A SINGLE-ARM EXPLORATORY STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF OLANZAPINE PROPHYLAXIS FOR OPIOID-INDUCED NAUSEA AND VOMITING (JORTC-PAL20)

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Introduction

Opioid-induced Nausea and Vomiting (OINV)
・Occurs in 20-40% of patients upon initiation or dose escalation of opioids.
・Tolerance develops within 5-7 days.
・Prophylactic antiemetic administration is recommended for patients with a history of OINV.
・Once nausea occurs, it can lead to non-adherence due to psychological barriers.
・Preventive antiemetic use lacks strong evidence in the literature and is largely based on physician discretion.

Olanzapine as an Antiemetic
・Atypical antipsychotic (multiple-receptor antagonist)
・Effective in preventing chemotherapy-induced nausea and vomiting (CINV) in highly emetogenic chemotherapy regimens.
・OINV can significantly impact patient quality of life and treatment outcomes.

Aim

To assess the efficacy and safety of using 5 mg OLZ in preventing OINV in patients with cancer receiving regular opioid therapy for cancer pain.

Key Eligibility Criteria

- Patients with moderate-to-severe cancer pain needed to treat with opioid analgesics such as morphine, oxycodone, hydromorphone and so on.
- ECOG PS 0–3.
- Ability to provide written informed consent.
- 18 years of age or older.
- Capable to take medicine orally.
- Expected life expectancy of 4 weeks or longer.
- Able to complete study assessments and comply with the study procedures.

Treatment procedure

All patients will receive OLZ (5 mg orally after dinner on days 1–5). If drowsiness or dizziness of G2 or greater is observed at visit 1, the dose of OLZ is reduced to 2.5 mg. Diphenhydramine is available as a rescue antiemetic for nausea and vomiting during study period as concomitant therapy.

Timepoint	Day1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Opioid therapy	X	X	X	X	X	X	X
5mg Olanzapine	X	X	X	X	X		

Endpoints

The primary endpoint :
The complete control (CC)* rate during the 5 days following the first regular opioid treatment with OLZ.
*CC:defined as no emetic episode, no use of rescue medication for nausea and no or low nausea (3 or less on a categorical scale of 11).

Secondary endpoints:
The complete response rate (CR)**
** CR:defined as no emetic episodes and no use of rescue medication
The proportion of patients with no emetic episode
The cumulative number of emetic episodes in patients who had at least one emetic episode during the study period (0–7 days after opioid initiation)
The proportions of patients with no nausea (CTCAE grade 2>)
The levels of numerical rating scale (0–10) of nausea
The proportion of patients with no use of rescue antiemetic medication Feasibility
Adverse events were graded according to CTCAE version 5.0.

Statistical analysis

For the primary endpoint, an exact binomial test (one-sided, upper-sided significance level, 5%) will be performed with a threshold value of 65%. Point estimates and 90% CIs will be estimated. A complete statistical analysis plan will be written prior to the data analysis. All statistical analyses will be performed using SAS (V.9.4; SAS Institute).

Results

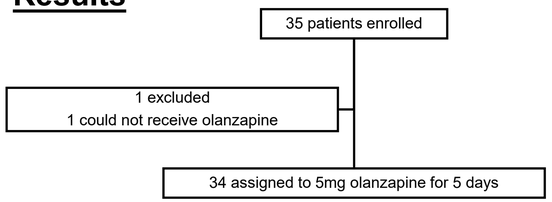

Figure1 Patient flow diagram

Table 1. Base line characteristics

Patient Characteristics	
Age, median (y)	58.8±14.8
Sex n (%)	
Female	19 (54.3%)
Male	16 (45.7%)
ECOG Performance status, n (%)	
0-1	24 (65.7%)
2	12 (34.3%)
Pain NRS (0-10)	5.9±2.2
Nausea NRS (0-10)	0.6±1.5
Daily oral morphine equivalent dose (mg/day)	21 (10-60)
Opioid type, n	
Hydromorphone	17
Tapentadol	9
Oxycodone	6
Morphine	2
Cancer type, n	
Digestive organ	9
Head and neck	8
Lung	7
Bone and Soft tissue	6
Other	5

Table2. Endpoints

End points	Overall period (5 days) (n=34)		Binomial distribution
	(%)	n	p-value
Complete control rate (CC)	76.5 %	26	0.1086
Complete response rate (CR)	79.4%	27	0.0390
Patients with "no emetic events"	85.3%	29	
Patients with “no nausea” or “worsen mild nausea”	79.4%	27	
Patients with "no additional antiemetics "	85.3%	29	
Completion rate of 5-day preventive olanzapine	85.3%	29	

Figure 2: Kaplan-Meier plot showing time to treatment failure for olanzapine

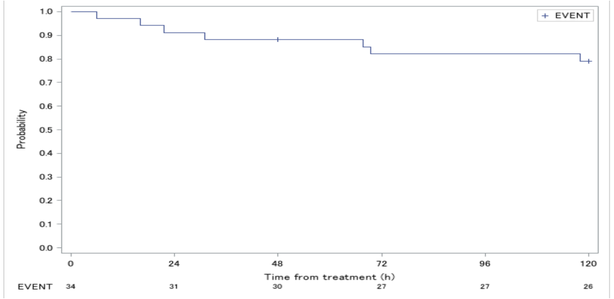

Figure 3: Kaplan-Meier plot showing time to vomiting for olanzapine

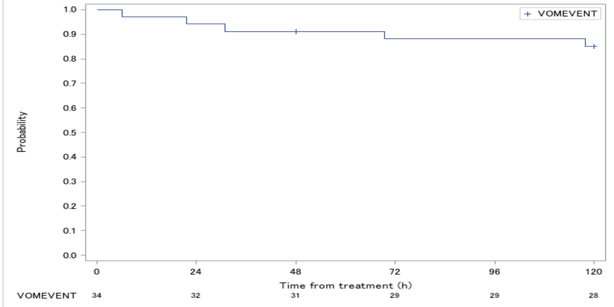

Table3. Treatment-related adverse events (CTCAE ver.5)

	Grade 1	Grade 2	Grade 3	Any Grade
Constipation	8(23.5%)	1(2.9%)	0	9 (26.5%)
Hiccups	1(2.9%)	0	0	1 (2.9%)
Somnolence	7(20.6%)	3(8.8%)	0	10 (29.4%)
Insomnia	5(14,7%)	1(2.9%)	0	6(17.6%)
Vertigo	3(8.8%)	0	0	3(8.8%)
Dry mouth	5(14.7%)	0	0	5(14.7%)
Other	4(11.8%)	0	0	4(11.8%)

●The point estimate for the CC for the primary endpoint was 76.5% (p=0.1086).
●The point estimate for the CR was 79.4%(p= 0.039).
●No severe adverse effect was observed during treatment period

Discussion

●The point estimate for the CC for the primary endpoint was 76.5%, which was well above the protocol-defined threshold of 65%, but did not exceed the expected value of 85%. And the test was not rejected, so preventive olanzapine for OINV was not judged to be effective. This does not mean ineffective, but should be considered as pending judgment, i.e. inconclusive as to whether it is effective or ineffective in the exploratory trial.

●There is no established evaluation for OINV, so CR, which is an outcome measure for CINV, was used in previous studies. However, we focused on nausea and set CC as primary endpoint. This study did not show effectiveness in CC, but suggested effectiveness in CR, so it is necessary to reconsider which measure is appropriate for future confirmative trials.

●Olanzapine 5mg as a prophylaxis for 5 days does not lead to any significant safety concerns. and was feasible for opioid initiation.

●As a limitation, this study was a single-centre, single-arm, open-label study, only Japanese participants, mainly middle-aged people

Ethics and Grant

●This study protocol was approved by National Cancer Center Hospital Certified Review Board (CRB3180008) and registered at the Japan Registry of Clinical Trials (jRCT) on 19 April 2022, as jRCTs 031220008.

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●Competing interests: None declared

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