ORIGINAL ARTICLE

Thalidomide for Control Delayed Vomiting in Cancer Patients Receiving Chemotherapy

Zhengxiang Han[1], Xuan Sun[1], Guan Jiang[2] and Xiuping Du[1]

ABSTRACT

Objective: To explore the efficacy and safety of thalidomide for the treatment of delayed vomiting, induced by chemotherapy in cancer patients.

Study Design: Randomized, double-blind controlled study.

Place and Duration of Study: The Oncology Department of Affiliated Hospital of Xuzhou Medical University, Jiangsu Xuzhou, China, from January 2012 to January 2014.

Methodology: A total of 78 cancer patients, who had delayed vomiting observed from 24 hours to 1 week after chemotherapy, were included in the study. Patients were divided in a treatment group (40 patients, 51.28%) and a control group (38 patients, 48.71%). The treatment group received thalidomide at an oral dose of 100 mg per night; 50 mg was added daily up to a dose of 200 mg per night, if the curative effect was suboptimal and the medicine was tolerated. Both the treatment and the control groups received a drip of 10 mg azasetron 30 minutes before chemotherapy. The control group only proportions of antiemetic effects and adverse reactions were compared using the χ^2 test. Antiemetic effects and adverse reactions were assessed from Odds Ratios (OR) with 95% Confidence Intervals(95% CI).

Results: The effective control rate of delayed vomiting in the treatment group was significantly higher than that in the control group (χ^2=5.174, p=0.023). No significant difference was found between the two groups in other adverse effects of chemotherapy. Karnofsky scores or the overall self-evaluation of the patients (p>0.05).

Conclusion: Thalidomide can effectively control the delayed vomiting of cancer patients receiving chemotherapy and the adverse reactions of the agent can be tolerated.

Key Words: *Thalidomide. Chemotherapy. Delayed vomiting.*

INTRODUCTION

Thalidomide (TLD) is a derivative of glutamic acid. It was initially used as a sedative agent to treat vomiting in pregnancy, but was withdrawn from the market as it caused a serious adverse reaction of fetal seal, like short limb deformity. In recent years, some studies have shown that TLD can inhibit the activation and proliferation of the capillary microvascular bed, suppress vascular endothelial cell apoptosis, and regulate T-lymphocyte immunocompetence.[1] So it may play a role in resisting tumor angiogenesis, inhibiting tumor cell growth and regulating immunity.[2] TLD is now widely used in research for the treatment of various tumors.

Delayed vomiting, the main adverse reaction of platinum containing chemotherapeutic agents, often occurs 24 - 48 hours after chemotherapy and can sometimes last for 5 - 7 days. If this adverse reaction is not treated in time, it will seriously affect the patient's quality of life, make the patient have a strong psychological fear of chemotherapy, and even affect the process of chemotherapy. In previous experiments, the authors confirmed that TLD had a certain soothing effect on the delayed vomiting reaction caused by cisplatin in rats.[3] However, to the best of the authors' knowledge, no report exists about its effect on delayed vomiting, evoked by clinical chemotherapy in oncology patients.

The aim of the current study was to explore the effect of TLD on delayed vomiting induced by chemotherapy in patients with malignant tumors.

METHODOLOGY

Cancer patients, who underwent chemotherapy in the Oncology Department from January 2012 to January 2014, were included in the study. Patients were included in the study based on computed tomography/magnetic resonance imaging, pathological histology and/or cytology and other special inspections, the patient had been diagnosed with a malignant tumor; the patient had received platinum-based chemotherapy for at least one cycle and had suffered from delayed vomiting, and the same patient had been treated with the same agents for two cycles of chemotherapy; there was no contraindication for the use of chemotherapy or, antiemetic agents and TLD; the Karnofsky score of performance status was not less than 60 points; and the patient and his/her family had known the state of illness before chemotherapy, had good compliance and had

Department of Oncology[1] / Dermatology[2], Affiliated Hospital of Xuzhou Medical College, Xuzhou, Jiangsu 221000, P.R. China.

Correspondence: Dr. Zhengxiang Han, Department of Oncology, Affiliated Hospital of Xuzhou Medical College, Xuzhou, Jiangsu 221000, P.R. China.
E-mail: dr.guanjiang@gmail.com

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signed informed consent forms for treatment on a voluntary basis. Patients were excluded, if they had vomiting due to a malignant brain tumor metastasis, intracranial hypertension, gastrointestinal obstruction, psychogenic vomiting or other reasons; had nausea, vomiting or treatment with antiemetic drugs 24 hours before chemotherapy; had with severe hepatic or renal function lesions, uncontrolled severe infection or another uncontrolled serious internal medical disease; patients taking other antiemetic agents or sedatives; patients who were allergic to or intolerant of TLD; and pregnant or lactating women.

All the patients included in the groups received platinum-drug-based combined chemotherapy. For lung cancer patients, a two-drug-combined NP (vinorelbine, cisplatin), TP (paclitaxel, cisplatin), GP (gemcitabine, cisplatin) or EP (etoposide, cisplatin) scheme based on DDP (cisplatin) or NDP (nedaplatin) was adopted; for gastric cancer patients, an ECF (epirubicin, cisplatin, 5-fluorouracil) or DCF (docetaxel, cisplatin, 5-fluorouracil) scheme was adopted; for ovarian cancer patients, a TP scheme was adopted. They were randomly double-blind allocated to a treatment group and a control group. In the treatment group, TLD (25 mg x 4 pills po qN) was taken 1 day before chemotherapy. If the patient had poor curative effect and could tolerate the adverse reactions, 50mg was added per night up to a dose of 200 mg/day. However, if the patient could not tolerate the adverse reactions after the increased dose, the original dose was maintained. In addition, azasetron (10 mg/day) was used in a slow intravenous drip 30 minutes before the chemotherapy. In the control group, azasetron (10 mg/day) alone was used in a slow intravenous drip 30 minutes before the chemotherapy. Curative effect was evaluated after two cycles.

Adverse reactions of vomiting were evaluated as per the National Cancer Institute-Common Terminology Criteria Adverse Events Version 4.0 (NCI-CTCAEV 4.0) standard. Classes of vomiting were as follows: class 1 (fully controlled): 1 - 2 episodes (separated by 5 minutes) in 24 hours; class 2 (partly controlled): 3 - 5 episodes (separated by 5 minutes) in 24 hours; class 3 (slightly controlled): ≥6 episodes (separated by 5 minutes) in 24 hours; tube feeding, TPN or hospitalisation indicated; class 4 (inefficient): life-threatening consequences; urgent intervention indicated; class 5 (inefficient): death. Effective control rate of vomiting = (number of fully controlled patients + number of partly controlled patients)/total number of patients x 100%. The condition of patients regarding vomiting was observed from 24 hours to 1 week after using DDP or NDP.

Adverse reactions of chemotherapy were evaluated in accordance with the World Health Organization Acute and Sub-acute Adverse Reaction Grading System of Anticancer Drugs (0-IV).[4] The scoring standard was formulated according to Karnofsky scoring. Compared with the score before treatment, a score that increased or decreased by over 10 points after treatment meant improvement or deterioration, whereas a score that increased or decreased by less than 10 points after treatment meant being stable.

The content of patient self-evaluation forms after treatment was divided into three classes: accepted, partly accepted and not accepted. Data are expressed as the mean ± standard deviation, and were analysed by statistical software (SPSS Base 16.0 for Windows; SPSS, Inc., Chicago, IL, USA) using the χ^2 test, as appropriate. P <0.05 was considered to indicate a statistically significant difference.

RESULTS

The patients were 26 - 75 years of age, with an average age of 50.3 ±12.5 years, and included 45 (57.69%) male patients and 33 (42.31%) female patients. Forty (51.28%) had lung cancer, 25 (32.05%) had gastric cancer, and 13 (16.67%) had ovarian cancer; 29 (37.18%) patients were in Stage I-II and 49 (62.82%) patients were in Stage III-IV. The treatment group contained 40 patients aged 29 - 75 years, with an average age of 50.4 ±12.3 years, and included 23 (57.50%) male and 17 (42.50%) female patients. In the treatment group, 21 (52.50%) patients had lung cancer, 12 (30.00%) had gastric cancer, and 7 (17.50%) had ovarian cancer; 16 (40.00%) patients were in stage I-II and 24 (60.00%) were in stage III-IV. The control group contained 38 patients aged 26 - 73 years, with an average age of 50.2 ±12.9 years, including 22 (57.89%) male and 16 (42.11%) female patients. In this group, 19 (50.00%) patients had lung cancer, 13 (34.21%) had gastric cancer, and 6 (15.79%) had ovarian cancer; 13 (34.21%) patients were in stage I-II and 25 (65.79%) were in stage III-IV. There was no significant difference in the gender (p=0.972), age (p=0.926), type of tumor (p=0.963), and course of disease (p=0.603) of the patients between the two groups (p >0.05).

In the treatment group, delayed vomiting was fully or partly controlled in 35 patients, with an effective control rate of 87.50%. In the control group, the delayed vomiting was fully or partly controlled in 25 patients, with an effective control rate of 65.79%. The difference in effective control rates between the two groups was statistically significant (χ^2=5.174, p=0.023; Table I).

There was no significant difference in other adverse reactions of chemotherapy between the two groups (p>0.05; Table II). Moreover, based upon statistical analysis of the change in Karnofsky scores, the difference between the two groups was not significant (p>0.05; Table III). In addition, there is no significant difference in the overall self-evaluation of the patients between the two groups (p >0.05; Table III).

Table I: Comparison of the effective control rate of delayed vomiting in the two groups.

Group	Number of patients	Class of vomiting				Number of fully controlled patients + partly controlled patients	Number of slightly controlled patients + inefficient patients	Effective rate (%)	χ^2	p
		Class 1	Class 2	Class 3	Class 4-5					
Treatment group	40 (51.28)	28 (70.00)	7 (17.50)	4 (10.00)	1 (2.50)	35 (87.50)	5 (12.50)	87.50 (35/40)	5.174	0.023
Control group	38 (48.72)	19 (50.00)	6 (15.79)	9 (23.68)	4 (10.53)	25 (65.79)	13 (34.21)	65.79 (25/38)		

Table II: Comparison of other adverse reactions to chemotherapy in the two groups.

Adverse reactions	Treatment group			Control group			χ^2	p
	Class I-IV	Class I-II (%)	Class III-IV (%)	Class I-IV	Class I-II (%)	Class III-IV (%)		
Reduced hemoglobin	17	16 (94.12)	1 (5.88)	18	17 (94.44)	1 (5.56)	0.187	0.666
Leukopenia	28	24 (85.71)	4 (14.29)	26	23 (88.46)	3 (11.54)	0.023	0.880
Thrombocytopenia	16	13 (81.25)	3 (18.75)	13	11 (84.62)	2 (15.38)	0.280	0.597
Constipation	24	19 (79.17)	5 (20.83)	19	15 (78.95)	4 (21.05)	0.788	0.375
Diarrhea	9	9 (100)	0	7	7 (100)	0	0.199	0.656
Hepatic and renal function lesion	8	8 (100)	0	6	6 (100)	0	0.235	0.628
Anaphylaxis	7	7 (100)	0	5	5 (100)	0	0.282	0.595
Mucositis	6	6 (100)	0	5	5 (100)	0	0.055	0.815
Alopecia	11	9 (81.82)	2 (18.18)	9	8 (88.89)	1 (11.11)	0.149	0.700
Peripheral neuropathy	5	5 (100)	0	4	4 (100)	0	0.074	0.785
Thrombus	1	1 (100)	0	0	0	0	0.962	0.327

Table III: Comparison of Karnofsky score change between the two groups (left) and comparison in the overall self-evaluation of patients between the two groups (right).

Karnofsky score						Group	The overall self-evaluation of patients					
p	χ^2	Worse	Stable	Improved	Number of patients		Number of patients	Accept	Partly Accept	Not Accept	χ^2	p
0.124	4.169	2 (5.00)	12 (30.00)	26 (65.00)	40	Treatment group	40	25 (62.50)	14 (35.00)	1 (2.50)	3.368	0.186
		6 (15.79)	15 (39.47)	17 (44.74)	38	Control group	38	23 (60.52)	10 (26.32)	5 (13.16)		

DISCUSSION

Chemotherapy is an important means of treating malignant tumors; however, the adverse reactions caused by chemotherapy can make patients fear chemotherapy, thus affecting their compliance.[5] For example, nausea and vomiting can not only affect quality of life but also increase fear of chemotherapy. The nausea and vomiting induced by chemotherapy is of two types: the acute type (0 - 24 hours) and the delayed type (24 - 120 hours). Owing to the application of 5-HT_3 receptor antagonists, the effective control rate of acute nausea and vomiting is 90%, but delayed nausea and vomiting is difficult to control and tends to be underestimated clinically.[6,7] Delayed vomiting is a common adverse effect of platinum chemotherapy; the incidence rate of delayed vomiting arising from DDP, in particular, can reach as high as 60 - 90%.[8] This symptom, if not controlled effectively, may lead to patients becoming intolerant to chemotherapy, exacerbate adverse reactions, and even delay cancer treatment.[6,9]

TLD introduced in the late 1950s and was given to pregnant women because of its moderate sedative and inhibiting effects on morning sickness.[10] Unfortunately, it led to severe neonatal congenital abnormality, and was thereby withdrawn. In recent years, research on TLD has been found to have potential anti-tumor effects, such as resisting proliferation of malignant tumor cells, inhibiting tumor angiogenesis, resisting tumor metastasis, regulating immunity, and correcting the cachexia status of cancer patients.[11-13] Therefore, at present, it has been widely used in the treatment of malignant tumors.

The current study shows that treatment with TLD significantly improves the effective control rate of delayed vomiting, caused by chemotherapy in patients with malignant tumors. Moreover, there was no significant difference in other adverse reactions of chemotherapy between the groups. Although TLD can induce constipation and the frequency of constipation in the treatment group was higher than that in the control group, the difference between groups was not significant. In addition, Karnofsky scores were not significantly different between the two groups, suggesting that patients can tolerate the adverse effects caused by TLD. Finally, the overall self-evaluation of the patients was

also not significantly different between the two groups, revealing that it has good treatment compliance and might, therefore, improve adherence to chemotherapy.

The reasons why TLD improves delayed vomiting induced by chemotherapy have been studied. Firstly, Hesketh *et al*.[14] proved that in the delayed vomiting reaction, the bonding point of substance P and its ligand, the Neurokinin 1 (NK1) receptor, plays a dominant role, and any change can lead to a change in vomiting signal transduction efficiency. Furthermore, the previous study by the present authors has shown that in rats TLD can alleviate pica behavior and soothe delayed vomiting induced by DDP, and the antiemetic effect may be related to a change in the level of the neurotransmitter substance P in the medulla oblongata and gastric antrum tissue.[3] Secondly, during chemotherapy, patients are prone to fear and anxiety, and TLD has a sedative effect. A previous study has shown that TLD is able to improve patients' sleep in perichemotherapy,[5] and it can be speculated that TLD is likely to improve the delayed vomiting reaction by easing tension.

CONCLUSION

TLD can effectively improve delayed vomiting induced by chemotherapy in patients with malignant tumors. TLD might, therefore, improve the quality of life of patients undergoing chemotherapy, which further expands the potential clinical indications of TLD in anti-tumor treatment.

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