海外派遣研究助成事業による研究の成果

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・研究に従事した外国の研究機関名 ・参加した国際学会・会議名	10th World Research Congress of the EAPC (第10回欧州緩和ケア学会)
渡航期間	自　2018年5月23日 至　2018年5月28日
・研究内容 ・国際学会・会議内容	緩和ケアに関する最新の研究成果について議論する

研究成果　（　要約：800字　）

今回私は、スイスのベルンで行われた第10回欧州緩和ケア学会において、がん患者におけるオピオイド誘発性便秘(OIC)に対するナルデメジンの効果と副作用について示説発表を行いました。本学会での演題応募数は約900に対し採択演題数は533であり、採択率は約60%でした。OIC治療薬として海外ではmethylnaltrexone(MNTX)、alvimopan、naloxegolの3剤が使用されていますが、今回研究を行ったナルデメジンは4番目の末梢性オピオイド受容体阻害薬(PAMORA)として注目されており、世界に先駆けて日本で承認されました。これまでナルデメジンに関して公表されているデータは全て、開発企業の主導で行われた治験におけるもので、実地診療における効果と副作用の実態を報告したものは我々の発表が世界初であります。さらに、治験で副作用の頻度は集計されているものの、どのような副作用への対処が適切であったかについては全くデータがありませんでした。今回の我々の発表で特に重要な点として、① これまで20%前後と報告されている下痢の副作用を、オピオイド開始早期からナルデメジンを開始することで大幅に減少させることができる、② ナルデメジンの投与開始により下痢が生じた際に下剤を中止すると、その後便秘となることが高頻度にみられる、③ 下痢の軽快後に起こる便秘を予防するためには、ナルデメジンを継続しつつ他の下剤を中止するのが有用と考えられることの3点が挙げられます。類薬のnaloxegolに関するシンポジウムではOICに関する包括的なレビューとディスカッションが行われ、他のがん症状緩和に関するセッションとあわせて今後の研究をどのように発展させていくかについて多くの有用な知見が得られました。最後に、本発表を支援して頂いたがん研究振興財団の皆様に心からの感謝をさせて頂きます。ありがとうございました。

Profile and management of adverse events during treatment by naldemedine, a novel peripherally-acting mu-opioid receptor antagonist (PAMORA), for cancer patients with opioid-induced constipation (OIC).

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BACKGROUND

- Opioid-induced constipation (OIC) is common and troublesome symptom in patients using opioids.
- Naldemedine, a novel peripherally-acting mu-opioid receptor antagonist (PAMORA), was approved for the treatment of OIC by Japanese regulatory authority in March 2017.
- Although efficacy and safety data among highly selected patients is available from pivotal studies, real-world evidence including appropriate management of adverse events is still lacking.

AIM

To obtain knowledge for effective and safer use of naldemedine for OIC patients

METHODS

- Multi-center, retrospective observational study by electronic chart review
- This study was approved by the institutional review board of each participating center

Eligibility criteria
- Received palliative care in participating centers
- Took at least one dose of naldemedine between April 2017 to March 2018
- Be prescribed regular opioids

Exclusion criteria
- Naldemedine had been started before the first visit to the participating centers
- Candidates or their family displayed opt-out denial of study participation

- We divided patients into two groups; patients who started naldemedine within 3 days (Early administration) or >3 days (Late administration) after the initiation of regular opioids
- We evaluated daily defecation counts and use of laxatives between -7 to +7 days from the day naldemedine started
- We also assessed the incidence of diarrhea and constipation within 7 days after the initiation of naldemedine
- Diarrhea was defined as Bristol stool scale of 6-7 and evaluated Grades using CTCAE ver.4.0
- Constipation was defined as <3 times per week or >72-hour absence of defecation

PROFILES OF NALDEMEDINE[1]

- Peripherally-acting mu-opioid receptor antagonist (PAMORA)
- Molecular weight: 742.84
- C_{max}: 2.02 ng/mL, T_{max}: 2.00 hr, $t_{1/2}$: 9.53 hr (N = 16)
- Given orally, 0.2 mg once daily
- Affinity to the opioid receptors *in vitro*:

Ki (nM)	mu	delta	kappa
Naldemedine	0.34 ± 0.03	0.43 ± 0.08	0.94 ± 0.08
MNTX	5.48 ± 1.11	3458 ± 306	32.1 ± 1.4

- Antagonistic activity to the opioid receptors *in vitro* (against DAMGO, enkephalin and GTPγS):

Kb (nM)	mu	delta	kappa
Naldemedine	0.50 ± 0.05	0.27 ± 0.03	0.44 ± 0.08
MNTX	55.9 ± 6.1	1082 ± 234	>271

1: Interview form of Synproic® ver.3. Shionogi & Co., Ltd, 2017.

RESULTS

Patients Characteristics

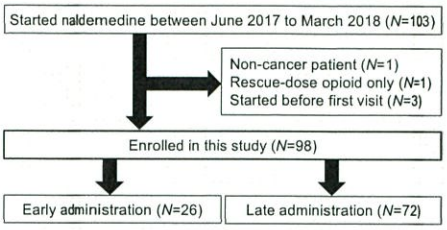


Fig 1: Flowchart of patients through this study.

Table 1: Baseline characteristics of study participants.

Category	Subcategory	N
Total		98
Age, mean (range), yr		68 (23-87)
Sex	Female	47 (48%)
	Male	51 (52%)
ECOG-PS	1	23 (24%)
	2	25 (26%)
	3	31 (32%)
	4	19 (20%)
No. of distant metastases, median (range)		2 (0-6)
Dietary intake*1	0-10%	18 (20%)
	20-40%	26 (29%)
	50-70%	17 (19%)
	80-100%	30 (33%)
Prescribed opioids	Morphine	13 (13%)
	Oxycodone	59 (60%)
	Fentanyl	18 (18%)
	Others*2	8 (8%)
Oral morphine equivalent dose, median (range), mg/day		30 (5-480)
Target symptom	Pain	90 (92%)
	Dyspnea	8 (8%)
Time from opioid initiation to first naldemedine dose, median (range), days		23 (0-1218)

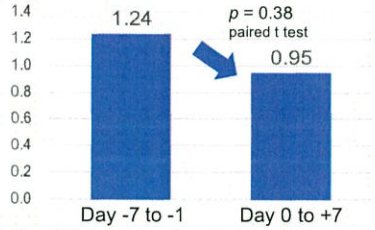
*1 Dietary intake of 7 patients was not assessed.
*2 Other opioids were tramadol (3), hydromorphone (2), codeine (2) and methadone (1).

Delivery of Naldemedine

- Median survival (from initiation of naldemedine) and duration of naldemedine administration estimated by Kaplan-Meier method were 64 and 25 days, respectively.
- Major reasons for the discontinuation of naldemedine were: unable to take oral drugs (77%), potential adverse events (8%), and termination of opioids (7%).

Daily Defecation Counts

Early administration (N = 22*)



Late administration (N = 57*)

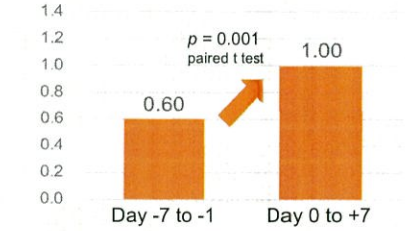


Fig 2A and 2B: Average number of defecation before and after the first dose of naldemedine.
* Four and fifteen patients in early and late administration groups were not assessed daily defecation counts through Day -1 to +1 (from the first naldemedine dose).

- Naldemedine significantly increased daily defecation counts in the Late administration group, whereas defecation counts were kept stable (or slightly decreased) in the Early administration group.

Incidence of Diarrhea

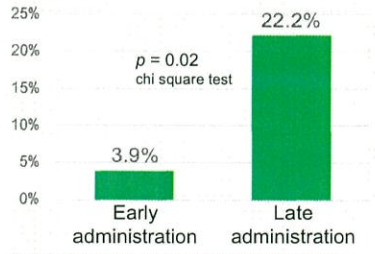


Fig 3: Incidence of diarrhea according to the groups.

Table 2: Grades of diarrhea according to the groups.

Group	Grade 1	Grade 2	Grade 3
Early	1 (4%)	0	0
Late	9 (13%)	4 (6%)	3 (4%)

- Other variables including age, sex, ECOG-PS, prescribed opioid or its dose, dietary intake, or defecation counts before naldemedine did not predict the diarrhea.
- Incidence and severity of diarrhea after the first dose of naldemedine was higher in the Late administration group.

Clinical Course of Diarrhea

Table 3: Clinical course of the patients who developed diarrhea.

Stopped naldemedine	Stopped other laxatives	N	Duration of diarrhea (days)	Constipation after the diarrhea improved
YES	YES	6	1, 1, 2, 2, 3, 4	5 (83%)
YES	NO	3	1, 5, 5	2 (67%)
NO	YES	6	1, 1, 1, 1, 3, 3	2 (33%)
NO	NO	2	1, 3	0 (0%)

CONCLUSIONS

- Since diarrhea after the initiation of naldemedine may associated with "peripheral" opioid withdrawal, the diarrhea can be reduced by starting naldemedine early.
- Constipation after the improvement of diarrhea is common; our findings suggest that the diarrhea should be managed by stopping other laxatives first, with continued naldemedine.
- Further prospective studies are warranted.

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