Research Paper

Efficacy of 5 mg Olanzapine in the Prevention and Treatment of Carboplatin-Induced Nausea and Vomiting in the Chinese Population

YUN AN, Z. H. LI[1], F. CHEN, CAIHONG JIANG, JUAN ZHAO, L. Z. ZHAO, YING JIANG, HUI LI, G. LIU, M. GU, LENGGAOWA DA, GAOWA JIN[1] AND Q. F. LI*

Department of Medical Oncology, Ordos Central Hospital, Baotou Medical College, Ordos 017000, [1]Department of Radiology, School of Public Health and Management, Wenzhou Medical University, Wenzhou, Zhejiang 325000, China

To investigate the efficacy and safety of low-dose 5 mg olanzapine triple regimen for prevention of carboplatin-induced nausea and vomiting in Chinese population. 56 patients with malignancies were treated with carboplatin (area under the curve≥5) chemotherapy. All patients received a triple antiemetic regimen of 5 mg olanzapine combined with 5-hydroxytryptamine-3 receptor antagonist and dexamethasone. The primary endpoint of the study was total control in the overall phase (0-120 h), acute phase (0-24 h) and delayed phase (25-120 h) in all patients. Secondary endpoints were total protection and complete response in the overall phase, acute phase and delayed phases. The impact of chemotherapy-induced nausea and vomiting on the quality of life was assessed by the functional living index-emesis. Olanzapine related side-effect was also recorded. The primary end points total control in the overall phase, acute phase and delayed phases were 62.50 % (35/56), 87.50 % (49/56) and 64.28 % (36/56) respectively. These end points total protection in the overall phase, acute phase and delayed phases were 82.14 % (46/56), 96.42 % (54/56) and 83.92 % (47/56) respectively. The complete response rate in the overall phase, acute phase and delayed phases were 91.07 % (51/56), 98.21 % (55/56) and 91.07 % (51/56) respectively. There was no effect on life-quality (score≥108) assessed by functional living index-emesis was 62.50 %.The most common olanzapine-related side effects were Grade I-II somnolence and weakness. The 5 mg olanzapine based triplet antiemetic regimen is effective and safe in the prevention carboplatin-induced nausea and vomiting in the Chinese population.

Key words: Olanzapine, carboplatin, chemotherapy-induced nausea and vomiting, 5-hydroxytryptamine-3 receptor antagonist, dexamethasone

Carboplatin is one of the important chemical drugs for the treatment of malignant tumors. In recent years, more and more clinical studies have confirmed that carboplatin will damage the immune function and normal tissue cells of patients during anti-tumor treatment and induce adverse reactions of which the most common is Chemotherapy-Induced Nausea and Vomiting (CINV). If CINV is not effectively prevented and controlled, it will not only have a negative impact on the quality of life of patients, reduce the compliance of patients, but also be forced to discontinue chemotherapy[1]. According to the risk of emesis, chemotherapeutic drugs are classified into four grades: High, moderate, low and slight emesis[2]. In guidelines published by the European Society of Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN)[3,4], a triple antiemetic regimen using Neurokinin-1 (NK-1) receptor inhibitors combined with 5-Hydroxytryptamine-3 Receptor Antagonist (5-HT_3RA) or serotonin-3 receptor inhibitors and dexamethasone is recommended to prevent CINV induced by carboplatin (Area Under the Curve (AUC)≥5) regimen. Studies have shown that carboplatin predisposes to delayed CINV during treatment[5]. Olanzapine is an antipsychotic with pharmacological effects on a variety of receptor systems and it is currently believed to inhibit CINV by binding to a variety of neurotransmitter receptors[6,7], and clinical studies at home and abroad have confirmed that the combination regimen of olanzapine 5~10 mg/d has a good effect in the prevention and treatment of CINV[8,9], especially delayed CINV[10]. In Japan, Yanai *et al.*[11] reported that 5 mg and 10 mg of olanzapine showed similar antiemetic effect, but the sedative effect

***Address for correspondence**
E-mail: 1729259137@qq.com

of 5 mg was weak. We conducted an efficacy study of low-dose olanzapine combined with a traditional dual antiemetic regimen for the prevention of carboplatin (AUC≥5)-induced CINV in a Chinese population and the study results are reported below:

MATERIALS AND METHODS

Clinical materials:

This study included 56 patients with histologically confirmed malignant tumors who received chemotherapy with carboplatin (AUC≥5) regimen in the Department of Medical Oncology of our hospital from September 2019 to June 2021. All patients received a combination of 5 mg olanzapine, 5-HT_3RA and dexamethasone. Baseline characteristics are listed in Table 1.

Eligibility criteria:

Inclusion criteria: Patients aged≥18 y with pathologically confirmed malignant tumors scheduled to receive carboplatin containing (AUC≥5) chemotherapy; Karnofsky performance scale≥70; there is no abnormality in liver and kidney function, blood routine and electrocardiogram before chemotherapy, including: White blood cell count>3.5×10^9/l, absolute neutrophil count>1.5×10^9/l, platelet count>85×10^9/l, alkaline phosphatase<2.5 Upper Limit of Normal (ULN), alanine transaminase<2.5 ULN, bilirubin<1.5 ULN, creatinine<1.5 ULN; 1 w before the enrollment, there were no symptoms of nausea and vomiting, and no olanzapine was used; there was no contraindication of chemotherapy in the evaluation of tumor location by Computed Tomography (CT), Magnetic Resonance Imaging (MRI); able to understand and describe patient-reported outcomes; patients must be fully aware of the trial and written consent must be obtained.

Exclusion criteria: Patients are excluded if they meet any of the following criteria. Patients who are unable to take oral drugs; long-term user of corticosteroid; patients who currently use quinolone antibiotics; patients with histories of hypersensitivity or allergy to olanzapine; patients who are undergoing radiotherapy simultaneously; patients who have uncontrolled symptomatic brain metastases; pregnant or breastfeeding female patients; patients with partial/complete gastrointestinal obstruction; patients who abuse illegal substances or have severe alcohol dependency; patients who have malignant tumor of digestive tract.

Research methods:

The antiemetic administrations in this study are shown in Table 1. Patients in the olanzapine triplet regimen group were given: Olanzapine 5 mg on d 1-4, 5-HT_3 tropisetron 5 mg and dexamethasone 10 mg on d 1. Antiemetics were administered at the start of carboplatin chemotherapy.

TABLE 1: BASELINE CHARACTERISTICS OF PATIENTS (n (%))

Characteristics	All patients (n=56)
Age (years)	62.07±8.206
≥55	48 (85.71 %)
Gender	
Female	29 (51.78 %)
Male	27 (48.22 %)
History of motion sickness	11 (19.64 %)
History of nausea with pregnancy in female	5 (20.83 %)
Alcohol use	
No consumption	40 (71.42 %)
<4 drinks per week	8 (14.28 %)
≥4 drinks per week	8 (14.28 %)
Smoking index	
No smoking	25 (44.64 %)
0~400	9 (16.07 %)
≥400	22 (39.28 %)
Type of malignance	
Lung cancer	32 (57.14 %)
Others	24 (42.86 %)
Chemotherapy cycle	
First-cycle	19 (33.92 %)
Second-cycle	14 (25.00 %)
Third-cycle	6 (10.71 %)
≥Fourth-cycle	17 (30.35 %)

End points:

We chose the Total Control (TC) rate as primary end point which defined as the absence of vomiting and no use of rescue medications and the maximum nausea score on 100 mm nausea scale was less than 5 mm during the Acute Phase (AP), Delayed Phase (DP) and Overall Phase (OP) after the initiation of carboplatin as the primary endpoint. Secondary endpoints are the Complete Response (CR) and Total Protection (TP) rate in the three phases. The CR rate is defined as the absence of vomiting and no use of rescue medications, while that of TP is the absence of vomiting and no use of rescue medications and the maximum nausea score on 100 mm nausea scale was less than 25 mm. Adverse Events (AEs) are graded according to Common Terminology Criteria for Adverse Events (CTCAE) V.4.0.

Follow-up:

Patients were recorded and self-reported the times and dates of vomiting or retching episodes, and the use of rescue treatments from the time of chemotherapy infusion (0 h) to the d 5. Patients were contacted in the mornings of d 2-5 to ensure the compliance with nausea categorical scale. Functional Living Index-Emesis (FLIE) questionnaire scoring was self-administered early on the d 5, directly following completion of final self-reports[12]. Notably, FLIE is a validated emesis and nausea specific questionnaire with nine nausea domain questions (items) and nine vomiting domain questions (items) and "no impact of CINV on daily life" represented means scores >6 on a 7-point scale (>108 in total)[13,14]. The time of treatment failure is defined as the time of first emetic episode or the use of rescue medication. All patients underwent post-treatment examination on d 6-8 and follow-up at d 19-21 and AEs related to olanzapine were recorded. AEs were graded according to CTCAE V.4.0.

Statistical analysis:

The sponsor managed the data and performed the analyses for this study. The hypothesis of this study was that the TC rate of 5 mg OZL in triplet group would be significantly higher than that of standard antiemetic doublet therapy. Other trials have shown that the TC rate of standard antiemetic therapy was about 40 %[15]. We believed that an improvement of more than 15 % in the TC rate would be clinically meaningful. Therefore, assuming that the null hypothesis of the TC rate is 55 % and the alternative hypothesis is 80 %, we calculated that a minimum of 50 patients were required to achieve a one-sided type I error of 0.1 % and 80 % of power, based on the exact binomial distribution. Because some dropouts were expected, we set the target sample size to 52 and the sample size calculation was performed by Statistical Analysis System (SAS) V.9.4 (Cary, North Carolina, United States of America).

RESULTS AND DISCUSSION

Four patients were excluded from the study due to misunderstanding of instruction of olanzapine and failed to administer the required dosage of olanzapine, 56 patients were therefore enrolled in this study.

Primary end points were compared. As shown in Table 2, the TC rates in the OP, AP and DP were 62.50 %, 87.50 % and 64.28 % respectively. The incidences of nausea and vomiting over time (every 24 h) for 5 d are presented in Table 3. The incidence of nausea and vomiting was higher on d 3-4 than on other days.

FLIE index reports were compared. According to FLIE, reports of no impact of CINV on daily life were exhibited by 62.50 % (35/56). The FLIE index of nausea or vomiting was listed below in Table 4.

The prevalence of major AEs upon treatment with olanzapine is shown in Table 5. In CTCAE version 4.0, there were no AEs greater than Grade III. The rates of severe symptoms were as low as 1.78 % for somnolence and 5.36 % for constipation.

TABLE 2: RESULTS OF EVALUATION INDICATORS AT EACH PERIOD

Endpoint	OP number (%)	AP number (%)	DP number (%)
TC	35 (62.50)	49 (87.50)	36 (64.28)
CR	51 (91.07)	55 (98.21)	51 (91.07)
TP	46 (82.14)	54 (96.42)	36 (83.92)

TABLE 3: THE INCIDENCE OF NAUSEA AND VOMITING OVER TIME (EVERY 24 h)

Day	Nausea	Vomiting
d 1	7 (12.50 %)	1 (1.78 %)
d 2	10 (17.85 %)	1 (1.78 %)
d 3	16 (28.57 %)	0 (0.00 %)
d 4	15 (26.78 %)	2 (3.57 %)
d 5	12 (21.42 %)	1 (1.78 %)

TABLE 4: FLIE INDEX

Items	All patients (56 cases)
Nausea FLIE score	52.80±3.25
Vomiting FLIE score	57.01±3.25
FLIE score	109.77±6.25

Note: FLIE indicates functional living index-emesis

TABLE 5: TREATMENT-RELATED AEs

Symptoms	Grade I	Grade II	Grade III
Somnolence	31 (55.36 %)	10 (17.85 %)	1 (1.78 %)
Fatigue	30 (53.56 %)	17 (30.36 %)	1 (1.78 %)
Anorexia	20 (35.71 %)	5 (8.93 %)	3 (5.36 %)
Hiccups	15 (26.78 %)	2 (3.57 %)	1 (1.78 %)
Constipation	15 (26.78 %)	8 (14.28 %)	3 (5.36 %)

Yang *et al.* conducted a meta-analysis on the efficacy of olanzapine in the prevention of CINV and confirmed that olanzapine was as effective as or superior to aprepitant in the prevention of CINV, while 5 mg and 10 mg olanzapine showed similar efficacy in CR in the delayed and total periods, and in order to reduce the risk of adverse reactions, 5 mg was recommended as the starting dose of olanzapine to further explore the best antiemetic regimen[10]. To further confirm the efficacy of low-dose olanzapine in the prevention of carboplatin (AUC≥5)-induced CINV in the Chinese population, we conducted a clinical study of 5 mg olanzapine combined with 5-HT_3RA and dexamethasone in the prevention of carboplatin (AUC≥5)-induced CINV in Ordos Central hospital in Inner Mongolia and finally 56 patients with no difference in baseline characteristics.

In this study, we selected TC focusing on nausea evaluation as the main study index. TC in the total period, AP and DP was 62.50 % (35/56), 87.50 % (49/56) and 64.28 % (36/56), respectively. In 2016, Hesketh *et al.* conducted a multi-center clinical phase III controlled study of NK-1 receptor inhibitors combined with serotonin-3 receptor inhibitors and dexamethasone in the prevention of carboplatin-induced CINV[16]. In this study, the TC rates in the OP, AP and DP of NK-1 receptor inhibitor group were 62.5 %, 80.7 % and 64.1 %, respectively, which were comparable to the TC rate in the low-dose olanzapine group in this study. It was further confirmed that 5 mg olanzapine was equivalent to NK-1 receptor inhibitors in the control of nausea induced by carboplatin in CINV. Sakai *et al.* reported a phase II clinical trial of low-dose olanzapine 5 mg for the prevention and treatment of CINV induced by carboplatin in thoracic malignancies and the results showed that TC was 86.00 %, 100 % and 86 % in the OP, AP and DP respectively, and CR was 94.00 %, 100 % and 94 % in the OP, AP and DP respectively[17]. Compared with the above phase II clinical trial, the TC rate (62.50 %, 87.50 %, 64.28 %) in all three periods in this study was lower, while the CR rate (91.07 %, 98.21 %, 91.07 %) was comparable, the difference may be due to the fact that in this phase II study in Japan, all patients with thoracic malignancies were included, accounting for 30.00 % of female patients and 50 % of patients without a history of alcohol consumption; while our study included patients with polyoma, in addition to patients with thoracic malignancies, some patients with gynecological malignancies and other malignancies were also included of which 51.78 % were female patients and 71.42 % had no history of alcohol consumption and it has been confirmed that female gender and no history of alcohol consumption are factors for the occurrence of CINV[18]. Mukhopadhyay *et al.* studied the role of 10 mg olanzapine in platinum-based CINV and the CR

rates in the OP, AP and DP in the olanzapine group were 94.00 %, 98.00 % and 96.00 %, respectively[19], which were comparable to the CR rates in each phase (91.07 %, 98.21 % and 91.07 %) in this study, indicating that 10 mg olanzapine and 5 mg olanzapine had comparable antiemetic efficacy against platinum-induced CINV. Among the secondary endpoints in this study, the TP in the OP, AP and DP in the low-dose olanzapine group were 82.14 % (46/56), 96.42 % (54/56) and 83.92 % (47/56), respectively, which were significantly higher than the TP rates in the rolapitant group (74 %, 88.5 % and 76 %) in the NK-1 receptor inhibitor multi-center controlled clinical phase III study for the prevention of carboplatin-induced CINV conducted by Hesketh *et al.* possibly due to the relatively small number of patients in our study[16]; the patients included in the above study were multiethnic population, while this study was a single northern Chinese population and more clinical studies are needed to confirm the efficacy of low-dose olanzapine and NK-1 receptor inhibitors in carboplatin-induced CINV.

In terms of side effects, the incidence of somnolence in this study was 75.00 % (42/56), which was comparable to the incidence of somnolence in the phase II clinical trial of low-dose olanzapine conducted by Sakai *et al.*[17] in Japan (76.00 %) and among the somnolence patients occurred in this study, mild somnolence reached 73.80 % (31/42), which indicated that the somnolence effect produced by 5 mg olanzapine was tolerable in the vast majority of patients and could even further improve the sleep quality and anxiety and depression psychological status of cancer patients. This study discovered a clear decrease of the incidence rate of anorexia, 50.00 % for patients in the olanzapine triplet regimen, which is consistent with results from other clinical reports[20]. Among them, the incidence of mild anorexia was 35.71 %, which we believe is related to the ability of olanzapine to prevent CINV to control nausea, significantly improve the appetite of chemotherapy patients and further improve the quality of life of patients.

For CINV, the control and prevention of nausea is more difficult and challenging, and it is also the most troublesome side effect for chemotherapy patients. This study showed that the triple regimen of low-dose olanzapine has definite efficacy and safety in preventing carboplatin (AUC≥5)-induced nausea and vomiting in the Chinese population, especially in controlling nausea, which is worthy of more clinical application and promotion.

Ethical approval:

This study was conducted with approval from the Ethics Committee of Ordos Central Hospital, Ordos Clinical College of Inner Mongolia Medical University (2019-005). This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

Author's contributions:

Yun An and Zhenhao Li contributed equally to this work.

Funding:

This study was supported by Ordos Health Commission Key Discipline Project.

Conflict of interests:

The authors declared no conflict of interest.

REFERENCES

1. Torres CH, Mazzarello S, Ng T, Dranitsaris G, Hutton B, Smith S, *et al.* Defining optimal control of chemotherapy-induced nausea and vomiting-based on patient's experience. Support Care Cancer 2015;23(11):3341-59.
2. Roila F, Molassiotis A, Herrstedt J, Aapro M, Gralla RJ, Bruera E, *et al.* 2016 MASCC and ESMO guideline update for the prevention of chemotherapy-and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol 2016;27:v119-33.
3. Hesketh PJ, Kris MG, Basch E, Bohlke K, Barbour SY, Clark-Snow RA, *et al.* Antiemetics: ASCO guideline update. J Clin Oncol 2020;38(24):2782-97.
4. NCCN guidelines. NCCN clinical practice guidelines in oncology: Antiemesis. Version 2. National Comprehensive Cancer Network 2020.
5. Waqar SN, Mann J, Baggstrom MQ, Waqar MA, Chitneni P, Williams K, *et al.* Delayed nausea and vomiting from carboplatin doublet chemotherapy. Acta Oncol 2016;55(6):700-4.
6. Cabaleiro T, López-Rodríguez R, Ochoa D, Román M, Novalbos J, Abad-Santos F. Polymorphisms influencing olanzapine metabolism and adverse effects in healthy subjects. Hum Psychopharmacol 2013;28(3):205-14.
7. Navari RM. Management of chemotherapy-induced nausea and vomiting. Drugs 2013;73(3):249-62.
8. Wang SY, Yang ZJ, Zhang L. Olanzapine for preventing nausea and vomiting induced by moderately and highly emetogenic chemotherapy. Asian Pac J Cancer Prev 2014;15(22):9587-92.
9. Nagashima K, Iwasa S, Yanai T, Hashimoto H, Suzuki K, Ohyanagi F, *et al.* A double-blind randomized Phase II study of olanzapine 10 mg versus 5 mg for emesis induced by highly emetogenic chemotherapy. Jpn J Clin Oncol 2015;45(2):229-31.
10. Yang T, Liu Q, Lu M, Ma L, Zhou Y, Cui Y. Efficacy of olanzapine for the prophylaxis of chemotherapy-induced nausea and vomiting: A meta-analysis. Br J Clin Pharmacol 2017;83(7):1369-79.

11. Yanai T, Iwasa S, Hashimoto H, Ohyanagi F, Takiguchi T, Takeda K, *et al.* A double-blind randomized phase II dose-finding study of olanzapine 10 mg or 5 mg for the prophylaxis of emesis induced by highly emetogenic cisplatin-based chemotherapy. Int j clin oncol 2018;23(2):382-8.
12. Martin AR, Pearson JD, Cai B, Elmer M, Horgan K, Lindley C. Assessing the impact of chemotherapy-induced nausea and vomiting on patient's daily lives: A modified version of the Functional Living Index-Emesis (FLIE) with 5 d recall. Support Care Cancer 2003;11(8):522-7.
13. Decker GM, DeMeyer ES, Kisko DL. Measuring the maintenance of daily life activities using the functional living index-emesis (FLIE) in patients receiving moderately emetogenic chemotherapy. J Support Oncol 2006;4(1):35-41.
14. Martin AR, Carides AD, Pearson JD, Horgan K, Elmer M, Schmidt C, *et al.* Functional relevance of antiemetic control: Experience using the FLIE questionnaire in a randomised study of the NK-1 antagonist aprepitant. Eur J Cancer 2003;39(10):1395-401.
15. Iihara H, Shimokawa M, Hayashi T, Kawazoe H, Saeki T, Aiba K, *et al.* A nationwide, multicenter registry study of antiemesis for carboplatin-based chemotherapy-induced nausea and vomiting in Japan. Oncologist 2020;25(2):e373.
16. Hesketh PJ, Schnadig ID, Schwartzberg LS, Modiano MR, Jordan K, Arora S, *et al.* Efficacy of the neurokinin-1 receptor antagonist rolapitant in preventing nausea and vomiting in patients receiving carboplatin-based chemotherapy. Cancer 2016;122(15):2418-25.
17. Sakai C, Shimokawa M, Iihara H, Fujita Y, Ikemura S, Hirose C, *et al.* Low-dose olanzapine plus granisetron and dexamethasone for carboplatin-induced nausea and vomiting in patients with thoracic malignancies: A Prospective Multicenter Phase II Trial. Oncologist 2021.
18. Sekine I, Segawa Y, Kubota K, Saeki T. Risk factors of chemotherapy-induced nausea and vomiting: Index for personalized antiemetic prophylaxis. Cancer Sci 2013;104(6):711-7.
19. Mukhopadhyay S, Kwatra G, Alice KP, Badyal D. Role of olanzapine in chemotherapy-induced nausea and vomiting on platinum-based chemotherapy patients: A randomized controlled study. Support Care Cancer 2017;25(1):145-54.
20. Nikbakhsh N, Sadeghi MV, Ramzani E, Moudi S, Bijani A, Yousefi R, *et al.* Efficacy of olanzapine in symptom relief and quality of life in gastric cancer patients receiving chemotherapy. J Res Med Sci 2016;21:88.

This article was originally published in a special issue, "Trending Topics in Biomedical Research and Pharmaceutical Sciences" Indian J Pharm Sci 2022:84(1) Spl Issue "220-225"