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Analysis of Nausea and Vomiting Induced by Three-Day as Compared with Single-Day Cisplatin-Based Chemotherapy

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Abstract

Background: Three-day cisplatin-based chemotherapy, which is related to reduce side effects, has been widely used in clinical practice in China. However, whether three-day cisplatin could reduce chemotherapy-induced nausea and vomiting (CINV) as compared with single-day cisplatin-based regimens was still obscure.

Methods: Patients received single-day cisplatin-based (75 mg/m2) chemotherapy or three-day cisplatin-based (25 mg/m2/day) chemotherapy and treated with neurokinin-1 receptor antagonist (NK-1 RA)-based triple regimens were selected. With the methods of liquid chromatography mass spectrometry (LC-MS/MS), the blood concentration of cisplatin was analyzed. Simultaneously, the complete response (CR) rate and complete protection (CP) rate were evaluated within 5 days after initiation cisplatin-based chemotherapy.

Results: Two hundred and sixty patients (sixty patients received single-day cisplatin-based chemotherapy and two hundred patients received three-day cisplatin-based chemotherapy) were selected. From the 4th day, the blood concentration of cisplatin in three-day cisplatin was higher than that in single-day cisplatin-based treatment and the difference was statistically significant ($P < 0.05$). In addition, the CR rate in the acute, delayed and overall phases were achieved in 96.7% vs 92.50%, 85% vs 88.50% and 83.3% vs 87.5% between the two groups. The CP rate were obtained in 78.33% vs 74%, 48% vs 44.5%, 46.67% vs 43.5%, respectively. Both showed no significant difference ($P > 0.05$).

Conclusion: Even though the blood concentration between single-day and three-day cisplatin regimens was different, the incidence of CINV was not significantly different between the two groups with the usage of NK-1 RA-based antiemetic agents.

Keywords: Chemotherapy-induced nausea and vomiting (CINV); Neurokinin-1 receptor antagonists based triple regimens; Three-day cisplatin; Single-day cisplatin

Abbreviations

CINV: Chemotherapy-induced nausea and vomiting

LC-MS/MS: Liquid chromatography mass spectrometry

CR: The complete response

CP: The complete protection

NK-1: Neurokinin-1

5-HT3: 5-Hydroxytryptamine-3

DDP: Cisplatin

DXM: Dexamethasone

Introduction

Chemotherapy-induced nausea and vomiting (CINV) remains one of the most feared adverse effects for cancer patients [1,2]. A combination of neurokinin-1 (NK-1) receptor antagonist (RA), dexamethasone and 5-hydroxytryptamine-3 (5-HT3) receptor antagonist have been shown to provide superior protection in both the acute and delayed phases of CINV [3, 4]. The guidelines recommend the use of the NK-1 RA-based triple regimens for the highly emetogenic forms of chemotherapy to further enhance the efficacy of antiemetic prophylaxis.

According to current guidelines [5, 6], cisplatin-based regimens are considered to be highly emetogenic forms of chemotherapy at high risk of CINV (> 90% frequency of emesis) [7]. Due to its adverse effects, cisplatin is limitedly used in high dose. Accordingly, multi-day cisplatin-based chemotherapy are recommended in Chinese patients, three days is common. The majority of clinical trials evaluated the efficacy of NK-1 RA-based triplet antiemetic prophylaxis have investigated in patients receiving single-day cisplatin-based chemotherapy [3, 4, 8]. Some studies also show that the NK-1 RA-based triple regimens are safe and effectively control CINV in patients undergoing multi-day cisplatin-based chemotherapy [9, 10]. However, whether three-day cisplatin could reduce CINV as compared with single-day cisplatin-based regimens in Chinese people was still obscure. Since the elimination half-life value of cisplatin has a prolonged ranging from 30.5 to 106 h, the different days of cisplatin administration affect the blood concentration of cisplatin within the plasma, which exert different nausea and vomiting effects. Hence, the aim of this study is to evaluate the blood concentration of cisplatin in patients receiving single-day cisplatin and three-day cisplatin-based chemotherapy and analyze the

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incidence of CINV between the two groups with the usage of NK-1 RA-based antiemetic agents.

Patients and Methods

This retrospective observational study was conducted from April 2018 to July 2020 at the Medical Oncology Department of Tianjin Medical University General Hospital, China. Patients were consecutively included if they received single-day cisplatin-based (75 mg/m^2) chemotherapy (single-day cisplatin group) or three-day cisplatin-based (25 mg/m^2/day) chemotherapy (three-day cisplatin group). All patients received the antiemetic regimens of NK-1 receptor antagonist (a single 150 mg dose of intravenous fosaprepitant or the three-day regimen of oral aprepitant), dexamethasone (the dosage was 6mg on day 1 followed by 3.75 mg on day 2-4) and 5-HT3 receptor antagonist (5 mg dose of intravenous tropisetron on day 1) (Figure 1). Data on CINV were recorded daily by the professionally nurses, commencing at the time of patient admission. Assessments of efficacy, tolerability and safety variables were recorded by the professionally nurses for 5 days.

With the methods of liquid chromatography mass spectrometry (LC-MS/MS), the total blood concentration of cisplatin were analyzed from the randomly selected fifty patients in the two groups. Blood samples were collected at 24h after cisplatin infusion of single-day cisplatin-based chemotherapy and at 48h of three-day cisplatin-based chemotherapy. An ACQUITY UPLC I-Class (Waters Corporation, Milford, MA, USA) was used to inject 10 μL aliquots of the processed samples on a ACQUITY UPLC BEH C18 column (2.1 x 50 mm, 1.7 μm, Waters Corporation, Milford, MA, USA) maintained at 40°C. The mobile phases used were acetonitrile (A) and water with 0.1% (v/v) formic acid (B). The LC gradient was shown in Table 1. Quantitation was achieved by MS-MS detection in positive ion modes for cisplatin (DDP)and dexamethasone DXM (IS), using a triple quad mass spectrometer (Waters Corporation, Milford, MA, USA). Source gas temperature, gas flow, and capillary voltage were set at 450°C, 800Lh^{-1}, and 3.0V. The multiple reaction monitoring (MRM) mode was used to optimize the mass spectrometry conditions of the detected substances. Mass spectrometry conditions was shown in Table 2. Data was processed by Masslynx V4.1. Plasma samples of 100uL were placed in a 1.5 mL EP tube, 30 uL 1% DDTC and 10 uL 200 ng/mL DXM internal standard solution were added, and placed in a 42 water bath for 40 min. Then, 4 vol of acetonitrile was added, vortex and centrifuged. The supernatants were carefully collected and diluted with water (0.1% formic acid) to a final sample solution of 20% acetonitrile.

Nausea and vomiting were assessed according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 5.0. Complete response (CR), defined as no vomiting and no use of rescue therapy. Complete protection (CP), defined as no nausea and vomiting. CR rate and CP rate were recorded in the acute phase (first 24 h after the start of cisplatin-based chemotherapy), delayed phase (24-120 h after the start of cisplatin-based chemotherapy) and

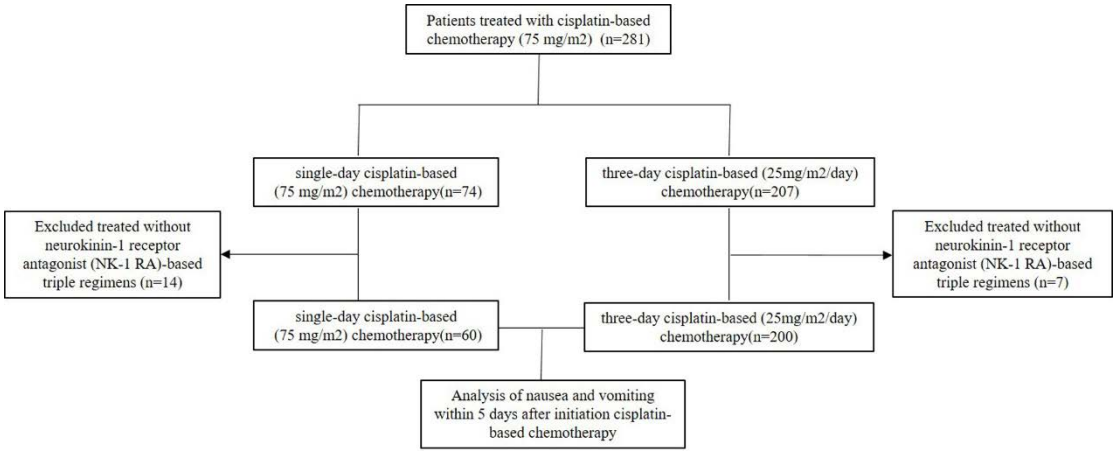

Figure 1: Procedures of the study.

Table 1: Gradient flow on LC-MS/MS.

Time (min)	Flow (mL.min^{-1})	A	B
0	0.35	5.0	95.0
0.50	0.35	5.0	95.0
1.00	0.35	75.0	25.0
1.50	0.35	90.0	10.0
2.50	0.35	95.0	5.0
4.00	0.35	95.0	5.0
5.00	0.35	5.0	95.0

Table 2: MS parameters.

Analyte	Parent ion [M$^+$] (m/z)	Product ion (m/z)	Orifice /V	Collision /V
DDP	492.00	116.10	40	25
DXM	393.37	355.30	22	10
DDP= cisplatin; DXM= dexamethasone				

overall phase (0-120 h after the start of cisplatin-based chemotherapy).

Statistical analyses were performed using SPSS software (version 22; SPSS, Inc). Measurement data were expressed as mean ± standard deviation (SD) and were analyzed with t test. Response rates were compared using the chi-square or Fisher's exact tests. All statistical tests were two-sided, with significance levels at $p < 0.05$.

Results

Patient characteristics

Two hundred and sixty patients (sixty patients received single-day cisplatin-based chemotherapy and two hundred patients received three-day cisplatin-based chemotherapy) were selected in this analysis. The baseline patient characteristics were listed in Table 3. The median age was 62 years, with a range of 30-85 years. All patients had good performance status, with ECOG scores of 0 or 1. There were no significant differences in median age, gender, disease, chemotherapy regimens and current chemotherapy cycle between the two groups. The percentage of patients who had well-known risk factors associated with CINV development were similar between groups.

Blood concentration of different dosage regimens of cisplatin

In the two groups, the total blood concentration of cisplatin was 730 ± 135 ng/ml *vs* 582 ± 176 ng/ml, 569 ± 105 ng/ml vs 774 ± 137 ng/ml, 443 ± 82 ng/ml vs 603 ± 107 ng/ml in days 3-5 (Figure 2). From the 4th day, the concentration of cisplatin in three-day cisplatin-based treatment was higher than that in single-day cisplatin-based treatment and the difference was statistically significant ($P < 0.05$).

Clinical CINV incidence of different dosage of cisplatin

With NK-1 RA-based triple regimens, the CR rate in the acute, delayed and overall phases was achieved in 96.7%, 85% and 83.3% in single-day cisplatin-based treatment; while it was obtained in 92.50%, 88.50%, 87.5% in three-day cisplatin-based treatment, respectively. The difference was not statistically significant ($P > 0.05$). Similarly, the differences of CP rate also did not reach statistical significance in the acute, delayed and overall phases between the two groups (78.33% vs 74%, 48% vs 44.5%, 46.67% vs 43.5%, $P > 0.05$) (Figure 3).

Discussion

The NK-1 RA-based triple regimens significantly improve the treatment of cisplatin-based highly emetogenic chemotherapy-related emesis [4, 8, 9]. However, few studies had directly compared the efficacy of NK-1 RA-based triple regimens in patients receiving single-day cisplatin-based chemotherapy and three-day cisplatin-based chemotherapy. Our study reveals that:

1) The blood concentration of cisplatin between single-day and three-day regimens was different.

2) With the usage of NK-1 RA-based triple regimens, the incidence of CINV was not significantly different between the two groups.

Cisplatin-based regimens are widely used in chemotherapy. One of the major obstacle for clinical use of drugs is toxicity [11]. The uptake of cisplatin into the cell exert their therapeutic as well as toxic effects. Since the uptake of cisplatin by cells was proportional to the total concentration of cisplatin, the difference of total blood concentration will have different potential inducing CINV. In the acute phase (0-24h), the cisplatin content varies significantly in patients between single-day and three-day cisplatin-based chemotherapy. In our study, we showed that the blood concentration of cisplatin in three-day cisplatin was higher than that in single-day cisplatin-based treatment from the 4th day. Therefore, the potential inducing CINV was different in the two groups.

Table 3: Baseline demographics and clinical characteristics of patients.

Variable	single-day cisplatin(N=60) (% of patient)	triple-day cisplatin (N=200) (% of patient)	P value
Median age(range)(years)	61(30-77)	62(31-85)	0.654
Female	27%	32%	0.524
Primary cancer diagnosis			0.457
Lung cancer	76%	72%	
Stomach cancer/Esophagus	4%	8%	
Others	20%	20%	
Chemotherapy regimen PP ± bevacizumab ± ICI	38%	34%	0.634
GP ± bevacizumab ± ICI	18%	15%	
EP ± ICI	22%	26%	
TP/DP ± bevacizumab ± ICI	10%	16%	
Others	12%	10%	
Current cycle number			0.138
1	38%	26%	
2	17%	24%	
3	22%	17%	
>3	23%	33%	
Age less than 60	30%	34%	0.517
History of morning sickness	12%	13%	0.786
History of CINV in the prior cycle	22%	28%	0.295
Sleep less than 7 hours before chemotherapy	23%	32%	0.199
Anticipatory nausea and vomiting	35%	34%	0.906
Use of antiemetics at home	10%	11%	0.746

P < 0.05 was considered statistically signifificant
PP-pemetrexed +cisplatin; GP-gemcitabine + cisplatin; EP-etoposide+cisplatin; TP-Paclitaxel+ cisplatin; DP-docetaxel + cisplatin; ICI-Immune checkpoint inhibitor

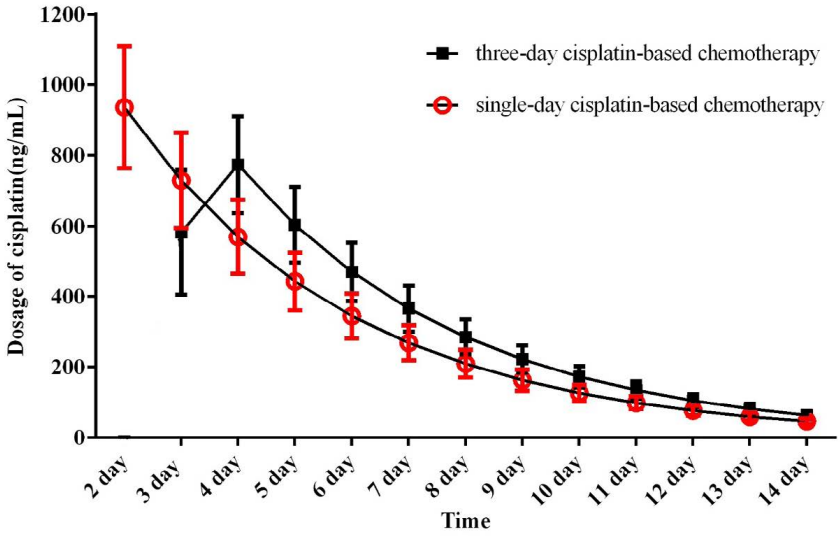

Figure 2: The blood data of different dosage of cisplatin. *p< 0.05 was considered statistically signifificant.

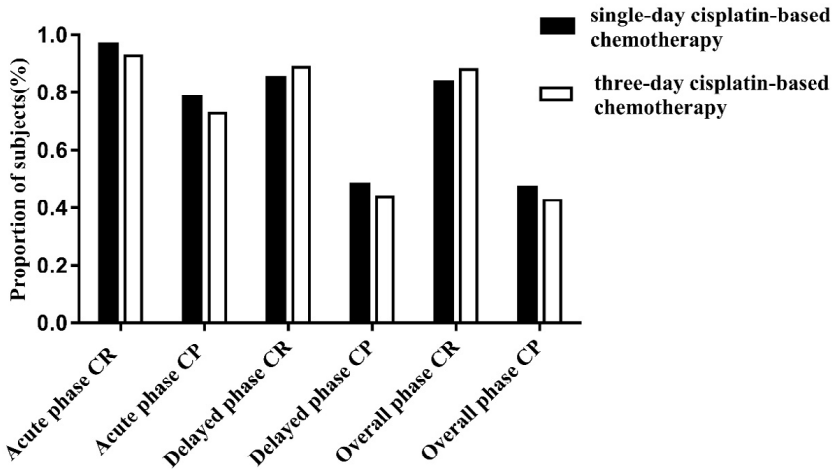

Figure 3: Proportion of patients with CR and CP in the acute (0-24h), delayed (24-120h) and overall (0-120 hours) phase following initiation of cisplatin-based chemotherapy were shown.

With 5-HT3 receptor antagonist and corticosteroid for antiemetic prophylaxis, CINV remains a significant problem for patients, especially who received cisplatin-regimens [12, 13]. Dong reported, in the acute phase the remission rate of nausea and vomiting were 69.4%, 77.6% in single-day cisplatin-based treatment (75 mg/m^2), and decreased more than 88.5%, 92.3% in three-day cisplatin-based treatment (25 mg/m^2/d), respectively ($P < 0.05$). While in the delayed phase, the remission rate of nausea and vomiting were 32.7%, 55.1% in single-day cisplatin-based treatment, and lower compared with 34.6%, 71.2% in three-day cisplatin-based treatment, but did not reach statistical significance ($P > 0.05$) [14]. Cisplatin of fractionated regimen could reduce the prevalence of CINV in the acute phase, but not in the delayed phase with 5-HT3 receptor antagonist and corticosteroid for antiemetic prophylaxis.

As we know, NK-1 RA-based triple regimens have been shown to provide superior protection both in the acute and in the delayed phases of CINV. Wu reported that aprepitant based triple regimens proved to be effective and well-tolerated in preventing CINV after administration of full-dose single-day cisplatin-based chemotherapy [15]. CR in the overall phase was 92.6% in aprepitant group in contrast to 79.93% in placebo group ($P < 0.01$). Li et al studied the efficacy of aprepitant, tropisetron and dexamethasone in patients receiving multiple-day cisplatin chemotherapy. A CR was achieved by 80.0% in the aprepitant group compared with 56.0% in the standard group during the overall phase ($P = 0.018$) [16]. While most studies compared NK-1 RA to placebo combined with 5-HT3 RA and dexamethasone in single-day cisplatin-based treatment or in multiple-day cisplatin-based treatment, few studies have directly compared the efficacy of the NK-1 RA-based triple regimens in patients receiving single-day cisplatin-based chemotherapy and three-day cisplatin-based chemotherapy. Our results confirm that NK-1 RA-based triple regimens significantly improved patient CR rate for vomiting in the overall period both in single-day cisplatin and three-day cisplatin-based chemotherapy, but there was less improvement regarding nausea and it is well consistent with previous studies data [14, 15, 17, 18]. Moreover, we directly assessed efficacy of the NK-1 RA-based triple regimens in patients receiving single-day cisplatin and three-day cisplatin-based chemotherapy and found that the NK-1 RA-based triple regimens have

the same efficacy in preventing CINV between single-day and three-day cisplatin regimens.

This study has some limitations. First, given the retrospective nature of the design, it is potential for bias. Second, due to the small number of patients in single-day cisplatin-based treatment, which may limit the power to detect statistical differences. Third, though the proportion of moderately emetogenic regimen gemcitabine is the same in the two groups, further data is needed to draw a final conclusion in the regimens with the same potential to induce CINV.

In conclusion, our studies demonstrated that although the blood concentration between single-day and three-day cisplatin regimens was different, the incidence of CINV was not significantly different between the two groups with the usage of NK-1 RA-based antiemetic agents. And we also need to proceed to a prospective randomised clinical trial to confirm it.

Ethical Approval and Consent to participate: All procedures performed in this study involving human participants were performed in accordance with the ethical standards of Tianjin Medical University General Hospital and with the 1964 Helsinki declaration and all subsequent revisions. Since this study was retrospective, obtaining informed consent from each patient was not required.

Consent for publication: Not applicable.

Availability of supporting data: The datasets generated during and analysed during the current study are available from the corresponding author on reasonable request.

Authors Contributions: Linlin Zhang and Hengjie Yuan designed the paper. Diansheng Zhong gave the administrative support. Hengjie Yuan provided the study materials. Ming Ding, Yinjuan Sun, Fanlu Meng, Xia Liu, Liyan Gu, Shasha Guan, Ai Gao and Zhicui Ju performed blood and data collection. Ping Xiao and Jingyue Zhang performed and analyzed the data. All authors performed the manuscript writing and approved the final manuscript.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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