Phase III Study of Comparing Dexamethasone on Day 1 with Day 1-4 with Combined Nurokinin-1 Receptor Antagonist, Palonosetron and Olanzapine in Cisplatin-based Chemotherapy: SPARED TRIAL

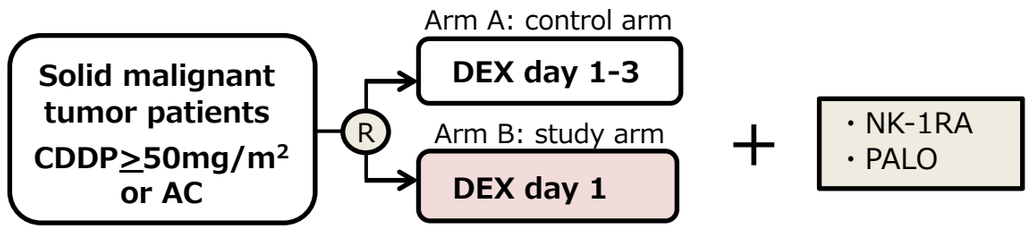
H. Minatogawa[1] , N. Izawa[2] , T. Kawaguchi[3] , T. Miyaji[4] , A. Yokomizo[1] , Y. Horie[2] , K. Shimomura[6] , K. Honda[7] , H. Morita[8] , N. Hida[9] , A. Tsuboya[10] , T. Tsuda [2], H. Iihara[11] , Y. Ohno[12] , T. Yamaguchi [13], T. Nakajima[2]

[1]St.Marianna University School of Medicine Hospital, Department of Pharmacy, Kawasaki, Japan. [2]St.Marianna University School of Medicine, Department of Clinical Oncology, Kawasaki, Japan. [3]Tokyo University of Pharmacy and Life Sciences, Department of Practical Pharmacy, Tokyo, Japan. [4]Graduate School of Medicine- The University of Tokyo, Department of Clinical Trial Data Management, Tokyo, Japan. [5]St.Marianna University School of Medicine Hospital, Pharmacy, Kawasaki, Japan. [6]Aichi Cancer Center Hospital, Department of Pharmacy, Nagoya, Japan. [7]Aichi Cancer Center Hospital, Department of Clinical Oncology, Nagoya, Japan. [8]St. Marianna University Yokohama City Seibu Hospital, Department of Pharmacy, Yokohama, Japan. [9]St.Marianna University School of Medicine, Department of Internal Medicine, Kawasaki, Japan. [10]St. Marianna University Kawasakishi Muncipal Tama Hospital, Department of Pharmacy, Kawasaki, Japan. [11]Gifu University Hospital, Department of Pharmacy, Gifu, Japan. [12]Gifu University Graduate School of Medicine, Department of Respirology, Gifu, Japan. [13]Tohoku University School of Medicine, Division of Biostatistics, Sendai, Japan.

Background

- Dexamethasone (DEX) is administered for multiple days to prevent chemotherapy-induced nausea and vomiting (CINV) to patients receiving high emetogenic chemotherapy (HEC). It has also been reported that DEX has notorious side effects[1)-3)].
- Our multicenter, randomized, double-blinded controlled trial **(DEX-1)**[4)] verified sparing DEX after day2 in HEC regimen. However, the benefit of DEX sparing was not indicated for patients receiving cisplatin (CDDP)-based HEC regimens in subgroup analysis.
- Recently, phase 3 trial demonstrated that olanzapine (OLZ) 5 mg improved CINV prevention in CDDP-based HEC regimens[5)]. Therefore, it is expected that addition of OLZ enables DEX sparing in CDDP-based HEC regimens.
- This study aims to evaluate the non-inferiority of DEX sparing compared with DEX on multiple days when combined with NK1 receptor antagonist (NK-1RA), palonosetron (PALO), and OLZ in CDDP-based HEC regimens.

DEX-1 trial [4)]

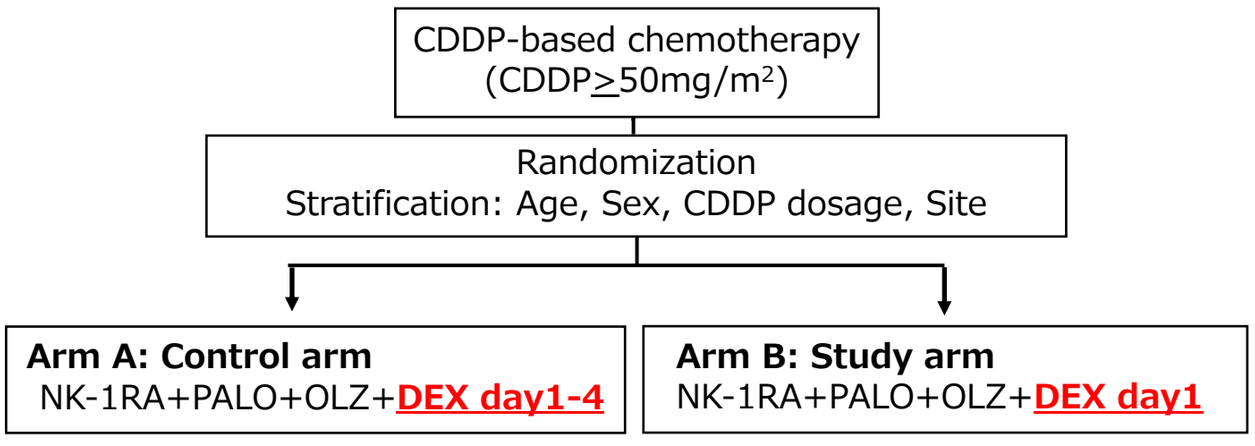


Subgroup analysis (CDDP-based)

		Arm A n=45	Arm B n=45	risk difference 95%CI	p value
CR (%)	Overall (0-120h)	66.7	57.8	-8.9% [-28.7%, 10.9%]	0.273
	Acute (0-24h)	95.6	95.6	0% [-11.9%, 11.9%]	0.007
	Delayed (24-120h)	68.9	57.8	-11.1% [-30.8%, 8.6%]	0.349

AC: anthracycline and cyclophosphamide combination therapy
CR: Complete response (No vomiting and no rescue use)

Study scheme



Study treatment

	day1	day2	day3	day4
Fosaprepitant iv /Aprepitant p.o.	150mg /125mg	/80mg	/80mg	
PALO iv	0.75mg			
OLZ p.o.	5mg	5mg	5mg	5mg
DEX iv	9.9mg			
DEX iv /Placebo iv		6.6mg /Placebo	6.6mg* /Placebo	6.6mg* /Placebo

*When using fosaprepitant, increase the dose of dexamethasone to 13.2mg.

Endpoints

➢ **Primary end point: CR rate in delayed phase**

➢ **Secondary end points:**

- **CR rate** in overall/ acute phase
- **CC rate, TC rate, No vomiting rate, No nausea rate** in overall/ acute/ delayed phase
- **Time to treatment failure** (i.e. time to first vomiting or using rescue, whichever occurred first)
- **Severity of nausea** in overall phase
- **Quality of Life** (EORTC QLQ-C30)
- **Adverse events** (CTCAE v4.0-JCOG and PRO-CTCAE™ v1.0)

CR: Complete response (No vomiting and no rescue use)
CC: Complete control (No vomiting, no rescue use and no significant nausea)
TC: Total control (No vomiting, no rescue use and no nausea)

Statistical methods

・Expected CR rate: 75% in both arms
・Noninferiority margin of difference in CR rate: -15.0%
・One-sided α: 0.025 ・Power: 80%
・Sample size: 280

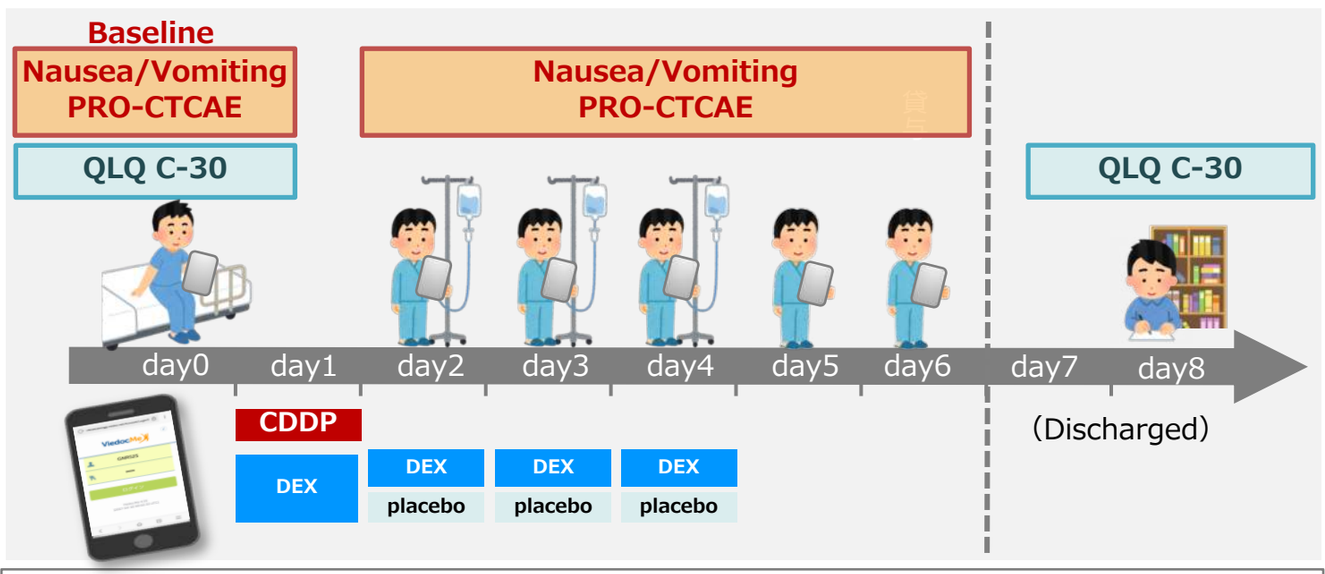
Evaluation Items: Patient reported outcome

Input to ePRO

- Nausea: numerical rating scale (day0, day2 to 6)
- Vomiting: presence or absence, count (day0, day2 to 6)
- PRO-CTCAE™ (version1.0) (day0, day2-6)
- EORTC QLQ-C30 version 3 (day0)

Fill in questionnaire (paper)

- EORTC QLQ-C30 version 3 (day8)



PRO-CTCAE items: nausea, vomiting, discouraged, sad or unhappy feelings, anxious, insomnia, decreased appetite, constipation, diarrhea, hot flashes, hiccups, fatigue, taste changes, dry mouth, mouth/throat sores, headache, bloating, somnolence, dysosmia

ePRO: electronic patient reported outcome

Key eligibility criteria

Major inclusion criteria

1. Patients with malignant tumor, excluding hematological malignancies, receiving first-line treatment with CDDP ≥ 50 mg/m² (previous use of moderately or low emetogenic chemotherapy is permitted).
2. Patients aged 20-74 years at the time of providing consent.
3. Patients with nausea and vomiting of grade 0 according to CTCAE v.4.0. in the 24 hours prior to enrolment.
4. Patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1.
5. Patients with adequate organ function.
6. Patients with expected prognosis of three months or more.

Major exclusion criteria

1. Patients receiving systemic glucocorticoid therapy.
2. Patients using antiemetics other than the trial drug.
3. Patients who receive moderately emetogenic chemotherapy within six days before and after CDDP administration (Minimally to low emetogenic agents are allowed)
4. Patients who receive radiation therapy to abdomen or pelvis within six days prior to enrollment until six days after CDDP.
5. Patients with symptomatic brain metastasis.
6. Patients with diabetes mellitus receiving treatment with insulin and/ or oral hypoglycemic agents, or patients with HbA1c (NGSP) ≥ 6.5 % (≥ 6.1 % in the event of JDS) less than 28 days prior to enrollment.
7. Patients with convulsive disorder requiring treatment with anticonvulsants.
8. Patients who are incapable of taking oral agents.

Recruitment

This trial was registered in the UMIN Clinical Trials Registry as UMIN000032269 and began from October 2018 in 11 institutes in Japan.

As of May 2019, 54 patients recruited.

Reference

1) J Vardy, wt al. Br J Cancer; 94: 1011-1015(2006)
2) Nakamura M, et al. Oncologist, 22(5): 592-600(2017)
3) Jeong Y, et al. Cancer Res Treat, 48(4): 1429-1437(2016)
4) Ito Y, Nakajima TE, et al. J Clin Oncol,36(10): 1000-1006(2018)
5) J Clin Oncol 37, 2019 (suppl; abstr 11503)

COI: This research is supported by AMED (Japan Agency for Medical Research and Development) under Grant Number 19ck0106501h0001.