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Thalidomide for prevention of chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy

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RESEARCH

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ABSTRACT

Background

Antiemetic guidelines recommend co-administration of agents to maximize the prevention of chemotherapy-induced nausea and vomiting (CINV), however, the control of delayed CINV is still not satisfactory. The purpose of this study was to evaluate the effectiveness and safety of thalidomide in the prevention of CINV.

Methods

Of 89 patients enrolled, 83 chemotherapy-naïve patients receiving highly emetogenic chemotherapy (cisplatin 70mg/m^2) were randomized into two groups: standard therapy group (ondansetron on day 1, metoclopramide and dexamethasone on days one to five) and thalidomide group (in addition to standard emesis prevention, patients received oral 100mg thalidomide on days one to five). Patients recorded nausea and vomiting episodes in a diary. The primary end point was the efficacy of thalidomide in controlling vomiting and nausea on days one to five post cisplatin, and the secondary end point was the safety of the thalidomide.

Results

No significant differences of complete response rates (no emesis, no use of rescue therapy and no nausea) were observed between the two groups, while the percentages of patients with complete response of delayed vomiting on day four and day five were higher in the thalidomide group, furthermore, the complete response rate of delayed nausea for thalidomide group and standard therapy group showed significant differences. Thalidomide group showed a similar safety profile as standard emesis prevention group.

Conclusion

Addition of thalidomide was generally well tolerated and improved prevention of CINV in patients receiving cisplatin-based chemotherapy to some degree, especially for delayed nausea.

Key Words

Thalidomide, highly emetogenic, CINV

What this study adds:

1. What is known about this subject?

The control of cisplatin-induced delayed nausea and vomiting is not adequate.

2. What new information is offered in this study?

Addition of thalidomide improved prevention of delayed nausea in patients receiving cisplatin-based chemotherapy.

3. What are the implications for research, policy, or practice?

Larger randomized, multi-centre trials are indicated to confirm the value of thalidomide in the control of delayed CINV.

Background

Chemotherapy-induced nausea and vomiting (CINV) is one of the most common and distressing adverse effect of chemotherapy, which can result in acid-base imbalances, nutrient depletion and significantly affect the patient's

quality of life.[1] During the last 20 years, great progress has been made in controlling CINV due to the introduction of some new antiemetic agents. According to NCCN Guidelines for antiemetic medication, prophylactic antiemetic regimens (5-HT3 receptor antagonist, NK1 receptor antagonist and dexamethasone) can decrease the incidence and severity of vomiting in the patients receiving highly emetogenic chemotherapy,[2] however, the control of delayed CINV is still not satisfactory and nausea is much harder to control than vomiting.[3–5]

Thalidomide, an oral agent with immunomodulatory and antiangiogenic properties, was first introduced to the market in 1956 as a non-barbiturate hypnotic to prevent morning sickness in pregnancy. In the early 1960s, thalidomide was withdrawn from the market after it caused children to be born with teratogenic deformities. Since that time, new clinical investigations demonstrated its action against inflammatory diseases and cancer.[6,7] Thalidomide was officially approved as a therapeutic agent in 2007 for treating erythema nodosum leprosum and multiple myeloma.[8,9]However, its sedative and antiemetic activities had been ignored. Due to its serious teratogenic effects, the prescription of thalidomide in the USA is under stringent monitoring by the System for Thalidomide Education and Prescribing Safety program.[6] If patients use effective contraception during the treatment the risk of foetal abnormalities could be avoided. To our knowledge, there is no study that has evaluated the efficacy of thalidomide in the prevention of CINV caused by cisplatin. Thus the prospective study was conducted to evaluate whether or not thalidomide can enhance protection against CINV when combined with 5-HT3 receptor antagonist, dexamethasone and metoclopramide in patients receiving their first cisplatin-based chemotherapy.

Method

Patients

This was a randomized, double-blind study. Eligible patients with histologically or cytologically confirmed malignancies were≥18 years, naïve to chemotherapy and scheduled to receive the chemotherapy including cisplatin (70mg/m^2). The other inclusion criteria were as follows: (1) KPS (Karnofsky performance status, KPS) ≥70, (2) neutrophil counts ≥1.5×10^9/L, platelets ≥100×10^9/L, total bilirubin ≤1.5×the upper limit of normal, and serum creatinine ≤1.25×the upper limit of normal. The primary exclusion criteria included severe cardiac or pulmonary disease, clinically significant neuromuscular disorder, history of thrombosis, use of any other antiemetic agents within 24 hours before chemotherapy, radiation therapy to the abdomen or pelvis within one month before chemotherapy or between study days one to five, and pregnancy or lactation. Fertile patients had to be using effective contraception. The primary tumours included gastric cancer, oesophageal cancer, lung cancer, cervical cancer and head and neck cancer. The protocol was approved by ethical review committees, and the study followed good clinical practice, from the Declaration of Helsinki principles, local laws and regulations. Written informed consent for participation in the study was obtained from participants.

Treatment

The chemotherapy regimens included cisplatin/5-flurouracil (DF regimen for head and neck, gastric, oesophageal or cervical cancer patients), cisplatin/etoposide (EP regimen for lung cancer patients). As the agent of high emetogenicity, cisplatin (70mg/m^2) was permitted intravenously 30 minutes only on day one, with the start of infusion designated as 0 hour. In addition to cisplatin, etoposide (80mg/m^2) and 5-fluorouracil (750mg/m^2) were given on days one to five, every three weeks. Patients were randomly assigned to received either standard therapy group (ondansetron 8mg intravenously on day one, metoclopramide 10mg orally three times daily and dexamethasone 4.5mg orally once daily on days one to five) or thalidomide group (additional thalidomide was given as 100mg once daily on days one to five). Placebo capsules matching thalidomide were used to maintain blinding. Patients could not receive additional antiemetic agents between days one to five unless they were given as a rescue therapy including intravenously dexamethasone 5mg, metoclopramide 10mg, or ondansetron 8mg.

Assessment

The primary efficacy end point for the study was the complete response (CR) which was calculated as the percentage of patients with no emesis, no use of rescue therapy and no nausea including CR during the acute (0～24h) and delayed (25～120h) phases. The overall phase was defined as 0～120h. From the start of the chemotherapy on day 1 through the morning of day 6, patients recorded daily episodes of CINV, including the information about the timing and number of emetic episode, severity of nausea. An emetic episode was defined as one or a sequence of occurrences of vomiting or retches. Severities of nausea and the other adverse effects were evaluated using NCI-CTCAE V2.0 (National Cancer Institute Common Terminology Criteria for Adverse Event V2.0, NCI-CTCAE V2.0) (Table 1).[10]The secondary end point was the safety of the thalidomide.

Statistical Analysis

Chi-square or Fisher exact test was used for statistical analysis. A two-sided $p<0.05$ was considered statistically significant. Statistical analyses were performed using the SPSS ver.12.0.

Results

Patients

A total of 89 patients were randomized into the study from April 2014 to October 2014. Six patients did not receive the protocol-required chemotherapy and thalidomide, therefore 83 patients represented the efficacy and safety analysis set populations. Thalidomide group had 40 patients and standard therapy group had 43 patients. The distributions of patients by gender, age, KPS, primary cancer diagnoses and the chemotherapy regimens were similar between the two groups. The clinical characteristics are shown in Table 2.

Efficacy

The CR defined as no emesis, no use of rescue therapy and no nausea. A trend of increased response was observed in the thalidomide group, although this trend wasn't seen as statistically significant (72.7 per cent *vs.* 64.1 per cent, p=0.076). The CR rates of vomiting in the acute phase between the two groups were similar (93 per cent *vs.* 91 per cent, p=0.767). The CR rates of vomiting in thalidomide regimen on days 4–5 were significantly higher than those in standard therapy group (93 per cent *vs.* 72 per cent, p=0.034; 95 per cent *vs.* 79 per cent, p=0.032), while there were no differences of the CR rates during the overall phase between the groups (85 per cent *vs.* 72 per cent, p=0.153). In comparison for the delayed nausea, the CR rates for thalidomide group were significantly superior to standard therapy on day two to five, and CR rate was also significantly higher for thalidomide group during the overall phase(75 per cent *vs.* 51 per cent, p=0.024). The percentages of patients in each group reaching CR on vomiting and nausea were shown in Tables 3 and 4.

Tolerability

All patients who received at least one dose of thalidomide were included in the analyses for safety. The overall incidence, type and intensity of treatment-related adverse events were comparable between the two groups (Table 5). Generally, the majority reported adverse effects of mild/moderate intensity. Only two patients (two per cent) experienced grade 3 adverse event (neutropenia). Besides vomiting and nausea, the most common adverse events were neutropenia, anorexia, constipation and fatigue. The side effects that seemed to show an increase following the thalidomide therapy were constipation (28 per cent), somnolence (13 per cent) and peripheral neuropathy (5 per cent), while no statistical differences were observed about the incidences of constipation and peripheral neuropathy. We observed that the incidence of anorexia for thalidomide group was significantly lower than that of standard group (15 per cent *vs.* 40 per cent, p=0.012) (Table 6). There were no treatment-related adverse events leading to discontinuation.

Discussion

Despite substantial recent progress, about 20～30 per cent of patients receiving highly emetogenic chemotherapy will have episodes of vomiting.[11,12] Although palonosetron and aprepitant have been shown to be effective in preventing acute and delayed vomiting,[13,14] patients are still troubled by nausea. Furthermore, both drugs are too expensive for Chinese patients to be widely used. Complete prevention remains challenging because individual factors should be considered e.g., physical condition of the patient, tumour status and so refining the antiemetic measures may be necessary.

The sedative effect of thalidomide led to its use initially as a drug for treating nausea and vomiting in pregnant women. The clinical value of thalidomide in controlling CINV should be evaluated. Liu et al.[15] found that thalidomide improved the prevention of mFOLFOX7 regimen-induced gastrointestinal side effects, while oxaliplatin and 5-fluorouracil were categorized as moderate and low risk group for CINV, respectively. Therefore, we conducted the randomized prospective trial to evaluate the effectiveness of thalidomide in controlling the CINV caused by the highly emetogenic agent—cisplatin.

The acute phase is usually defined as starting with the first dose of the antineoplastic and continuing until 24 hours after administration of the last dose of antineoplastic of the regimen. The delayed phase is usually defined as starting at the end of the acute phase and continuing for three to seven days. Compared with cisplatin, the other agents used in the regimens, such as 5-fluorouracil and etoposide were less emetogenic, so in the study the acute and delayed phase was defined based on the usage of cisplatin.

In our study, the rates of vomiting were lower in thalidomide group on days four to five, which suggested that addition of thalidomide may improve the protection of delayed vomiting to some degree. In thalidomide group, rates of delayed nausea were obviously lower than those in standard therapy group on days two through five. The result showed that addition of thalidomide could prevent delayed

nausea satisfactorily.

The doses of thalidomide ranged from 300mg/d to 800mg/d when it was used for cancer therapy.[16,17] In our study, the thalidomide dose of 100mg /d was shown to be effective in controlling CINV and tolerated for the patients. No thalidomide-associated grade 3～4 adverse effects were observed. The main thalidomide-associated adverse events were grade 1～2 constipation, somnolence and peripheral neuropathy, however, the incidences were lower than those reported previously which could be related to the relatively lower dosage of thalidomide.[15] The safety profile did not suggest that thalidomide regimen enhanced the toxicity of chemotherapy. However, the optimal dosage of thalidomide in controlling of CINV was uncertain.

Thalidomide has been used for treatment of cancer cachexia by downregulating TNF-αand IL-6 production, improving appetite and increasing body weight.[18,19] In the present study, although the patients received a short thalidomide treatment, we also observed that thalidomide decreased the incidence of anorexia by 25 per cent.

Metoclopramide is recommended for low emetogenic chemotherapy regimens in NCCN Antiemesis Guidelines,[20] however, in this study the proportions of no emetic episodes(91 per cent for acute phase, 72 per cent for overall phase) and no nausea(84 per cent for acute phase, 51 per cent for overall phase)in the standard therapy group (combination of metoclopramide, dexamethasone and ondansetron) were similar to those reported previously with palonosetron or aprepitant,[21-23] and no patient experienced dystonic reactions. It was suggested that metoclopramide may be also suitable for controlling highly emetogenic chemotherapy-induced nausea and vomiting.

Conclusion

In conclusion, our study demonstrated that the addition of thalidomide to a regimen of metoclopramide, dexamethasone and ondansetron result in superior prevention of CINV in patients receiving cisplatin-based highly emetogenic chemotherapy to some degree, especially for delayed nausea, and the thalidomide regimen was generally well tolerated. It is an effective and safe antiemetic. Additional larger randomized, multi- centre trials are indicated to confirm the value and the optimal dosage of thalidomide in the control of delayed CINV.

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PEER REVIEW

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CONFLICTS OF INTEREST

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ETHICS COMMITTEE APPROVAL

Ethics Committee approval was obtained from the Institutional Ethics Committee of The Second Affiliated Hospital of Anhui Medical University prior to the commencement of the study.

Table 1: Assessment of nausea and anorexia

	Nause	Anorexia
1	slight nausea but no influence on food intake	intake of a little solid food
2	obvious nausea, influence on food intake	liquid diet
3	serious nausea, no intake of food	no food intake

Table 2: Patients' characteristics of the two groups

	Thalidomide (n=40)	Standard therapy (n=43)
Sex		
Male	28	29
Female	12	14
Median age, years(range)	57(42-75)	54(44-74)
KPS		
90-100	31	33
70-80	9	10
Primary tumour		
gastric	8	6
oesophageal	6	8
lung	9	12
cervical	11	12
head and neck	6	5

Table 3: CR rates of two groups on vomiting

	Thalidomide (n=40)	Standard therapy (n=43)	*p*
Day 1	37(93%)	39(91%)	0.767
Day 2	35(87%)	38(88%)	0.902
Day 3	34(85%)	35(81%)	0.661
Day 4	37(93%)	31(72%)	0.034
Day 5	38(95%)	34(79%)	0.032
Overall	34(85%)	31(72%)	0.153

Table 4: CR rates of two groups on nausea

	Thalidomide (n=40)	Standard therapy (n=43)	*p*
Day 1	34(85%)	36(84%)	0.872
Day 2	34(85%)	28(65%)	0.037
Day 3	32(80%)	24(56%)	0.018
Day 4	35(88%)	27(63%)	0.009
Day 5	34(85%)	25(58%)	0.006
Overall	30(75%)	22(51%)	0.024

Table 5: Summary of most common adverse events

	Thalidomide (n=40)	**Standard therapy (n=43)**	***p***
At least one adverse event	36(90%)	38(88%)	0.811
Serious adverse event	1(3%)	1(2%)	0.958
Most common adverse event			
neutropenia	22(55%)	24(56%)	0.940
anorexia	6(15%)	17(40%)	0.012
constipation	11(28%)	9(21%)	0.484
fatigue	8(20%)	9(21%)	0.916
somnolence	5(13%)	1(2.3%)	0.025
peripheral neuropathy	2(5%)	1(2.3%)	0.247

Table 6: Efficacy of both groups on anorexia

Group	**Anorexia**				**%**	***p***
	grade 0	**grade 1**	**grade 2**	**grade 3**		
Thalidomide (n=40)	34	6	0	0	15%	0.012
Standard (n=43)	26	10	7	0	40%	