 52% after 8 cycles, while that in control group was 55% and 75% respectively. The grade of neurotoxicity in experimental group was notably lower than that in control group after 4 cycles. There was significant difference in the occurrence rate of oxaliplatin-induced neurotoxicity between two groups after 4 cycles (P=0.043). However, there was no adequate statistical power detected after 8 cycles (P=0.050). We speculated that this phenomenon was due to the modest sample size, single centre design and the chronic, cumulative oxaliplatin-induced neurotoxicity.

In summary, our date confirmd that analgecine could be effective in delaying the occurrence of oxaliplatin-induced neurotoxicity and reducing the grade of neurotoxicity. Larger prospective studies are needed to verify the clinical application of analgecine in treatment of oxaliplatin associated neurotoxicity.

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