Yonago Acta Medica 2023;66(2):208–213 doi: 10.33160/yam.2023.05.002 *Original Article*

Olanzapine for The Prevention of Nausea and Vomiting Caused by Chemoradiotherapy with High-Dose Cisplatin for Head and Neck Cancer

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ABSTRACT

Background Chemotherapy-induced nausea and vomiting (CINV) are the most common and distressing adverse events in patients receiving anticancer therapy. Radiotherapy also induces nausea and vomiting, so concurrent chemoradiotherapy-induced nausea and vomiting (CRINV) are significant problems for patients undergoing chemoradiotherapy. Conventionally, three-drug combination therapy with dexamethasone, 5-hydroxytryptamine type 3 (5-HT3) receptor antagonist, and neurokinin-1 (NK1) receptor antagonist has been used to prevent CRINV induced by concurrent chemoradiotherapy with cisplatin for patients with head and neck cancer (HNC). Nonetheless, CRINV still remains a problem. The effectiveness of adding olanzapine to prevent CINV has been reported, suggesting the efficacy of four-drug combination therapy for CRINV. However, its effectiveness has hardly been reported in patient receiving chemoradiotherapy for HNC.

Methods A total of 109 patients with HNC who received concurrent chemoradiotherapy with cisplatin from April 2014 to March 2021 were included and divided into the following two groups according to antiemetic treatment regimen: the conventional group (Con group; $n = 78$) who received three-drug combination therapy and the olanzapine group (Olz group; Olz group, $n = 31$) who received four-drug combination therapy with olanzapine. Acute (0 to 24 h from cisplatin) and delayed (25 to 120 h from cisplatin) CRINV were then compared using the Common Terminology Criteria for Adverse Events.

Results No significant difference in acute CRINV were observed between both groups ($P = 0.5761$, Fisher's exact test). However, the Olz group had a significantly lower incidence rate of delayed CRINV over Grade 3 compared to the Con group ($P = 0.0318$, Fisher's exact test).

Conclusion Four-drug combination therapy with olanzapine was effective in suppressing delayed CRINV due to chemoradiotherapy with cisplatin for HNC.

Key words chemoradiotherapy; cisplatin; head and neck cancer; nausea and vomiting; olanzapine

Chemotherapy-induced nausea and vomiting (CINV) are the most common and distressing adverse events in patients receiving anticancer therapy.[1] CINV not only negatively affect the patients' quality of life (QOL) but also reduce treatment adherence. Despite the marked improvement in the management of CINV, they remain important adverse events of treatment.[1, 2] Three-drug combination therapy with dexamethasone, palonosetron, and aprepitant has been standard treatment for the prevention of CINV.[3] Recent phase 3 studies had reported that adding olanzapine to the three-drug combination antiemetic therapy reduced the incidence of CINV.[3, 4] As such, a four-drug combination therapy with olanzapine, dexamethasone, palonosetron, and aprepitant should be considered for the prevention of CINV, especially when using highly emetogenic chemotherapy (HEC).[5, 6] Cisplatin (CDDP), a HEC, has been the standard regimen for concurrent chemoradiotherapy for head and neck cancer (HNC). CDDP is concomitantly administrated at a dose of 100 mg/m^2 every 3 weeks during radiotherapy for HNC. Given that high-dose cisplatin administration frequently induces CINV, symptom control is very important for maintaining patient's QOL and adherence to chemoradiotherapy.

Radiation-induced nausea and vomiting (RINV), otherwise known as cancer treatment-related emesis, is clinically important and can be distressing for patients.[7] During concurrent chemoradiotherapy for HNC, distinguishing between CINV and RINV is difficult. Nonetheless, controlling chemoradiotherapy-induced nausea and vomiting (CRINV) is critical.

Four-drug combination antiemetic therapy might

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Abbreviations: CDDP, Cisplatin; CINV, Chemotherapy-induced nausea and vomiting; CRINV, Chemoradiotherapy-induced nausea and vomiting; CTCAE, Common Terminology Criteria for Adverse Events; HEC, highly emetogenic chemotherapy; HNC, head and neck cancer; IMRT, Intensity-modulated radiotherapy; NK1, neurokinin-1; RINV, Radiation-induced nausea and vomiting; 5-HT3, 5-hydroxytryptaminetype 3;

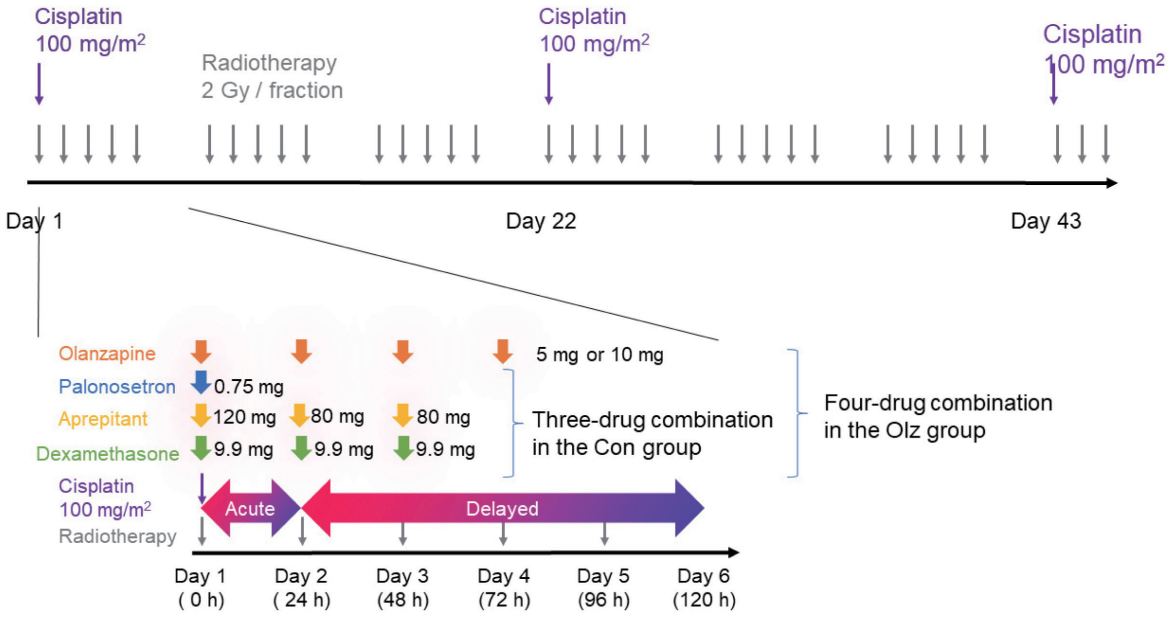

Fig. 1. The scheme of the treatment.

be especially useful for preventing CRINV in patients receiving chemoradiotherapy for HNC, considering its relatively higher dose of CDDP compared to other cancer treatments. However, the efficacy of four-drug combination antiemetic therapy in patients receiving chemoradiotherapy for HNC is still unclear.

The current study focused on the antiemetic effects of olanzapine and sought to elucidate whether four-drug combination therapy with olanzapine would be more effective against CRINV compared to the conventional three-drug combination therapy during concurrent chemoradiotherapy for HNC.

MATERIALS AND METHODS

Patients

From April 2014 to March 2021, patients who underwent concurrent chemoradiotherapy with cisplatin for HNC at Tottori University Hospital were enrolled to this study. Thereafter, we retrospectively analyzed their electronic medical records and divided patients into the following two groups: the conventional group (Con group) who received the conventional three-drug combination antiemetic therapy with dexamethasone, palonosetron, and aprepitant and the olanzapine group (Olz group) who received four-drug combination antiemetic therapy with dexamethasone, palonosetron, aprepitant, and olanzapine.

Treatment

All patients underwent concurrent chemoradiotherapy for HNC. Cisplatin was administered three times weekly at a dose of 100 mg/m^2 for three cycles concurrent with radiotherapy. Dexamethasone was administered intravenously at a dose of 9.9 mg from days 1 to 4; palonosetron, a 5-hydroxytryptamine type 3 (5HT-3) receptor antagonist, was administered intravenously at a dose of 0.75 mg on day 1; and aprepitant, a neurokinin-1 (NK1) receptor antagonist, was administered orally at a dose of 125 mg on day 1 and 80 mg on days 2 and 3. Aprepitant was replaced with fosaprepitant in patients with severe dysphagia. An additional dose of aprepitant was administered on days 4 and 5 when patients had CRINV.

Olanzapine was administered orally at a dose of 5 or 10 mg from days 1 to 4. Given that olanzapine is covered by Japanese National insurance for nausea and vomiting in 2017, patients treated after 2017 who had no history of diabetes received four-drug combination therapy. Patients treated before 2017 or with a history of diabetes received three-drug combination antiemetic treatment.

Radiotherapy was performed 5 days/week. Intensity-modulated radiotherapy (IMRT) was performed to preserve the salivary gland function. More recently, however, the proportion of patients receiving IMRT has been increasing.

The scheme of the treatment is shown in Fig. 1.

Outcomes

CRINV were defined according to the terminology

and grading categories stated in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. and graded. Acute CRINV were defined as nausea and vomiting from 0 to 24 h after CDDP administration. Delayed CRINV were defined as nausea and vomiting from 25 to 120 h after CDDP administration. Patients who did not experience any CRINV were defined as those having a complete response. Given that various confounding factors appear as treatment progresses, only nausea and vomiting at the time of initial administration were evaluated.

Adverse events (constipation, hiccups, somnolence, insomnia, dry mouth, and dizziness) were also assessed from days 1 to 6 according to CTCAE version 4.0.

Statistical analysis

Statistical analyses were conducted using GraphPad Prism 9 (GraphPad Software, CA, USA). Unpaired t-test with Welch's correction was used to compare age and estimated glomerular filtration rate (eGFR) between the two study groups; chi-square test was used for comparisons in primary site, stage, and the number of induction chemotherapy; and Fisher's exact test was used for comparisons in other characteristics. For all analyses, $P < 0.05$ was considered statistically significant.

Ethical declaration

Our study protocol was approved by the Institutional Review Board of our university (No. 19A191). This study was conducted in accordance with the Declaration of Helsinki (adopted by the World Medical Association General Assembly in Helsinki in 1964, including subsequent revisions) and "Ethical Guidelines for Medical and Health Research Involving Human Subjects" (December 2014, Ministry of Education, Culture, Sports, Science and Technology, Japan). In accordance with the "Ethical Guidelines for Medical and Health Research Involving Human Subjects," informed consent for participation from patients was obtained by providing study-related information on the home page and at our outpatient department.

RESULTS

A total of 109 patients (Con group, $n = 78$; Olz group, $n = 31$) underwent concurrent chemoradiotherapy for HNC during the study period. The baseline characteristics of the patients are shown in Table 1. No significant differences in age, sex, primary site, stage, pathological diagnosis, eGFR, and the number of induction chemotherapy were observed between both groups. The prevalence of diabetes was significantly higher in the Con group ($P = 0.0318$, Fisher's exact test), whereas the rate of IMRT was significantly higher in the Olz group ($P < 0.0001$, Fisher's exact test). The mean dose of CDDP in the initial chemoradiotherapy administration. The mean CDDP dose was 89.9 and 95.6 mg/m^2 in the Con and Olz groups, respectively, with the latter having a significantly higher dose compared to the former ($P = 0.0042$, t-test with Welch's correction analysis).

The dose of olanzapine was 5 mg in 23 of 31 patients (74.2%) and 10 mg in 8 of 31 patients (25.8%). In the Olz group, one patient received fosaprepitant intravenously instead of aprepitant orally. In the Con group, one patient received aprepitant in days 4 and 5.

Table 2 shows the severity of acute CRINV (0 to 24 hours from CDDP administration) and delayed CRINV (25 to 120 hours from CDDP administration) evaluated using CTCAE. The number of patients who experienced acute CRINV over Grade 3 was 4 (5.1%) and 0 (0%) in the Con and Olz groups, respectively, with no significant difference between both groups ($P = 0.5761$, Fisher's exact test). The number of patients who experienced delayed CRINV over Grade 3 was 11 (14.1%) and 0 (0%) in the Con and Olz groups, respectively, with the later having a significantly lower incidence rate compared to the former ($P = 0.0318$, Fisher's exact test).

Table 3 shows the complete response rate of acute and delayed CRINV. The number of patients who did not experience any acute CRINV (i.e., those who had a complete response) was 46 (59%) and 22 (71%) in the Con and Olz groups, respectively. Although complete response was more common in the Olz group, no significant difference was observed between both groups ($P = 0.2794$, Fisher's exact test). The number of patients who did not experience any delayed CRINV (i.e., those who had a complete response) was 20 (25.6%) and 12 (38.7%) in Con and Olz groups, respectively, with no significant differences between both groups ($P = 0.2433$, Fisher's exact test).

Table 4 shows the incidence and severity of adverse events. The frequency of constipation, hiccups, insomnia, and dry mouth over Grade 1 was not significantly different between the two groups ($P = 0.1519$, 0.9999, 0.9999, and 0.6725, respectively, Fisher's exact test). The frequency of somnolence and dizziness over Grade 1 was significantly higher in the Olz group ($P = 0.0020$ and 0.0024, respectively, Fisher's exact test). However, no patients experienced any severe adverse events over Grade 3 in both groups.

DISCUSSION

The current study focused on the antiemetic effects of olanzapine and sought to elucidate whether four-drug combination therapy with olanzapine would be more

Table 1. Characteristics of patients in the Con and Olz groups

		Con group (n = 78)	Olz group (n = 31)	P value
Age (yr)	Mean	64.2	61.6	0.2255*
Sex (no.) (%)	Male	71 (91)	25 (80.6)	0.4288‡
	Female	7 (9)	6 (19.4)	
Primary site (no.) (%)	Hypopharynx	24 (30.8)	15 (48.4)	0.1902†
	Oropharynx	12 (15.4)	6 (19.3)	
	Larynx	16 (19.2)	2 (6.5)	
	Nasal cavity and paranasal sinus	8 (10.3)	1 (3.2)	
	Others	12 (15.4)	7 (22.6)	
Stage (no.) (%)	I and II	16 (20.5)	5 (16.1)	0.8507†
	III	13 (16.7)	6 (19.4)	
	IV	49 (62.8)	20 (64.5)	
Histology (no.) (%)	SqCC	74 (94.9)	29 (93.5)	> 0.9999‡
	Non-SqCC	4 (5.1)	2 (6.5)	
eGFR (ml/min)		86.77	82.85	0.5464*
Diabetes mellitus (no.) (%)		11 (14.1)	0 (0)	0.0318‡
IMRT (no.) (%)		31 (39.7)	30 (96.8)	< 0.0001‡
Cisplatin (mg/m^2)		89.9	95.6	0.0042*
Induction chemotherapy (no.) (%)	None	32 (41)	7 (22.5)	0.0701†
	1 cycle	27 (34.6)	10 (32.3)	
	2 cycles	19 (24.4)	14 (45.2)	
Dose of olanzapine (no.) (%)	5 mg	0 (0)	23 (74.2)	
	10 mg	0 (0)	8 (25.8)	

*t-test with Welch's correction. †Chi-square test. ‡Fisher's exact test. IMRT, intensity-modulated radiation therapy; SqCC, squamous cell carcinoma; yr, year(s).

Table 2. Severity of acute and delayed chemoradiotherapy-induced nausea and vomiting evaluated using Common Terminology Criteria for Adverse Event version 4.0

Severity of CRINV		Con group (n = 78)	Olz group (n = 31)	P value
Acute CRINV (0–24 h after chemotherapy)				
	Grades 0–2	74	31	0.5761
	Grade 3	4	0	
Delayed CRINV (25–120 h after chemotherapy)				
	Grades 0–2	67	31	0.0318
	Grade 3	11	0	

CRINV, chemoradiotherapy-induced nausea and vomiting.

effective against CRINV compared to the conventional three-drug combination therapy during concurrent chemoradiotherapy for HNC. We revealed that the addition of olanzapine to conventional three-drug combination therapy effectively suppressed the delayed CRINV due to concurrent chemoradiotherapy with high-dose cisplatin for HNC. Furthermore, adverse events related to the addition of olanzapine were not severe but controllable.

Despite the marked improvement in the treatment

Table 3. Complete response rate of acute and delayed chemradiootherapy-induced nausea and vomiting

Complete response	Con group ($n = 78$)	Olz group ($n = 31$)	*P* value
Acute CRINV (0–24 h after chemotherapy)			
Yes	46	22	0.2794
No	32	9	
Delayed CRINV (25–120 h after chemotherapy)			
Yes	20	12	0.2433
No	58	19	

CRINV, chemoradiotherapy-induced nausea and vomiting.

Table 4. Treatment-related adverse events

	Con group ($n = 78$)			Olz group ($n = 31$)		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Constipation	40	14	0	25	1	0
Hiccups	14	12	0	4	6	0
Somnolence	2	0	0	6	1	0
Insomnia	7	0	0	2	0	0
Dizziness	0	2	0	7	0	0
Dry mouth	5	0	0	1	0	0

of CINV, these adverse events remain an important concern during cancer treatment. Phase 3 studies on the addition of olanzapine to conventional three-drug combination therapy with dexamethasone, palonosetron, and aprepitant revealed considerable efficacy in suppressing CINV among patients receiving HEC treatment.[3, 4]

CRINV have also been common adverse events among patients receiving chemoradiotherapy for HNC given its relatively higher dose of CDDP compared to other cancer treatments.[8] As such, four-drug combination antiemetic therapy with olanzapine might be especially useful for preventing CRINV due to chemoradiotherapy for HNC. Nonetheless, the efficacy of four-drug combination antiemetic therapy among patients receiving chemoradiotherapy for HNC is still unclear. The current study demonstrated that four-drug combination antiemetic therapy was useful in preventing delayed CINV compared to conventional three-drug combination therapy.

CDDP, a well-known HEC, has been dose dependently associated with the incidence rate of CINV.[9–11] The current study showed that the mean CDDP dose was significantly higher in the Olz group, suggesting that the Olz group was at increased risk for CRINV compared to the Con group. RINV, which have also been associated with cancer treatment,[7] are clinically important and can be distressing for patients. Furthermore, RINV cause patients to delay or refuse further treatment. IMRT is a type of high-precision radiotherapy that can increase the radiation dose to the tumor and decrease that to surrounding normal tissues. The frequency of IMRT use for the purpose of alleviating salivary gland disorders after radiotherapy has been increasing; however, IMRT use carries higher risk for RINV compared to conventional three-dimensional conformal radiation therapy.[12] The current study showed that the CDDP dose and IMRT use were significantly higher in the Olz group compared to the Con group, suggesting that the Olz group was at increased risk for CRINV. Nevertheless, acute CRINV was not significantly increased in the Olz group, which indicated that the addition of olanzapine to conventional three-drug combination therapy might be effective in suppressing acute CRINV. Furthermore, delayed CRINV was significantly lower in the Olz group, indicating that the addition of olanzapine to conventional three-drug combination therapy was effective in suppressing delayed CRINV due to chemoradiotherapy for patients with HNC concurrently receiving high-dose CDDP.

There was a mixture of patients receiving two

different doses of olanzapine in the Olz group. A previous report suggested that a 5-mg olanzapine prophylactic regimen may be as effective as a 10-mg olanzapine regimen.[13] Thus, we did not perform statistical analysis to compare the efficacy of olanzapine between two dosages for the prevention of CRINV in this study.

This study has several limitations. Complete responses were more frequent in the Olz group, although no significant difference was observed between both groups. Given the retrospective, single-center design of the current study, we believe that the lack of a significance difference between the groups could be attributed to the insufficient number of cases enrolled.

Considering that olanzapine can induce fetal hyperglycemia, such as diabetic ketoacidosis, olanzapine is contraindicated in patients with diabetes mellitus.[14] None of our patients who received four-drug combination therapy with olanzapine had diabetes, suggesting a difference between the two groups in terms of the presence of diabetes. Although studies on diabetes increasing the frequency of CINV have not been accepted in the best of our knowledge, we cannot completely rule out the effects of diabetes on the results of the current study.

In conclusion, four-drug combination therapy with olanzapine was effective in suppressing delayed CRINV due to chemoradiotherapy with cisplatin for HNC.

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The authors declare no conflict of interest.

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