CLINICAL TRIAL NOTE

A randomized, double-blind, placebo-controlled phase III trial evaluating olanzapine 5mg combined with standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting in patients receiving cisplatin-based highly emetogenic chemotherapy.

J-FORCE STUDY

J-SUPPORT and the Fourth agent "Olanzapine" Resist Cisplatin Emetogenesity.

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Background

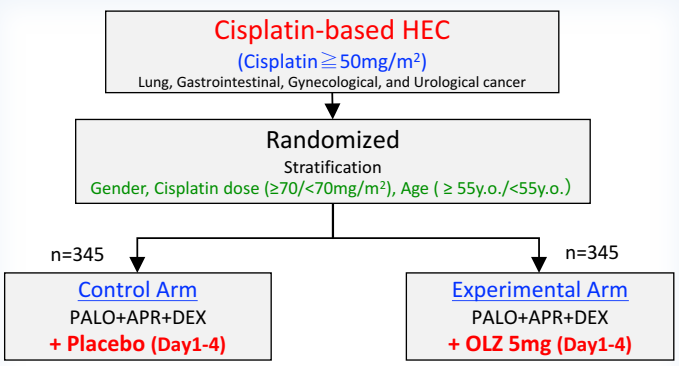
Olanzapine (OLZ) is effective for chemotherapy-induced nausea and vomiting (CINV). Although 10mg of OLZ is widely used for CINV, patient sedation may be a concern.
In Japan, three phase II studies revealed the efficacy and safety of 5mg of OLZ combined with palonosetron (PALO), aprepitant (APR), and dexamethasone (DEX) for CINV induced by cisplatin-based chemotherapy.
In these studies, complete response (CR: no vomiting, no rescue) in the delayed phase (24-120h) was 83-95%. Compared with 10mg, 5mg of OLZ seemed to be equally effective and less sedative.
The aim of this phase III study is to evaluate the efficacy of 5 mg of OLZ as compared with placebo, in combination with APR, PALO, and DEX, for the control of CINV induced by cisplatin-based chemotherapy.
This multi-institutional phase III study is supported by J-SUPPORT (Japan Supportive, Palliative and Psychosocial Oncology Group) and AMED (Japan Agency for Medical Research and Development).
This trial was registered in the UMIN Clinical Trials Registry as UMIN000024676 and began from February, 2017 in 30 institutes in Japan.

Phase II studies to examine 4-drug antiemetic regimen (PALO+APR+DEX +OLZ 5mg) for cisplatin-based HEC in JAPAN.

Study	n	OLZ	CR rate: Acute phase	CR rate: Delayed phase
TRIPLE study PALO+APR+DEX arm (Hashimoto et al. ASCO 2013, Suzuki et al. Ann Oncol 2016)	414 (Lung, GI, Neck)	-	92%	67%
Abe et al. (MASCC 2015, ESMO 2015 Support Care Cancer 2016)	40 (Gyne)	5mg (Day 0-5)	98%	95%
Nakashima et al. (MASCC 2016, JJCO 2017)	30 (Lung)	5mg (Day 1-5)	100%	83%
Hashimoto, Yanai et al. (ASCO 2016)	77 (Lung, GI, Neck)	5mg (Day 1-4)	99%	85%
	76 (Lung, GI, Neck)	10mg (Day 1-4)	100%	77%

randomized

Study Scheme



Primary endpoint is complete response rate in the delayed phase (24-120h).
We expect the delayed phase CR rate of the placebo and OLZ arms to be 65% and 75%, respectively. A total of **690 cisplatin-naïve patients** are required to achieve 80% power for a one-sided significance level of 0.025.

Evaluation of parameters

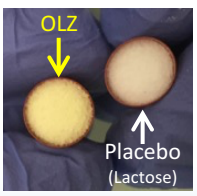
Endpoint	Acute 0-24h	Delayed 24-120h	Overall 0-120h
Complete response rate (no emesis, no rescue)	○	●	○
Complete control rate (no emesis, no rescue, and no more than mild nausea)	○	○	○
Total control rate (no emesis, no rescue, and no nausea)	○	○	○

- ○ Time to treatment failure (i.e., time to first emetic episode or time to administration of rescue therapy, whichever occurred first).
- ○ Severity of nausea.
- ○ Severity of anorexia.
- ○ Severity and influence to daily life of sleepiness.
- ○ Adverse event.

● Primary endpoint ○ Secondary endpoint

Blinding

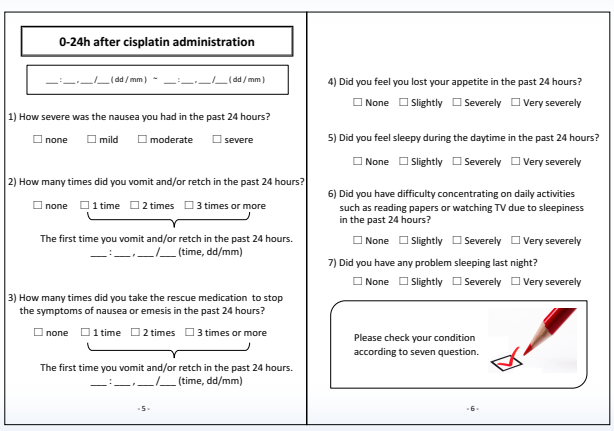
Swedish orange capsules designed for double-blind clinical trials is used (Capsugel DBcaps®). Size D capsule which can fill 2.5mg was selected for this study because of easy to take.
OLZ capsule is filled with 1% Zyprexa® granule and placebo capsule is filled with lactose. Patients are randomly assigned to receive either a 5 mg OLZ dose or placebo on days 1–4, in combination APR (or fosaprepitant : FOS), PALO, and DEX.
Patients take 2 capsules (2.5mg x 2) orally after supper (around 19 o'clock).



Study treatment

	Day 1	Day 2	Day 3	Day 4
OLZ / Placebo 2.5mg Capsule	2Cap	2Cap	2Cap	2Cap
PALO	0.75mg			
APR	125mg	80mg	80mg	
DEX	12mg	8mg	8mg	8mg
or				
FOS	150mg			
DEX	12mg	8mg	16mg	16mg

Patient symptom diary



0-24h after cisplatin administration

__:__ , __/__ (dd/mm) ~ __:__ , __/__ (dd/mm)

1) How severe was the nausea you had in the past 24 hours?
☐ none ☐ mild ☐ moderate ☐ severe

2) How many times did you vomit and/or retch in the past 24 hours?
☐ none ☐ 1 time ☐ 2 times ☐ 3 times or more
The first time you vomit and/or retch in the past 24 hours.
__:__ , __/__ (time, dd/mm)

3) How many times did you take the rescue medication to stop the symptoms of nausea or emesis in the past 24 hours?
☐ none ☐ 1 time ☐ 2 times ☐ 3 times or more
The first time you vomit and/or retch in the past 24 hours.
__:__ , __/__ (time, dd/mm)

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4) Did you feel you lost your appetite in the past 24 hours?
☐ None ☐ Slightly ☐ Severely ☐ Very severely

5) Did you feel sleepy during the daytime in the past 24 hours?
☐ None ☐ Slightly ☐ Severely ☐ Very severely

6) Did you have difficulty concentrating on daily activities such as reading papers or watching TV due to sleepiness in the past 24 hours?
☐ None ☐ Slightly ☐ Severely ☐ Very severely

7) Did you have any problem sleeping last night?
☐ None ☐ Slightly ☐ Severely ☐ Very severely

Please check your condition according to seven question.

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Key eligibility criteria

Inclusion criteria

1. Receives the cisplatin (>=50mg/m²)-based chemotherapy for the first time.
2. 20-75 years old at the enrollment.
3. ECOG performance status 0-2.
4. No symptomatic brain metastasis/carcinomatosis.
5. Not taking a medicine regularly, for example, 5HT3 receptor antagonists, NK1 receptor antagonists, corticosteroids, anti dopamine agonists, phenothiazine tranquilizers, antihistamine drugs, benzodiazepine agents, etc. within 48 hours prior to enrollment.

Exclusion criteria

1. In need of antiemetics at the enrollment.
2. Has diabetes mellitus with use of antidiabetics and has value measured HbA1c (NGSP) >= 6. 5 or HbA1c (JDS) >= 6.1 at the enrollment.
3. Has symptomatic ascites that need therapeutic drainage.
4. Psychotic using antipsychotic drug.
5. Either received abdominal or pelvic irradiation within 6 days prior to enrollment or to receive abdominal or pelvic concurrent chemoradiotherapy.
6. Habitual smoker.

COI: We have no potential conflict of interest to disclose.