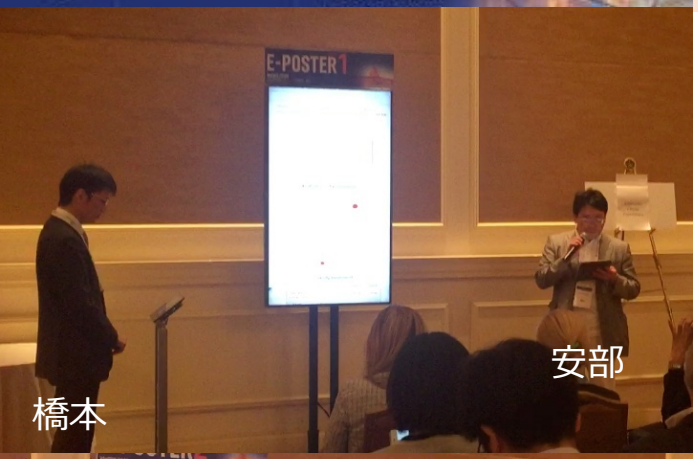

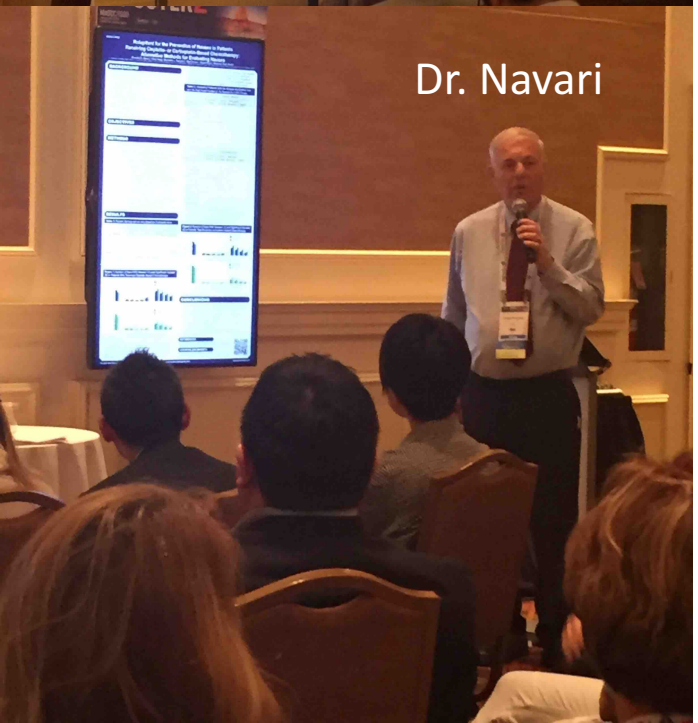

J-SUPPORT 1604

J-FORCE STUDY News Letter Vol. 2

J-SUPPORT and **F**orth agent **O**lanzapine **R**esist **C**isplatin **E**metogenesity.

参加施設の先生方

J-FORCE試験では大変お世話になりありがとうございます。
試験開始から約4ヶ月半経ちましたが、登録総数は112/690例となりました。これまでのご尽力に感謝申し上げます。

① 先日ワシントンで開催されたMASCC 2017に出席し、J-FORCE STUDYのClinical Trial Noteを発表してきました。

② CINVに対するOLZについてディベートが行われ、Navari先生がin favorの、Roila先生がagainstのspeakerでした。スライド2, 3, 4に内容をまとめました。国際的にはまだまだエビデンスが十分ではないというのがディベートおよびMASCC制吐薬ガイドラインWGの見解で、Navari P3 1試験のみでは不十分、5mgを検証すべき、というのが国際レベルでの状況です。ディベートでは、J-FORCE STUDYも紹介され、J-FORCE STUDYは国際的にも注目されています。

③ 試験薬のOLZですが、まだ未承認薬ではありますが、6月中旬に保険適用となりました。保険適用になることは患者さんにとっては良いことですが、CINVに対するOLZの適正使用については前述の通り、まだまだ質の高いエビデンスの集積が望まれている状況で、保険適用になっても、J-FORCE STUDYの意義は変わりません。本試験の意義についての患者さんへの説明がこれまでよりもお時間、お手数をおかけしますが、よろしくお願いいたします。

これまでの皆様のご協力に心より感謝申し上げるとともに、引き続きご協力のほどよろしくお願いいたします。

研究代表者　静岡がんセンター婦人科　安部正和
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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.

Masakazu Abe [1], Takako Yanai [2], Kazuhisa Nakashima [3], Yasuyuki Hirashima [1], Haruyasu Murakami [3], Satoshi Hamauchi [4], Hiroshi Ishikawa [5], Michiru Sakurai [5], Takuhiro Yamaguchi [6], Sadamoto Zenda [7], Yousuke Uchitomi [7], Hiroyuki Terakado [2], Satoru Iwasa [8], Hironobu Hashimoto [2]

[1]Department of Gynecologic Oncology, Shizuoka Cancer Center, [2]Department of Pharmacy, National Cancer Center Hospital, [3]Department of Thoracic Medical Oncology, Shizuoka Cancer Center, [4]Department of Gastrointestinal Medical Oncology, Shizuoka Cancer Center, [5]Department of Pharmacy, Shizuoka Cancer Center, [6]Department of Biostatistics, Tohoku University Graduate School of Medicine, [7]Japan Supportive, Palliative and Psychosocial Oncology Group , [8]Department of Gastrointestinal Medical Oncology, National Cancer Center Hospital

Background

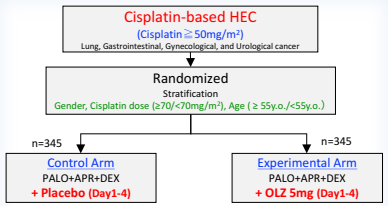
Olanzapine (OLZ) is effective for chemotherapy-induced nausea and vomiting (CINV). Although 10mg of OLZ is widely used for CINV, patient sedation may be a concern. In Japan, three phase II studies revealed the efficacy and safety of 5mg of OLZ combined with palonosetron (PALO), aprepitant (APR), and 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, JCO 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

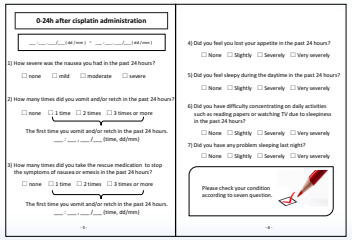
Blinding

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



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.

Olanzapine: a prime drug or not?
A debate

In favour

Rudolph Navari , USA

Professor of Medicine, Assistant Dean and Director,
Indiana University School of Medicine South Bend, USA.
Member of the Board of the MASCC

Against

Fausto Roila , Italy

Director in the Medical Oncology Division, S. Maria Hospital, Terni, Italy.
Member of the Board of the MASCC
Subject Editor of ESMO clinical recommendations on supportive/palliative care
Leader of the Italian Group for Antiemetic Research
The organizers of the MASCC Consensus Conference on antiemetics

In favour

Against

これまでの主なOlanzapine試験

- ✓ P1で10mg推奨（DLT: sedation）
  Passik SD, Cancer Invest, 2004
- ✓ Short term use of olanzapine appears to be effective in controlling CINV in patients receiving HEC
  Navari RM, et al, J Support Oncol, 2011
- ✓ Olanzapine appears to have significant efficacy in delayed nausea
  Olanzapine vs DEX
  Tan L, et al, J Exp Clin Cancer Res, 2009
  Olanzapine vs Aprepitant
  Navari RM, et al, J Support Oncol, 2011
- ✓ Olanzapine effective in “Breakthrough CINV”
  Olanzapine vs Metoclopramide
  Navari RM, et al, Supp Care Cancer, 2013
- ✓ Olanzapine effective in patients receiving CCRT
  Olanzapine vs Fosaprepitant
  Navari RM, et al, J Comm Supp Oncol, 2016

(5HT3RA+DEX)+ Olanzapine vs NK1RA

Navari studyのshortcomings

- ✓ Open studyまたはsample sizeが少ない二重盲検試験。
- ✓ Sample sizeが少ない（全期間のCRにおいて15%位の大きな差を検証するようなSample size設定）。
- ✓ 試験デザインが定義されていない：
  優越性試験？　非劣性試験？　同等性試験？
- ✓ 10mgのOLZにgrade 3 or 4のtoxicityが本当にないのか？
  有害事象の検証が不十分。

Conclusion 1

- ✓ Due to the low quality of the studies it is not possible to conclude that olanzapine is superior or not inferior to a NK1 RA in the prevention of cisplatin-induced acute and delayed emesis.
- ✓ More well done randomized double-blind studies should be carried out to demonstrate the superiority in the control of nausea of olanzapine with respect to a NK1 RA when both are combined with DEX and a 5HT3 RA.

In favour

Against

Olanzapine in Highly Emetogenic Chemotherapy
5HT3RA+DEX+NK1RA+ Olanzapine vs Placebo
Navari RM, et al, New Engl J Med, 2016

OLZとInternational Antiemetic Guidelines

- ✓ NCCN: OLZ+NK-1+5HT3+Dex for HEC
  OLZ+5HT3+Dex for HEC
- ✓ MASCC/ESMO: await OLN Phase III publication; expect update
- ✓ ASCO: new guidelines completed, await publication

Future Studies

1) Dose: 5mg vs 10mg (Efficacy vs Toxicity)
J-FORCE STUDYが紹介されました
2) Multiple cycles
3) Treatment of established NAUSEA AND EMESIS
(CLINICAL TRIALS GOV. NCT 03137121)
4) OLZ+NK-1+5HT3+Dex vs OLZ+5HT3+Dex
(Alliance Clinical Trials in Oncology, study launch, 2017)
5) OLN in SCT (UAB, study launch, 2017)

Olanzapine added to NK1RA (4-drug regimen)

- ✓ 3剤＋OLZ 5mgは3剤より良いことが示唆。
  Abe M et al. Support Care Cancer 2015
- ✓ 3剤＋OLZ 10mgは3剤+Placeboよりも良い成績。
  Navari RM et al. N Engl J Med 2016
- ✓ 3剤＋OLZ 5mgは、3剤＋OLZ 10mgと同等の成績。
  眠気は有意差なかったが、5mgで軽い傾向。
  Hashimoto H et al. J Clin Oncol 2016

Conclusion 2

- ✓ A dose-finding study should be carried out to identify the least toxic dose of olanzapine (maintaining its efficacy).
- ✓ Subsequently, two large well conducted studies (in cisplatin-treated and AC/EC-treated patients) using this dose should be carried out to confirm Navari's results.