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Efficacy and safety of ondansetron orally soluble pellicle for preventing moderate- to high-emetic risk chemotherapy-induced nausea and vomiting

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Abstract

Objective Ondansetron orally soluble pellicle can serve as an alternative option for preventing nausea and vomiting in patients who receive chemotherapy. However, there is a lack of clinical evidence regarding ondansetron. This study aimed to explore the efficacy and safety of ondansetron in patients with malignant tumours who received chemotherapy drugs with a moderate-to-high emetic risk.

Methods In total, 163 patients with malignant tumours received 24 mg of ondansetron via orally soluble pellicles at 30 min before chemotherapy (8 mg each time for three consecutive administrations). The incidence rates of nausea and vomiting in the three days after chemotherapy were recorded.

Results Regarding the effect of ondansetron on vomiting, the complete response (zero episodes of vomiting), major response (1–2 episodes of vomiting), minor response (3–5 episodes of vomiting), and failure (> 5 episodes of vomiting) rates were 96.9%, 1.2%, 1.2%, and 0%, respectively. The major efficacy rate for vomiting (complete response + major response rates) was 98.1%. Moreover, 96.3% of patients did not experience nausea, 2.5% of patients experienced mild nausea, 1.2% of patients experienced moderate nausea, and 0.0% of patients experienced severe nausea. The major efficacy rate for nausea (no nausea) was 96.3%. Age > 65 years was negatively associated with major efficacy for vomiting, and a chemotherapy regimen involving cisplatin was negatively associated with major efficacy for nausea. A total of 42 (25.8%) patients experienced adverse events. The most common adverse events were elevated levels of alanine transaminase (6.7%), elevated levels of aspartate transaminase (3.7%), fatigue (3.7%), and cough (2.5%).

Conclusion Ondansetron orally soluble pellicle shows good antiemetic efficacy and high safety in patients with malignant tumours who receive chemotherapy drugs with a moderate-to-high emetic risk.

Keywords Ondansetron orally soluble pellicle, Moderate-to-high emetic risk chemotherapy, Nausea and vomiting, Efficacy, Safety

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Introduction

Cancer is one of the most severe threats to human health, resulting in approximately 10.0 million deaths annually [1]. Despite recent progress in targeted therapies and immune therapies, chemotherapy remains the fundamental treatment option for cancer patients [2–5]. Chemotherapy drugs effectively eliminate tumour cells and can be administered as treatments at advanced stages or perioperatively [6, 7]. However, chemotherapy can induce several adverse events, such as cardiac toxicity, hepatic dysfunction, myeloid suppression, fatigue, and nausea and vomiting [5]. Among these adverse events, nausea and vomiting are quite common and can strongly affect the quality of life of patients receiving chemotherapy [8]. The guidelines issued by Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology (MASCC/ESMO) have classified the antineoplastic agents into minimal, low, moderate, or high emetic risk, in which moderate-to-high indicates emetic risk in above 30% of patients [8]. For patients receiving chemotherapy drugs with a moderate-to-high emetic risk, antiemetics such as neurokinin 1 (NK1) receptor antagonists, 5-hydroxytryptamine-3 (5-HT3) receptor antagonists, and steroids should be administered [9]. However, not all patients respond to these antiemetics.

Ondansetron is a 5-HT3 receptor antagonist that has been widely applied to prevent nausea and vomiting induced by chemotherapy drugs that have a moderate-to-high emetic risk [10]. Ondansetron can be administered via intramuscular injection, intravenous injection, or oral tablets; the latter approach may prevent adverse events induced by injection, such as infection and bleeding [11]. However, some patients may have difficulty swallowing tablets after chemotherapy, especially due to the risk of nausea and vomiting [12, 13]. An orally soluble form of ondansetron could solve this issue. The drug would dissolve rapidly in the mouth, with or without water, thereby providing an appropriate option for patients with swallowing difficulty [14]. Notably, a previous study revealed that orally soluble ondansetron is bioequivalent to ondansetron oral tablets in healthy adults [15]. However, the efficacy and safety of orally soluble ondansetron for preventing chemotherapy-induced nausea and vomiting still lack sufficient clinical evidence.

This study aimed to evaluate the efficacy and safety of ondansetron orally soluble pellicles for preventing nausea and vomiting in patients with malignant tumours who received chemotherapy drugs with a moderate-to-high emetic risk.

Methods

Patients

The inclusion criteria for the patients were as follows: (i) diagnosed with a malignant tumour by histological or cytological methods; (ii) aged ≥ 18 years; (iii) received chemotherapy drugs with a moderate-to-high emetic risk (shown in detail in Supplementary Table 1); (iv) had a life expectancy > 6 months; and (v) had an Eastern Cooperative Oncology Group performance status (ECOG PS) score ≤ 2. The exclusion criteria for patients were as follows: (i) diseases that caused nausea or vomiting unrelated to chemotherapy, such as gastrointestinal or neurological disorders; (ii) intractable vomiting caused by intestinal obstruction, active infections, or other conditions; (iii) nausea or vomiting within 24 h before treatment; (iv) allergic to ondansetron; or (v) pregnancy. The study received permission from the Ethics Committee of Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology and adhered the Declaration of Helsinki. Patients provided informed consent.

Treatment and assessment

This study did not involve changing the chemotherapy regimens (based on the patients' situations and wishes, as well as the physician's recommendations) of the enrolled patients. The chemotherapy regimens that the patient received included GP (gemcitabine and cisplatin), TP (Taxol and cisplatin), EP (etoposide and cisplatin), PP (pemetrexed and cisplatin), DF (dacarbazine and fluorouracil) or CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone). The patients received ondansetron via orally soluble pellicles (Aiqisu®, Jiangsu Hengrui Medicine Co., Ltd., China) to prevent nausea and vomiting after receiving chemotherapy drugs with a moderate-to-high emetic risk. Patients were given 24 mg of ondansetron via orally soluble pellicles (8 mg each time for three consecutive administrations) at 30 min before chemotherapy.

Patients were asked to record incidences of nausea and vomiting for three days after chemotherapy. Vomiting was categorized into four grades: complete response was defined as zero episodes of vomiting; major response was defined as 1–2 episodes of vomiting; minor response was defined as 3–5 episodes of vomiting; and failure was defined as more than 5 episodes of vomiting. The major efficacy of vomiting was defined as a complete response plus a major response. Nausea was categorized into four grades: no nausea was defined as no nausea at all; mild nausea was defined as nausea that did not interfere with daily life; moderate nausea was defined as nausea that interfered with daily life; and severe nausea was defined as bedridden with nausea. The major efficacy of nausea was defined as the absence of nausea. Adverse events were also recorded.

Statistical analysis

SPSS 25.0 (IBM, USA) was used to perform statistical analyses. The baseline characteristics of the patients are presented as the means ± standard deviations (SDs) or frequencies (percentages). The incidences of nausea, vomiting, and adverse events of the patients are presented as numbers (percentages). Mann–Whitney U test was used for the comparison of major efficacy of patients with different ECOG PS, TNM stage, and number of involved organs with metastases. Fisher's exact test was used for the comparison of major efficacy of patients with different age, gender, smoke, drink, hypertension, diabetes mellitus, coronary artery disease, tumour types, brain metastasis, emetic risk, chemotherapy drugs, NKI receptor antagonists' combination, and steroid drugs combination. *P* values less than 0.05 were considered significantly different.

Table 1 Baseline characteristics

Baseline characteristics	Patients (*N* = 163)
Age (years), mean ± SD	60.8 ± 0.8
Male, n (%)	134 (82.2)
Smoke, n (%)	104 (63.8)
Drink, n (%)	80 (49.0)
Hypertension, n (%)	34 (20.9)
Diabetes mellitus, n (%)	10 (6.1)
Coronary artery disease, n (%)	9 (5.5)
ECOG PS, n (%)	
0	7 (4.3)
1	152 (93.2)
2	4 (2.5)
Tumor types, n (%)	
Lung	95 (58.3)
Gastrointestinal	37 (22.7)
Head and neck	16 (9.8)
Breast cancer	9 (5.5)
Other*	6 (3.7)
TNM stage#, n (%)	
I	3 (2.0)
II	15 (10.0)
III	46 (30.7)
IV	86 (57.3)
Number of involved organs with metastases, n (%)	
0	81 (49.7)
1	37 (22.7)
2	21 (12.9)
3	22 (13.5)
4	2 (1.2)
Brain metastasis, n (%)	16 (9.9)
Emetic risk, n (%)	
Moderate	130 (79.8)
High	33 (20.2)
Chemotherapy drugs, n (%)	
Nedaplatin	89 (54.6)
CDDP	20 (12.3)
Oxaliplatin	20 (12.3)
Carboplatin	10 (6.1)
Other	24 (14.7)
NK1 receptor antagonists' combination, n (%)	
Yes	153 (93.9)
No	10 (6.1)
Steroid drugs combination, n (%)	
Yes	153 (93.9)
No	10 (6.1)

*, other tumour type included thymic cancer, pancreatic cancer, ovarian cancer, and liver cancer. #, only 150 cases had available data for analysis. SD, standard deviation; ECOG PS, eastern cooperative oncology group performance status; TNM, tumor-node-metastasis; CDDP, cis-Dichlorodiamineplatinum; NK1, neurokinin 1

Results

Patient characteristics

A total of 163 patients with malignant tumours who received chemotherapy drugs with a moderate-to-high emetic risk between June 2023 and December 2023 were enrolled in this study. The mean age of the 163 enrolled patients was 60.8 ± 0.8 years, and 134 (82.2%) were males. Ninety-five (58.3%) patients had lung cancer, 37 (22.7%) patients had gastrointestinal cancer, 16 (9.8%) patients had head and neck cancer, 9 (5.5%) patients had breast cancer, and 6 (3.7%) patients had other cancers. In terms of chemotherapy drugs, 89 (54.6%) patients received nedaplatin, 20 (12.3%) patients received cis-dichlorodiamineplatinum (CDDP), 20 (12.3%) patients were given oxaliplatin, 10 (6.1%) patients received carboplatin, and 24 (14.7%) patients received other chemotherapy drugs. In addition, 153 (93.9%) patients received a combination of neurokinin 1 receptor antagonists, and 153 (93.9%) patients received a combination of steroid drugs. More details of the enrolled patients are shown in Table 1.

Efficacy for vomiting and nausea

Regarding the efficacy of vomiting, 158 (96.9%) patients achieved a complete response, 2 (1.2%) patients achieved a major response, 2 (1.2%) patients had a minor response, and 1 (0.7%) patient was assessed as failure (Fig. 1). The major efficacy rate of vomiting was 98.1%.

In terms of nausea efficacy, 157 (96.3%) patients did not experience nausea, 4 (2.5%) patients experienced mild nausea, 2 (1.2%) patients experienced moderate nausea, and no (0.0%) patients experienced severe nausea (Fig. 2). The major efficacy rate of nausea was 96.3%.

Associations of patient characteristics with major efficacy of vomiting and nausea

Only age > 65 years was associated with a lower possibility of achieving major efficacy of vomiting ($P = 0.041$), whereas other characteristics, including patients' demographic characteristics, comorbid diseases, tumour characteristics, chemotherapy drugs, or combination

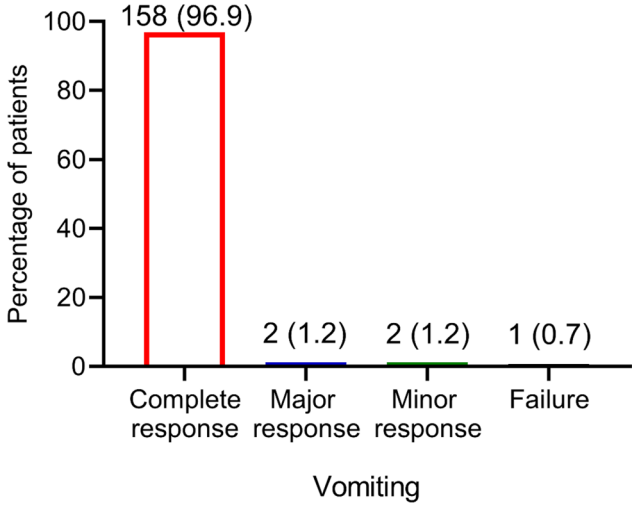

Fig. 1 Efficacy of ondansetron orally soluble pellicles for preventing vomiting

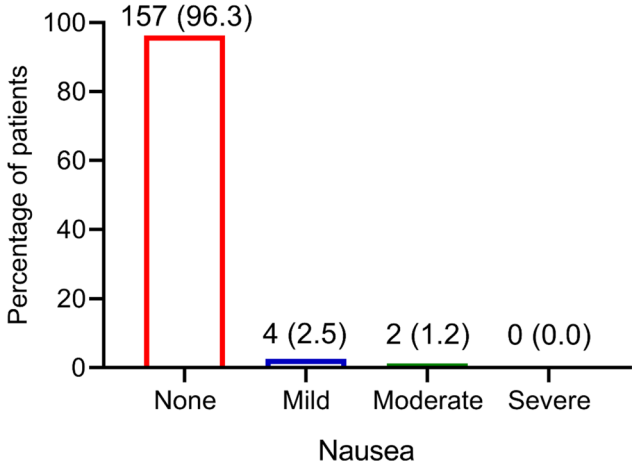

Fig. 2 Efficacy of ondansetron orally soluble pellicles for preventing nausea

treatment, were not associated with major efficacy of vomiting (all $P>0.05$) (Table 2).

In addition, high emetic risk was associated with a lower possibility of achieving major efficacy of nausea ($P=0.016$). Chemotherapy drugs were associated with the possibility of achieving major efficacy of nausea ($P=0.009$). Specifically, the major efficacy rates of nausea were 98.9%, 80.0%, 95.0%, 100.0%, and 100.0%, respectively, among patients receiving nedaplatin, CDDP, oxaliplatin, carboplatin, and other chemotherapy drugs. However, patients' demographic characteristics, comorbid diseases, tumour characteristics, and combination treatment were not associated with the major efficacy of nausea (all $P>0.05$) (Table 3).

Safety profile

A total of 42 (25.8%) patients experienced adverse events. In detail, 11 (6.7%) patients had elevated levels of alanine transaminase (ALT), 6 (3.7%) patients had elevated levels of aspartate transaminase (AST), 6 (3.7%) patients experienced fatigue, 4 (2.5%) patients experienced cough, 3 (1.8%) patients experienced hiccups, and 12 (7.4%) patients experienced other adverse events (Table 4). All cases of elevated ALT and AST levels were categorized as grade I adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The other adverse events were categorized as grade I or II. No grade III or above adverse events were observed.

Discussion

Chemical drugs not only kill tumour cells but also induce oxidative stress, inflammation, apoptosis, and necrosis in the gastrointestinal tract [16]. Neurotransmitters such as substance *P*, dopamine, and serotonin are subsequently released by enterochromaffin cells and bind to receptors, including 5-HT3 and NK1, which can activate the emetic reflex and induce nausea and vomiting [17]. Therefore, the 5-HT3 receptor antagonist ondansetron effectively inhibited chemotherapy-induced nausea and vomiting. According to a previous study, the rate of no acute nausea or vomiting was 75% in the 81 patients who received 8 mg ondansetron plus dexamethasone orally prior to receiving chemotherapy with a moderate emetic risk; moreover, the incidence of grade 3 chemotherapy-induced nausea and vomiting was 1% [18]. Another study revealed that in glioma patients who received adjuvant temozolomide, 8 mg of ondansetron on days 1–5 resulted in a complete control (defined as no nausea, vomiting or antiemetic rescue medication) rate of 54.5% [19]. The current study revealed that the complete response rate of vomiting was 96.9%, and the no nausea rate was 96.3%, which were numerically higher than those reported in previous studies [18, 19]. The possible explanations are as follows. (1) The current study used ondansetron orally soluble pellicles, which can be easily swallowed [14]. Considering that some patients might have difficulty swallowing tablets, including those encountering anticipatory nausea and vomiting or those with head and neck tumours, orally soluble pellicles of ondansetron might be easier to swallow and reduce the risk of improper administration. (2) In the present study, the dose of ondansetron orally soluble in pellicles was 24 mg, which was higher than that used in previous studies [18, 19]. The current guidelines generally recommend a combination regimen for preventing chemotherapy-induced nausea and vomiting, including a 5-HT3-receptor antagonist, an NK1-receptor antagonist, and dexamethasone, with or without olanzapine (depending on the emetogenicity of chemotherapy) [20, 21]. The dose of ondansetron

Table 2 The association between major efficacy of vomiting and baseline characteristics of patients

Baseline characteristics	Major efficacy of vomiting		*P* value
	No	Yes	
Age (years)			0.041
≤65	0 (0.0)	106 (100.0)	
>65	3 (5.3)	54 (94.7)	
Gender			1.000
Female	0 (0.0)	29 (100.0)	
Male	3 (2.2)	131 (97.8)	
Smoke			0.554
No	0 (0.0)	59 (100.0)	
Yes	3 (2.9)	101 (97.1)	
Drink			0.116
No	0 (0.0)	83 (100.0)	
Yes	3 (3.8)	77 (96.3)	
Hypertension			1.000
No	3 (2.3)	126 (97.7)	
Yes	0 (0.0)	34 (100.0)	
Diabetes mellitus			1.000
No	3 (2.0)	150 (98.0)	
Yes	0 (0.0)	10 (100.0)	
Coronary artery disease			1.000
No	3 (1.9)	151 (98.1)	
Yes	0 (0.0)	9 (100.0)	
ECOG PS			0.898
0	0 (0.0)	7 (100.0)	
1	3 (2.0)	149 (98.0)	
2	0 (0.0)	4 (100.0)	
Tumour types			0.767
Lung	3 (3.2)	92 (96.8)	
Gastrointestinal	0 (0.0)	37 (100.0)	
Head and neck	0 (0.0)	16 (100.0)	
Breast cancer	0 (0.0)	9 (100.0)	
Other	0 (0.0)	6 (100.0)	
TNM stage[#]			0.203
I	0 (0.0)	3 (2.0)	
II	0 (0.0)	15 (10.1)	
III	2 (100.0)	44 (29.7)	
IV	0 (0.0)	86 (58.1)	
Number of involved organs with metastases			0.102
0	3 (3.7)	78 (96.3)	
1	0 (0.0)	37 (100.0)	
2	0 (0.0)	21 (100.0)	
3	0 (0.0)	22 (100.0)	
4	0 (0.0)	2 (100.0)	
Brain metastasis			1.000
No	3 (2.0)	144 (98.0)	
Yes	0 (0.0)	16 (100.0)	
Emetic risk			0.495
Moderate	2 (1.5)	128 (98.5)	
High	1 (3.0)	32 (97.0)	
Chemotherapy drugs			0.707
Nedaplatin	2 (2.2)	87 (97.8)	
CDDP	1 (5.0)	19 (95.0)	
Oxaliplatin	0 (0.0)	20 (100.0)	

Table 2 (continued)

Baseline characteristics	Major efficacy of vomiting		*P* value
	No	Yes	
Carboplatin	0 (0.0)	10 (100.0)	
Other	0 (0.0)	24 (100.0)	
NK1 receptor antagonists' combination			1.000
Yes	3 (2.0)	150 (98.0)	
No	0 (0.0)	10 (100.0)	
Steroid drugs combination			1.000
Yes	3 (2.0)	150 (98.0)	
No	0 (0.0)	10 (100.0)	

#, only 150 cases had available data for analysis. ECOG PS, eastern cooperative oncology group performance status; TNM, tumour-node-metastasis; CDDP, cis-Dichlorodiamineplatinum; NK1, neurokinin 1

in the recommended combination regimen is 8 mg orally or 0.15 mg/kg intravenously injected prior to chemotherapy [20, 21]. The current study revealed that 24 mg ondansetron in the form of orally soluble pellicles could effectively prevent chemotherapy-induced nausea and vomiting, which provides potential evidence for alternative regimens to prevent chemotherapy-induced nausea and vomiting.

The results of the present study revealed that age>65 years was associated with a lower possibility of achieving major efficacy of vomiting in patients receiving ondansetron via orally soluble pellicles for the prevention of nausea and vomiting induced by chemotherapy with a moderate-to-high emetic risk. However, several studies have shown that older patients have a lower risk of chemotherapy-induced nausea and vomiting [22, 23], which contradicts our findings. A possible explanation is that the sample size of this study was relatively small. Thus, the findings of this study could be affected by occasional cases. Our data also revealed that CDDP was associated with a lower possibility of achieving major nausea. A possible explanation is that CDDP is considered a highly emetogenic chemical [8]. Therefore, 24 mg of ondansetron orally soluble pellicles might be insufficient to prevent chemotherapy regimen-induced nausea and vomiting in these patients. Consequently, a combination regimen, such as the addition of olanzapine, should be considered to further prevent nausea and vomiting in these patients. Further studies could also consider adjusting the usage and dosage of ondansetron based on the emetic risk of chemotherapy to improve the prevention of nausea and vomiting induced by chemotherapy with a moderate-to-high emetic risk.

The most commonly reported adverse events of ondansetron are fatigue, headache, and transient increases in liver function indices [24–27]. Most studies have reported that administering ondansetron to prevent chemotherapy-induced nausea and vomiting is generally safe and tolerable [24–27]. In the present study, the most commonly occurring adverse events were elevated levels of alanine transaminase, elevated levels of aspartate transaminase, and fatigue. However, these adverse events were more likely to be associated with the usage of chemotherapy, rather than ondansetron. Constipation, a common adverse event related to ondansetron, was observed in three patients in this study. Moreover, most adverse events were tolerable and manageable. These data indicate the safety of ondansetron orally soluble pellicles for preventing nausea and vomiting induced by chemotherapy drugs with a moderate-to-high emetic risk.

Several limitations to the current study should be noted. First, this study was single-armed, and the efficacy and safety of ondansetron orally soluble pellicles should be further verified by randomized controlled trials. Second, the relatively insufficient sample size might have impaired the statistical power of the current study. Third, in addition to chemotherapy, radiotherapy and surgical resection can also induce nausea and vomiting. Therefore, the efficacy of ondansetron orally soluble pellicles for preventing radiotherapy- and surgical resection-induced nausea and vomiting should be further explored. Fourth, the gender was imbalanced in this study. The potential reason was that the majority of cancer type was lung cancer and gastrointestinal cancer, which were more likely to affect males. Although the association analyses showed that gender was not associated with the achievement of major efficacy of nausea or vomiting, studies should consider to include patients with a balanced gender to verify the effect of ondansetron orally soluble pellicles.

Conclusively, ondansetron orally soluble pellicles effectively prevent nausea and vomiting in patients with malignant tumours who receive chemotherapy drugs with a moderate-to-high emetic risk. This preventive treatment was also found to be safe. However, further randomized, controlled trials with larger sample sizes are needed for verification.

Table 3 The association between major efficacy of nausea and baseline characteristics of patients

Baseline characteristics	Major efficacy of nausea		*P* value
	No	Yes	
Age (years)			0.666
≤65	5 (4.7)	101 (95.3)	
>65	1 (1.8)	56 (98.2)	
Gender			1.000
Female	1 (3.4)	28 (96.6)	
Male	5 (3.7)	129 (96.3)	
Smoke			1.000
No	2 (3.4)	57 (96.6)	
Yes	4 (3.8)	100 (96.2)	
Drink			0.437
No	2 (2.4)	81 (97.6)	
Yes	4 (5.0)	76 (95.0)	
Hypertension			0.345
No	6 (4.7)	123 (95.3)	
Yes	0 (0.0)	34 (100.0)	
Diabetes mellitus			1.000
No	6 (3.9)	147 (96.1)	
Yes	0 (0.0)	10 (100.0)	
Coronary artery disease			1.000
No	6 (3.9)	148 (96.1)	
Yes	0 (0.0)	9 (100.0)	
ECOG PS			0.153
0	1 (14.3)	6 (85.7)	
1	5 (3.3)	147 (96.7)	
2	0 (0.0)	4 (100.0)	
Tumour types			0.078
Lung	3 (3.2)	92 (96.8)	
Gastrointestinal	0 (0.0)	37 (100.0)	
Head and neck	2 (12.5)	14 (87.5)	
Breast cancer	0 (0.0)	9 (100.0)	
Other	1 (16.7)	5 (83.3)	
TNM stage[#]			0.821
I	0 (0.0)	3 (2.1)	
II	0 (0.0)	15 (10.3)	
III	1 (20.0)	45 (31.0)	
IV	4 (80.0)	82 (56.6)	
Number of involved organs with metastases			0.648
0	2 (2.5)	79 (97.5)	
1	2 (5.4)	35 (94.6)	
2	2 (9.5)	19 (90.5)	
3	0 (0.0)	22 (100.0)	
4	0 (0.0)	2 (100.0)	
Brain metastasis			1.000
No	6 (4.1)	141 (95.9)	
Yes	0 (0.0)	16 (100.0)	
Emetic risk			0.016
Moderate	2 (1.5)	128 (98.5)	
High	4 (12.1)	29 (87.9)	
Chemotherapy drugs			0.009
Nedaplatin	1 (1.1)	88 (98.9)	
CDDP	4 (20.0)	16 (80.0)	
Oxaliplatin	1 (5.0)	19 (95.0)	

Table 3 (continued)

Baseline characteristics	Major efficacy of nausea		*P* value
	No	Yes	
Carboplatin	0 (0.0)	10 (100.0)	
Other	0 (0.0)	24 (100.0)	
NK1 receptor antagonists' combination			1.000
Yes	6 (3.9)	147 (96.1)	
No	0 (0.0)	10 (100.0)	
Steroid drugs combination			0.320
Yes	5 (3.3)	148 (96.7)	
No	1 (10.0)	9 (90.0)	

#, only 150 cases had available data for analysis. ECOG PS, eastern cooperative oncology group performance status; TNM, tumour-node-metastasis; CDDP, cis-Dichlorodiamineplatinum; NK1, neurokinin 1

Table 4 Adverse events

Adverse events	Patients (*N* = 163)
Total, n (%)	42 (25.8)
Elevation of ALT, n (%)	11 (6.7)
Elevation of AST, n (%)	6 (3.7)
Fatigue, n (%)	6 (3.7)
Cough, n (%)	4 (2.5)
Hiccup, n (%)	3 (1.8)
Other, n (%)	12 (7.4)

ALT, alanine transaminase; AST, aspartate transaminase

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-13406-z.

Supplementary Material 1

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None.

Author contributions
YP substantially contributed to the conception and the design of the study. LS and JM were responsible for the acquisition and analysis of the data. YZ and XY were responsible for interpretation of the data. GL, GP and Y Li contributed to manuscript drafting or critical revisions of the intellectual content. Y Luo and JB approved the final manuscript to be published, and HH agreed to be accountable for all aspects of the work, so that any questions relating to research integrity or scientific accuracy in any part of the study are appropriately investigated and resolved. All authors have read and approved the final manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study received permission from the Ethics Committee of Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology and adhered the Declaration of Helsinki. Patients provided informed consent.

Consent to publish
Not Applicable.

Competing interests
The authors declare no competing interests.

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