European Review for Medical and Pharmacological Sciences 2019; 23: 5441-5448

Effects of compound porcine cerebroside and ganglioside on neurotoxicity caused by oxaliplatin chemotherapy: preliminary results

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Abstract. – OBJECTIVE: Oxaliplatin has shown good anti-tumour activity in the treatment of tumours involving the digestive system. However, its application is limited because of severe neurotoxicity in some patients. The purpose of this study was to evaluate whether compound porcine cerebroside and ganglioside (CPCG) can reduce or prevent oxaliplatin-induced neurotoxicity.

PATIENTS AND METHODS: Patients with digestive system tumour who received oxaliplatin-based chemotherapy were retrospectively divided into experimental and control groups according to the receipt of CPCG during chemotherapy. Adverse events at the end of each chemotherapy cycle were recorded. We compared the incidence of neurotoxicity between the two groups and graded the neurotoxicity symptoms using the Common Terminology Criteria for Adverse Events v5.0.

RESULTS: The study included 115 patients (experimental group, 57; control group, 58). The number of chemotherapy cycles (6.65 *vs.* 6.41, p=0.540) and oxaliplatin dose (775.92 mg/m^2 *vs.* 724.20 mg/m^2, p=0.250) were comparable between the two groups. All patients developed grade 1 to 3 neurotoxicity; grade 4–5 neurotoxicity was not observed. The incidence of neurotoxicity and the probability of advanced neurotoxicity were significantly lower in the experimental group than in the control group (p<0.05). After a 6 to 18 months follow-up, the two groups showed no significant differences in the chemotherapy response and recurrence rate (p=0.846).

CONCLUSIONS: CPCG reduces oxaliplatin-induced neurotoxicity without reducing the efficacy of oxaliplatin-based regimens; thus, it can be used for preventing oxaliplatin-induced neurotoxicity in patients with cancer.

Key Words:
Cerebroside, Ganglioside, Neurotoxicity syndromes, Oxaliplatin, Retrospective study.

Introduction

Oxaliplatin has shown good anti-tumour activity in the treatment of tumours involving the digestive system[1-3]. However, its application is limited because of severe neurotoxicity in some patients[3,4]. Oxaliplatin-mediated neurotoxicity affects the peripheral nerves and is classified as acute or chronic. Acute neurotoxicity includes coldness-induced paraesthesia and painful dysaesthesia, with a high prevalence rate of 80% to 90%[4-6]. The mechanism underlying acute neurotoxicity involves effects on voltage-gated sodium channels residing on the membranes of nerve fibres. In contrast, chronic neurotoxicity develops when oxaliplatin attacks the nuclear DNA of neurons and leads to platinum-DNA adducts; this damage leads to changes in the neuronal morphology and neuronal damage or death. The prevalence of severe chronic neurotoxicity is 15% to 20%[4-6].

Currently, there is no effective treatment for oxaliplatin-induced neurotoxic side effects. Clinically, preventive treatments such as the infusion of calcium or magnesium ions for sodium channel blockade are often used to minimise the neurotoxicity. However, infusions increase the clearance rate of oxaliplatin and reduce its anti-tumour effect[7,8]. Studies have suggested that glutathione can prevent the accumulation of platinum in the dorsal root ganglion (DRG); therefore, it is useful for preventing and treating oxaliplatin-induced chronic neurotoxicity[9,10]. Amifostine is also useful for paclitaxel- and cisplatin-induced neurotoxicity[11]. However, there is no clear evidence of its role in the prevention and treatment of neurotoxicity caused by oxaliplatin. Although venlafaxine has been shown to reduce the acute neurotoxicity of oxaliplatin[12], studies have suggested that it may affect oxidative stress and reduce the treatment efficacy[13]. More-

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over, L-acetyl-carnitine (LAC) was found to be a promising agent against platinum-induced neurotoxicity; however, its use is limited to patients receiving taxane-free chemotherapy[14].

Ganglioside-monosialic acid (GM1) reduces neurotoxicity caused by oxaliplatin without affecting its anti-tumour efficacy[15,16]. It is formed from glycosphingolipids and monosialic acid and belongs to a specific class of gangliosides[17]. Gangliosides can restore the activity of sodium-potassium ATPase and calcium-magnesium ATPase and interact with nerve growth factor (NGF) to promote neural regeneration and repair. In addition, gangliosides can reduce neuronal damage by inhibiting lipid peroxidation and eliminating oxygen-free radicals[17-19]. The present study used a compound preparation including gangliosides, a micro-molecule polypeptide, and hypoxanthine. As described above, gangliosides, including GM1, play an important role in nerve generation, development, differentiation, and restoration. Micro-molecule polypeptides are widely involved in the synthesis and transport of various substances and play roles in the production and transmission of signalling substances in the human body and provision of energy for life activities, particularly to the brain and nerve tissues[20]. Hypoxanthine improves the body's substance and energy metabolism, accelerates the reconstruction of damaged tissues, and promotes the recovery of normal physiological functions in pathological cells and hypoxic tissues[21,22].

Compound porcine cerebroside and ganglioside (CPCG; Jilin Buchang Pharmaceutical Corp. LTD, Tonghua city, Jilin province, PR China) has been applied to nerve injury-related diseases involving the brain and spinal cord as well as cases involving peripheral nerve injuries. It has been shown to protect the nerves and minimise nerve damage and degeneration. The purpose of this study was to evaluate the effects of CPCG on oxaliplatin-induced neurotoxicity. To this end, we included 115 patients who received oxaliplatin-based chemotherapy with (experimental group) or without (control group) CPCG therapy and compared the prevalence and severity of neurotoxicity between the two groups.

Patients and Methods

We retrospectively reviewed data for 115 patients with digestive system tumours who received oxaliplatin-based chemotherapy between September 2017 and September 2018 at the Beijing Friendship Hospital, Capital Medical University. The inclusion criteria were as follows: age, 18–75 years, with an expected survival time of >3 months; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; presence of malignant tumours treated with a chemotherapy regimen containing oxaliplatin; normal routine blood test findings within 3 days before chemotherapy, with an absolute neutrophil count of >1.5 $\times 10^9$/L, platelet count of >80 $\times 10^9$/L, and haemoglobin level of >80 g/L; aspartate aminotransferase and alanine aminotransferase levels that were lower than twice the upper limit of normal; serum creatinine level that was lower than the upper limit of normal; and absence of neurotoxicity symptoms before treatment.

Chemotherapy was not performed if the patients had any serious systemic diseases or complications, severe malnutrition, or weight loss of more than 10% in the last month. Moreover, it was interrupted in the event of progressive disease or serious adverse reactions.

All 115 patients included in the study received chemotherapy containing oxaliplatin, including the following regimens.

XELOX = oxaliplatin (130 mg/m^2) on day 1 and capecitabine (1000 mg/m^2) twice daily on days 1–14, q21d.

SOX = oxaliplatin (130 mg/m^2) on day 1 and tegafur, gimeracil, and oteracil potassium (60 mg/m^2 for a body surface area of >1.4 m^2 or 40 mg/m^2 for a body surface area of <1.4 m^2) twice daily on days 1–14, q21d.

FOLFOX = oxaliplatin (85 mg/m^2) on day 1, fluorouracil (400 mg/m^2) as an intravenous bolus on day 1, fluorouracil (2400 mg/m^2) administered continuously for 46 h (intravenous) from days 1–3, and leucovorin (400 mg/m^2) on day 1, q14d.

The patients were divided into two groups depending on the use or non-use of CPCG therapy. The experimental group included patients who received an infusion of CPCG 10 mL (including gangliosides 2.4 mg, micro-molecule polypeptide 32 mg, and hypoxanthine 1.25 mg) 30 min before and 1 day after oxaliplatin infusion. The control group included patients who did not receive any neuroprotective therapy. The protocol of our study and the use of patient data were approved by the Ethics Committee of our institution.

All adverse events at the end of each chemotherapy cycle were recorded, and neurotoxicity, if present, was graded using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (US Department of Health and Human Services). The criteria was summarized as Table I.

Table I. Common Terminology Criteria for Adverse Events (CTCAE) v5.0 criteria used for grading oxaliplatin-induced neurotoxicity symptoms in 115 patients with cancer who received various oxaliplatin-containing chemotherapy regimens with or without CPCG therapy.

Standard setting unit	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	Asymptomatic	Moderate symptoms, and/or limiting instrumental ADL	Severe symptoms, and/or limiting self-care ADL	Life-threatening consequences and/or urgent intervention indicated	Death caused by neurotoxicity

ADL = activities of daily living; CPCG = compound porcine cerebroside and ganglioside.

The most severe grade among those for all recorded events was considered the final neurotoxicity grade for each patient.

All patients who receive neoadjuvant or palliative chemotherapy had measurable target lesions. Evaluations of clinical efficacy were performed after every two cycles of 21-day regimens or every three cycles of 14-day regimens. On the basis of the Response Evaluation Criteria In Solid Tumours (RECIST), clinical efficacy was categorized as follows: complete response (CR), defined as the disappearance of all visible lesions after chemotherapy; partial response (PR), defined as a reduction in the sum of the longest diameter (LD) of all target lesions by at least 30% relative to baseline; stable disease (SD), defined when the criteria for PR or PD were not met; and progressive disease (PD), defined as an increase of at least 20% in the minimum sum of LDs of all target lesions since the start of treatment, or the appearance of new lesions.

All data in this study were analyzed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). Chi-square or Fisher's exact tests were used to compare unordered categorical variables between the two groups. Measurement data were compared using Student's *t*-tests. Ordered categorical variables were compared using Mann–Whitney U tests. Neurotoxicity grades were compared between the two groups using ordinal logistic regression. A p-value of <0.05 was considered statistically significant.

Results

There were 57 and 58 patients in the experimental and control groups, respectively. Of the 115 patients, seven received neoadjuvant chemotherapy for gastric cancer, 27 received post-operative chemotherapy for gastric cancer, nine received neoadjuvant chemotherapy for colorectal cancer, 59 received post-operative chemotherapy for colorectal cancer, three received palliative chemotherapy for colorectal cancer, six received post-operative chemotherapy for duodenal cancer, and four received post-operative chemotherapy for cholangiocarcinoma. General and clinical characteristics of all patients are listed in Table II. There were no significant differences between groups in terms of the sex distribution, diagnosis and treatment goals, smoking history, alcohol consumption history, presence of hypertension, diabetes, and cardiovascular or cerebrovascular disease, chemotherapy regimen, and efficacy of chemotherapy (Table II). The patients were aged 26 to 74 years, with an average age of 57.97 years. The average age was 58.65 years in the experimental group and 57.29 years in the control group, with no significant difference (Table III). The number of chemotherapy cycles in the experimental group ranged from one to eight (average, 6.65), while the total oxaliplatin dose ranged from 117.65 to 1033.01 mg/m^2 (average, 775.92 mg/m^2). The number of chemotherapy cycles in the control group also ranged from one to eight (average, 6.41 cycles), while the total oxaliplatin dose ranged from 117.58 to 1021.05 mg/m^2 (average, 724.20 mg/m^2). There were no significant differences in the number of chemotherapy cycles and total oxaliplatin dose between the two groups (Table III).

Neurotoxic side effects were recorded after each chemotherapy cycle and before the start of the next cycle. All patients exhibited grade 1–3 neurotoxicity; grade 4–5 neurotoxicity was not observed in any patient. The incidences of neurotoxicity in the experimental and control groups were as follows: grade 1, 66.67% and 46.55%; grade 2, 22.81% and 32.76%; and grade 3, 10.53% and 20.69%, respectively. The overall incidence (grade 2–3) was significantly lower in the experimental group than in the control group (p=0.026, Mann–Whitney U test; Fig-

Table II. General information and clinical characteristics of 115 patients with cancer who received oxaliplatin-based chemotherapy regimens with (experimental group) or without (control group) CPCG therapy.

Groups		Experimental group		Control group		*p*-value
		n	%	n	%	
Sex	Male	32	56.14	37	63.79	0.402
	Female	25	43.86	21	36.21	
Diagnosis	Preoperative gastric cancer	3	5.26	4	6.90	0.198
	Postoperative gastric cancer	10	17.54	17	29.31	
	Preoperative colorectal cancer	6	10.53	3	5.17	
	Postoperative colorectal cancer	31	54.39	28	48.28	
	Colorectal cancer metastasis	0	0.00	3	5.17	
	Postoperative duodenal cancer	5	8.77	1	1.72	
	Postoperative cholangiocarcinoma	2	3.51	2	3.45	
Smoking	Yes	19	33.33	22	37.93	0.607
	No	38	66.67	36	62.07	
Alcohol	Yes	18	31.58	18	31.03	0.741
	No	39	68.42	40	68.97	
Hypertension	Yes	21	36.84	22	37.93	0.904
	No	36	63.16	36	62.07	
Diabetes	Yes	11	23.91	10	17.24	0.775
	No	46	80.70	48	82.76	
Cardiovascular or cerebrovascular disease	Yes	5	8.77	7	12.07	0.563
	No	52	91.23	51	87.93	
Chemotherapy regimen	SOX	16	28.07	23	39.66	0.219
	XELOX	40	70.18	35	60.34	
	FOLFOX	1	1.75	0	0.00	
Chemotherapy efficacy	CR	0	0.00	0	0.00	0.846
	PR	2	3.51	1	1.72	
	SD	5	8.77	5	8.62	
	PD	2	3.51	4	6.90	
	Adjuvant therapy	48	84.21	47	81.03	
	Recurrence	0	0.00	1	1.72	

CPCG = compound porcine cerebroside and ganglioside; XELOX = oxaliplatin/capecitabine; SOX = oxaliplatin/tegafur, gimeracil and oteracil potassium; FOLFOX = oxaliplatin/fluorouracil /leucovorin; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

ure 1). While the prevalence of severe neurotoxicity (grade 3) was significantly lower in the experimental group than in the control group (10.53% vs. 20.69%), that of mild neurotoxicity (grade 1) was significantly higher in the experimental group than in the control group (66.67% vs. 46.55%; Tables IV and V). There was a significant difference in the probability of neurotoxic side effects between the two groups, with the probability of advanced neurotoxicity being significantly lower in the experimental group than in the control group (p=0.027, ordinal logistic regression; Table IV). After 6 to 18 months of follow-up, the two groups showed no significant differences in the chemotherapy response and recurrence rate (p=0.846; Table II). One patient in the control group who underwent radical resection of sigmoid colon

Table III. Age, number of chemotherapy cycles, and total oxaliplatin dose for 115 patients with cancer who received oxaliplatin-based chemotherapy regimens with (experimental group) or without (control group) CPCG therapy.

Groups	Experimental group	Control group	*p*-value
Age	58.65	57.29	0.485
Number of chemotherapeutic cycles	6.65	6.41	0.540
Total oxaliplatin dose	775.92	724.20	0.250

CPCG = compound porcine cerebroside and ganglioside.

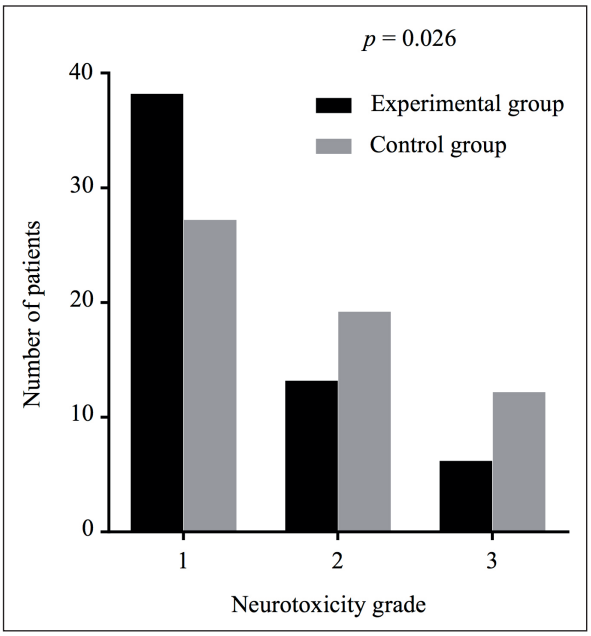

Figure 1. Comparison of neurotoxicity between cancer patients who received oxaliplatin-based chemotherapy with compound porcine cerebroside and ganglioside (CPCG) therapy (experimental group) and those who received the same chemotherapy without CPCG therapy (control group) total N=115).

cancer was found to have liver metastases at the end of eight cycles of the XELOX regimen. No tumour recurrence or metastasis was found throughout the follow-up period for the other patients who received post-operative chemotherapy.

In the experimental group, one patient developed severe vomiting and diarrhoea and refused to continue treatment after one cycle. In addition, one patient refused to continue treatment after six cycles and two patients who developed severe (grade IV) myelosuppression refused to continue after one cycle. In the control group, one patient refused to continue treatment after one cycle, one refused to continue after three cycles, one refused to continue after four cycles, and one refused to continue after five cycles because of severe neurotoxicity (hypogeusia, dizziness, insomnia). Furthermore, some patients in the control group discontinued chemotherapy because of severe complications: severe (grade IV) myelosuppression after one cycle (n = 1); grade III myelosuppression with severe vomiting after three cycles (n = 1); grade IV myelosuppression and severe thrombocytopenia after four cycles (n = 3); moderate dyspnea, severe dizziness, and grade III myelosuppression, necessitating a reduction in the oxaliplatin dosage twice until the fifth cycle, until it was no longer possible to reduce the dosage (n = 1); severe vomiting and myelosuppression after five cycles (n = 1); and grade IV myelosuppression after five cycles (n = 1).

Discussion

Neurotoxicity is a common adverse effect of oxaliplatin and associated with both single and cumulative doses of the drug[4-6]. It significantly reduces the patient's quality of life and results in the discontinuation of chemotherapy. This adverse effect frequently necessitates dose adjustment, which compromises the anti-tumour treatment[4]. Acute oxaliplatin-induced neurotoxicity is believed to be caused by over excitation of the peripheral nerves due to temporary inhibition of the activity of ion channels on nerve cells and increased sensitivity of the transient receptor potential (TRP) channels on sensory neurons. The mechanism underlying chronic neurotoxicity mediated by oxaliplatin is similar to that described for other platinum-based drugs, which involves an attack on the nuclear DNA of neurons, leading to platinum-DNA adducts. The platinum-DNA adducts formed by damage to the nuclear DNA of neurons cause mitochondrial dysfunction in neurons and apoptosis or death of DRG cells[5]. Drugs used against oxaliplatin-induced neurotoxicity include calcium ions, magnesium ions,

Table IV. Comparative ordinal logistic regression analysis of data pertaining to 115 patients with cancer who received oxaliplatin-based chemotherapy regimens with (experimental group) or without (control group) CPCG therapy.

		Regression co-efficient	SE	Wald	df	p-value	95% CI	
							Lower	Upper
Dependent variable	Grade = 1.00	−0.134	0.257	0.272	1	0.602	−0.637	0.369
	Grade = 2.00	1.335	0.296	20.281	1	0.000	0.754	1.915
Independent variable	Class = 1.00	−0.824	0.372	4.910	1	0.027	−1.553	−0.095
	Class = 2.00	0.000			0			

CPCG = compound porcine cerebroside and ganglioside; 95% CI = 95% confidence interval; df = degree of freedom; SE = standard error.

Table V. Prediction of the neurotoxicity grade in 115 patients with cancer who received oxaliplatin-based chemotherapy regimens with (experimental group) or without (control group) CPCG therapy.

		Neurotoxicity grade		
		1	2	3
Experimental group	Observed value	38	13	6
	Predictive value	37.96	13.14	5.90
	Predicative probability (%)	66.60	23.05	10.35
Control group	Observed value	27	19	12
	Predictive value	27.06	18.85	12.09
	Predicative probability (%)	46.65	32.50	20.84

CPCG = compound porcine cerebroside and ganglioside.

glutathione, amifostine, and venlafaxine, all of which have limited efficacy or affect the anti-tumour activity of oxaliplatin. GM1 has been shown to prevent or reduce oxaliplatin-induced neurological damage[15]. CPCG, which was used in our study, is a compound preparation including GM1. To our knowledge, no other study has assessed its usefulness for the prevention of oxaliplatin-mediated neurotoxicity.

CPCG includes a variety of gangliosides. GM1 is one of its components, in addition to others such as sialic acid, micro-molecule polypeptides, and hypoxanthine. GM1 and other gangliosides participate in functions of perception; transmission of intracellular and extracellular information; and cell identification, adhesion, growth, and differentiation[17-19]. Moreover, gangliosides function as receptors for certain neurotransmitters, hormones, viruses, and interferons and are involved in the differentiation, regeneration, and repair of neural tissues as well as the conduction of nerve impulses and intercellular recognition. In addition, they can accelerate the regeneration and repair of damaged nerve tissues, minimise the release of amino acids with excitotoxicity, and reduce cytotoxicity and angioedema[18,19]. Sialic acid is a neurotransmitter of cerebrosides and gangliosides. It plays a crucial role in facilitating brain tissue development and brain cognition and is an important nutrient that facilitates learning and cognition[23,24]. Micro-molecule polypeptides and amino acids are widely involved in the synthesis and transport of various substances including the production and transmission of signaling substances in the human body, providing energy for life activities, especially in the brain and in nerve tissues[21]. Hypoxanthine can improve the body's substance and energy metabolism, accelerate the recovery of damaged tissue, and promote physiological functions of pathological cells and tissues recovering from hypoxia[21,22].

In the present study, the prevalence of oxaliplatin-induced neurotoxicity, including severe neurotoxicity, was significantly lower in the experimental group than in the control group (p=0.026). Moreover, the neurotoxicity grade was significantly lower in the experimental group (p=0.027). These results suggest that the use of CPCG can significantly reduce the neurotoxicity of oxaliplatin. Previous studies have suggested that GM1 can prevent or reduce oxaliplatin-induced neurological damage. In a study of 120 patients randomly assigned to an experimental group (n = 60) treated with GM1 and a control group (n = 60), the prevalence of neural injury was lower in the experimental group (68.33%) than in the control group (78.33%). In addition, the prevalence of grade 3 neurotoxicity was significantly lower in the experimental group (8.33%) than in the control group (28.33%)[15]. The patterns for the overall prevalence of neurotoxicity and the incidence of grade 3 neurotoxicity in our study were consistent with those observed in the aforementioned study involving GM1 treatment[15]. However, because of different experimental designs, we cannot make direct comparisons between the two studies. A randomized controlled trial with a large sample size is required to compare the effects of the two drugs in terms of the prevention and alleviation of oxaliplatin-induced neurotoxicity.

Conclusions

We showed that CPCG can reduce the neurotoxicity caused by oxaliplatin and it is an effective

drug for the prevention of highly neurotoxic side effects caused by the drug. Moreover, this drug does not affect the efficacy of oxaliplatin-based chemotherapy regimens. Thus, it can be used for preventing oxaliplatin-induced neurotoxicity in patients with cancer.

Acknowledgements

This work was supported by a grant from the National Key Technologies R&D Program (Grant No. 2015BAI13B09).

Conflict of Interests

The Authors declare that they have no conflict of interests.

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