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 against gastrointestinal cancer, oxaliplatin is considered to be associated with severe sensory neurotoxicity. According to previous studies, vitamin E, 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 to be effective in reducing oxaliplatin-induced neurotoxicity and be applicable for patients with gastrointestinal tumors who would be treated with oxaliplatin-based chemotherapy.

Keywords: Analgecine - oxaliplatin-induced neurotoxicity

Introduction

The incidence and mortality rates of gastrointestinal carcinoma, including gastric and colorectal cancers, are still high in China. Among them, 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 former includes transient symptoms, e.g., cold related paresthesia, dysesthesia or jaw stiffness, and muscle cramps. The latter causes numbness and tingling, affecting 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., vitamin E, 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 urgent need to develop 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 mechanism of analgecine is considered as follows: first, directly affect hypothalamus to regulate the activities of neuroendocrine and cellular automaticity, consequently relieve the symptoms 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.
Materials and Methods

Eligibility 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 6 months, 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 cause, had received prior 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 Common Terminology Criteria for Adverse Events (CTCAE; version 3), which describe the four grades as follows: grade 1, loss of deep tendon reflexes or paresthesia, 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 grade 4, 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.

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 (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 occurrence rates of grade 1, 2, 3, 4 neurotoxicity were 6.7%, 9.5%, 4.8%, 0%, in experimental group respectively, while those in control group were 25%, 15%, 12.5%, 0.5%, respectively. The overall incidence of occurrence 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% versus 75%, P=0.050). The proportion of patients who received analgescine experienced significant 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 majorit
of patients receiving oxaliplatin-based chemotherapy developing different grades of neurotoxicity, which can seriously affect 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 affecting 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 oncolgists. 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 occurrence of grade 1-2 vomiting 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 injured 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 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 confirmed 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.

Acknowledgements

Dr. Xin-En Huang is supported by Traditional Chinese Medicine Scientific Research Project (LZ11091) and Jiangsu Province fourth stage “333 high- level Personnel Training Project” third levels of talent cultivating object.

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