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Factors for Discontinuation of Naldemedine Therapy in a Palliative Ward

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Abstract

Background/Aim: Opioid-induced constipation (OIC) is a common adverse drug event in patients undergoing chronic pain therapy. Naldemedine is an oral, peripherally acting μ-opioid receptor antagonist that improves bowel movement without affecting opioid pain relief. In palliative wards, many patients experience malnutrition caused by cachexia and systemic inflammation because of cancer progression. We investigated whether the C-reactive protein-to-albumin ratio (CAR) affects the continuation of naldemedine therapy in a palliative ward.

Patients and Methods: We included Japanese patients in the palliative ward of Fujita Health University Hospital between April 2020 and August 2023 in this retrospective observational study. The log-rank test was used to compare the continuation rates of naldemedine over 14 days. Cox proportional hazards analysis was performed using the terms morphine-equivalent daily dose <30 mg and CAR ≥0.888.

Results: Eighty patients were divided into continuation (n=58) and discontinuation (n=22) groups. The proportion of patients with a CAR ≥0.888 was significantly higher in the discontinuation group than in the continuation group (p=0.020). Cox proportional hazards analysis showed that morphine-equivalent daily dose <30 mg was not a factor for discontinuation of naldemedine therapy (hazard ratio=1.040, p=0.929) but CAR ≥0.888 was (hazard ratio=3.251, p=0.035).

Conclusion: A high CAR (≥0.888) was a risk factor for the discontinuation of naldemedine therapy in a palliative ward. Our results suggest that physicians and pharmacists should monitor CAR as a marker of malnutrition and systemic inflammation before initiating naldemedine therapy.

Keywords: Naldemedine, palliative ward, opioid-induced constipation, C-reactive protein-to-albumin ratio.

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Introduction

Opioid-induced constipation (OIC) is a common adverse event in patients receiving chronic pain therapy and is not self-limiting. Thus, OIC reduces quality of life (1) and adherence (2) in patients with cancer pain. Naldemedine is an oral, peripherally acting μ-opioid receptor antagonist that improves bowel movement without affecting opioid pain relief (3) and constipation-related quality of life in patients administered regular doses of opioids (4). Naldemedine *versus* placebo for OIC study (COMPOSE-1 and COMPOSE-2 trials) excluded patients who received morphine equivalents of under 30 mg/day (5) thus, the efficacy and safety of naldemedine in such patients remain unclear. Because lowering the dose of opioids improves OIC (6), patients who use low-dose opioids might have other causes of constipation.

A clinical trial in Japan evaluated the effect of naldemedine on OIC for 14 days (4). Thus, the period for evaluating the treatment effects of naldemedine therapy is recognized as being 14 days; however, some patients who did not benefit discontinued naldemedine therapy for 14 days. Thus, naldemedine therapy may show poor cost-effectiveness in such patients.

The C-reactive protein-to-albumin ratio (CAR) indicates the degree of systemic inflammation and malnutrition. The CAR has been reported to be a predictor of the tolerability of adjuvant chemotherapy (7), survival duration (8-12), and recurrence of gastric cancer (13). In palliative wards, many patients experience malnutrition caused by cachexia and systemic inflammation. In these patients, distinguishing between malnutrition-induced constipation and OIC is difficult. The assessment of systemic inflammation and malnutrition might be useful in the decision to initiate naldemedine therapy in a palliative ward. In addition, elucidating the factors for the continuation of naldemedine might contribute to improving its cost-effectiveness in palliative wards. Here, we investigated whether CAR and <30 mg morphine equivalents per day affected the continuation of naldemedine therapy in a palliative ward.

Table I. *Conversion ratio of the morphine-equivalent daily dose.*

	Intravenous or subcutaneous administration	Oral administration	Transdermal administration
Morphine	0.5	1.5	N/A
Tramadol	5	7.5	N/A
Hydromorphone	0.06	0.3	N/A
Oxycodone	0.75	1	N/A
Fentanyl	0.015	N/A	0.05
Tapentador	N/A	5	N/A

N/A: Not available.

Patients and Methods

Study design and inclusion criteria. We included Japanese patients in the palliative ward of Fujita Health University Hospital between April 2020 and August 2023 in this retrospective observational study. All data were collected from the electronic medical records at Fujita Health University Hospital. Patients for whom naldemedine treatment was initiated before entering the palliative ward were excluded, as were patients with missing data. Patients for whom naldemedine treatment was initiated in the palliative ward were divided into continuation and discontinuation groups. The criterion for dividing the patients into these two groups was the discontinuation of naldemedine within 2 weeks of its initiation.

Data collection. Data collected included age, sex, serum albumin, serum transthyretin, serum C-reactive protein, CAR, serum aspartate aminotransferase, serum alanine aminotransferase, estimated glomerular filtration rate (eGFR), serum urea nitrogen, and serum sodium and potassium levels. Baseline characteristics were measured before the initiation of naldemedine treatment. The morphine-equivalent daily dose was calculated using the conversion ratio (Table I). The eGFR was calculated using the revised equations for eGFR in Japan (14).

Statistical analyses. Continuous variables are presented as the mean±standard deviation or median (interquartile

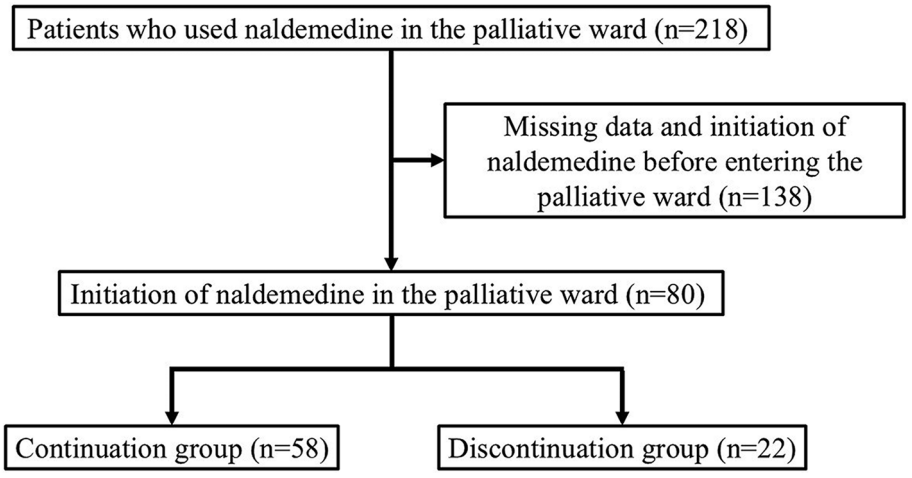

Figure 1. *Study protocol.*

range). Categorical variables are presented as counts and proportions. The baseline characteristics of the patients were compared between the two groups using the Mann-Whitney *U*-test or Student's *t*-test for continuous variables and the chi-square test for categorical variables. The Shapiro-Wilk test was used to evaluate normality. Receiver operating characteristic (ROC) curve analysis was used to determine the CAR cut-off value for predicting naldemedine discontinuation. The log-rank test was used to compare the continuation rates of naldemedine over 14 days. Cox proportional hazards analysis was performed using the terms of morphine-equivalent daily dose <30 mg and CAR ≥0.888. Statistical significance was set at $p<0.05$. All statistical analyses were performed using SPSS software (version 27.0; IBM, Armonk, NY, USA).

Ethics approval. This study was approved by the Ethics Board of Fujita Health University Hospital (ethical approval number: HM23-510; date of approval: April 15, 2024) and conducted in accordance with the principles of the Declaration of Helsinki.

Results

Baseline characteristics. A total of 218 patients were included in this study, and those who for whom naldemedine was initiated before entering the palliative ward or who had missing data were excluded (n=138). Eighty patients were divided into continuation (n=58) and discontinuation (n=22) groups (Figure 1). The Shapiro-ilk test showed that the data set of serum albumin showed normality; thus, Student's *t*-test was used for comparison between the two groups. Age; proportion of males; morphine-equivalent daily dose; proportion of morphine-equivalent daily dose under 30 mg; and serum albumin, serum transthyretin, serum C-reactive protein, CAR, serum aspartate aminotransferase, serum alanine aminotransferase, eGFR, serum urea nitrogen, serum sodium, serum potassium, and proportion of primary cancer cases were not significantly different between the two groups (Table II). ROC curve analysis showed that the cut-off value of CAR to predict naldemedine discontinuation was 0.888, with sensitivity of 0.818 and specificity of 0.534 (Figure 2A). The proportion of patients with CAR ≥0.888 was significantly higher in the discontinuation group than in the continuation group ($p=0.020$) (Table II).

Rate of naldemedine continuation and factors for discontinuation of therapy. The results of the log-rank test are shown in Figure 2B. The average duration of continuous naldemedine therapy was 13.2 (95% confidence interval=12.5-14.0) days in patients with CAR<0.888 and 11.6 (95% confidence interval=10.5-12.6)

Table II. *Baseline characteristics of study patients.*

	Characteristic	Continuation group (n=58)	Discontinuation group (n=22)	*p*-Value
Age, years	Median (IQR)	75.0 (69.5-80.3)	75.0 (70.8-79.8)	0.838[a]
Sex, n (%)	Male	24 (41.4)	13 (59.1)	0.156c
ME daily dose, mg	Median (IQR)	30.0 (20.0-40.0)	20.0 (18.8-56.3)	0.930[a]
	<30 mg, n (%)	28 (48.3)	12 (54.5)	0.617[c]
Serum albumin, g/dl	Mean±SD	2.867±0.704	2.627±0.661	0.170[b]
Serum transthyretin, mg/dl	Median (IQR)	11.0 (7.13-15.7)	9.60 (6.88-14.5)	0.422[a]
Serum CRP, mg/dl	Median (IQR)	3.14 (0.98-8.32)	5.47 (2.77-10.5)	0.112[a]
CAR	Median (IQR)	1.17 (0.31-3.28)	2.45 (0.97-3.79)	0.095[a]
	≥0.888, n (%)	31 (53.4)	18 (81.8)	0.020[c]
Serum AST, U/l	Median (IQR)	27.0 (19.0-51.8)	30.5 (25.0-45.0)	0.298[a]
Serum AlT, U/l	Median (IQR)	19.0 (10.0-46.5)	16.0 (10.0-27.0)	0.308[a]
eGFR, ml/min/1.73m^2	Median (IQR)	67.0 (48.8-94.9)	63.4 (46.9-80.1)	0.467[a]
Serum BUN, mg/dl	Median (IQR)	14.8 (11.9-24.6)	19.9 (13.1-30.1)	0.198[a]
Serum sodium, mEq/l	Median (IQR)	136 (133-139)	136 (129-139)	0.427[a]
Serum potassium, mEq/l	Median (IQR)	4.25 (4.00-4.60)	4.40 (3.90-4.73)	0.746[a]
Primary cancer, n (%)	Pancreatic	12 (20.7)	2 (9.1)	0.636[c]
	Lung	10 (17.2)	3 (13.6)	
	Colorectal	8 (13.8)	5 (22.7)	
	Breast	3 (5.2)	2 (9.1)	
	Other	25 (43.1)	10 (45.5)	

ALT: Alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; CAR: C-reactive protein (CRP)/albumin ratio; eGFR: estimated glomerular filtration rate; IQR: interquartile range; ME: morphine-equivalent; SD: standard deviation; TTR: transthyretin. [a]Mann-Whitney *U*-test; [b]Student's *t*-test; [c]chi-squared test. Statistically significant *p*-values are shown in bold.

days in patients with CAR≥0.888. The rate of naldemedine therapy continuation in patients with CAR ≥0.888 was lower than in patients with CAR <0.888 ($p<0.005$).

Cox proportional hazards analysis showed that but CAR ≥0.888 was a significant factor for therapy discontinuation (hazard ratio=3.251, 95% confidence interval=1.085-9.737, $p=0.035$).

Reason for discontinuation of naldemedine therapy. The reasons for the discontinuation of naldemedine therapy are shown in Table III. Difficulty with oral administration was the most frequent reason for discontinuation of naldemedine therapy (72.7%), whilst abdominal pain was a cause in only 4.5%.

Table III. *Reason for discontinuation of naldemedine.*

Reason for discontinuation	Number of patients (%)
Difficulty in oral administration	16 (72.7)
Discontinuation of opioid therapy	2 (9.1)
Abdominal pain	1 (4.5)
Delirium	1 (4.5)
Other	2 (9.1)

Discussion

Our study revealed that the morphine-equivalent daily dose was not a factor for discontinuation of naldemedine therapy, but a high CAR was a significant factor.

OIC occurs even when the opioid dose used is low; thus, OIC management should be initiated at the initial stage of opioid treatment. However, the COMPOSE-1 and COMPOSE-2 trials excluded patients who received <30 mg of morphine equivalents per day. Thus, the rate of naldemedine therapy continuation in patients receiving such low doses were not examined in these trials. Naldemedine ameliorates the inhibition of small-intestinal transit by morphine in a dose-dependent manner (15). Therefore, the morphine dose may be associated with the effect of naldemedine. The daily dose of morphine equivalents did not affect the decision to

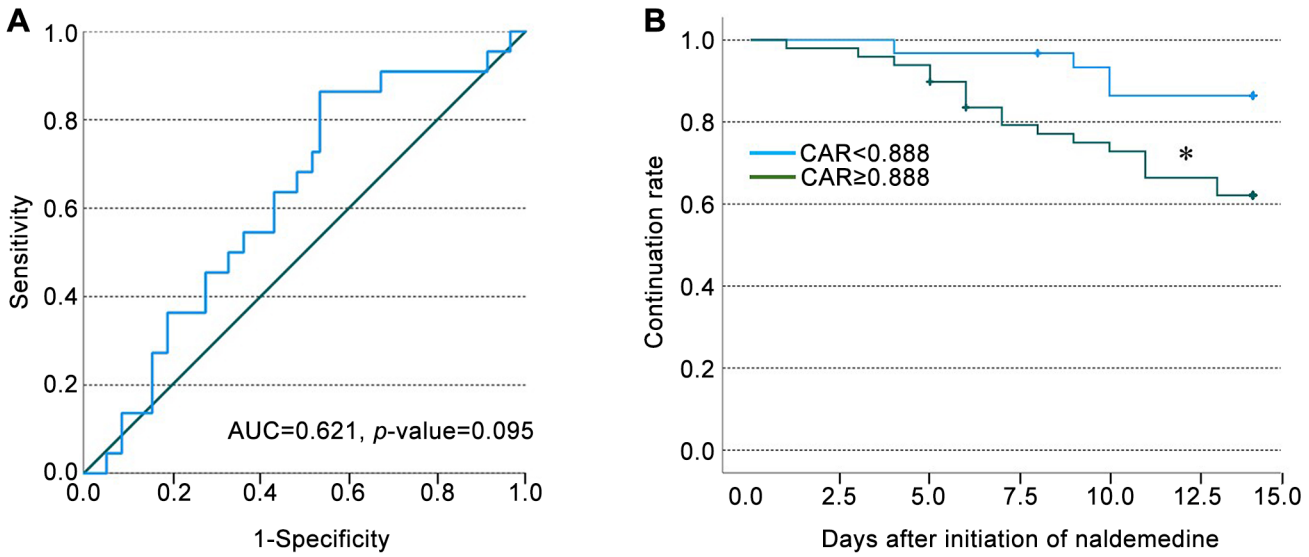

Figure 2. *Receiver operating characteristic (ROC) curve and the rate of continuation of naldemedine over 14 days. (A) The ROC curve shows the ability of C-reactive protein-to-albumin ratio (CAR) to predict discontinuation of naldemedine therapy. The cut-off value of CAR was 0.888, with sensitivity of 0.818 and specificity of 0.534. (B) Kaplan-Meier curve indicating the rate of naldemedine continuation for 14 days. In patients with CAR<0.888, naldemedine was administered for an average of 13.2 (95% confidence interval=12.5-14.0) days whilst in patients with CAR≥0.888, administration continued for 11.6 (95% confidence interval=10.5-12.6) days. *Significantly different at p<0.05 (log-rank test).*

discontinue naldemedine. The clinical dose of naldemedine might have been set at a level with sufficient antagonistic action. In addition, causes of constipation in palliative wards are multiple because of cancer progression and cachexia. Patients receiving low-dose morphine may also have other causes of constipation.

We propose a cutoff value of 0.888 for the CAR based on the results of the ROC curve analysis in this study. This value was higher than that reported in a previous study evaluating the association between the CAR and early recurrence after gastrectomy (CAR=0.131) (16). A CAR cutoff of 0.03 was proposed as a factor indicating reduced survival of Japanese patients with gastric cancer (10). Patients with chemotherapy tolerance maintain a good performance status. Over 60% of patients in our study had a high CAR (≥0.888), and the proportion of these patients discontinuing naldemedine therapy was high. Our CAR cutoff value was higher than in previous studies; however, those studies did not target patients in a palliative ward. Although the performance status was not measured in our study, most patients had cancer-related complications.

Difficulty with oral administration was the main reason for discontinuation of naldemedine therapy in the present study. In the COMPOSE-4 trial, the most frequent reason for study discontinuation was gastrointestinal disorders, including diarrhea, vomiting, reduced appetite, and pyrexia (17). Although five patients (3.8%) discontinued naldemedine therapy because of primary cancer-related complications in COMPOSE-5 (17), the number of discontinuations due to gastrointestinal disorders was four (3.1%). COMPOSE-5 was a 12-week extension study; thus, the frequency of primary cancer-related complications tended to be higher than that in COMPOSE-4; the details of the primary cancer-related complications were not shown in that report. However, our results followed a similar trend, in which difficulty in oral administration was the main reason for discontinuation. The criteria for the initiation of naldemedine therapy did not differ between palliative and other wards. However, our results suggest that physicians and pharmacists should monitor CAR as a marker of malnutrition and systemic inflammation before initiating naldemedine therapy. The volume of dietary

intake is commonly correlated with the stool volume. The cause of constipation may not be opioid-related when the volume of dietary intake decreases in patients in a palliative ward. In addition, these patients tend to experience difficulty with oral administration because of their worsening general condition.

In Japan, the cost of a naldemedine tablet is approximately $2. The initiation of naldemedine therapy is expected to improve OIC over a period of 14 days; however, in a palliative ward, the cost benefits may not be adequate because of therapy discontinuation caused by worsening systemic symptoms.

This study had some limitations. Firstly, we did not directly assess the effectiveness of naldemedine because information on assessment using the Bristol Stool Scale was lacking. Secondly, the duration of concomitant laxative use differed among the patients. Therefore, we were unable to evaluate the effects of concomitant laxatives. Thirdly, this was a single-center, retrospective study. Fourthly, there was no significant difference in the ROC curve analysis because the number of participants was small. Therefore, further multicenter studies are warranted.

In conclusion, high CAR (≥0.888) was a risk factor for the discontinuation of naldemedine therapy in a palliative ward. Our results suggest that physicians and pharmacists should monitor CAR as a marker of malnutrition and systemic inflammation before initiating naldemedine therapy.

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Conflicts of Interest

The Department of Pharmacotherapeutics and Informatics, to which Takaki Kanie, Tomohiro Mizuno, Takenao Koseki, Yukiko Kakumae, Takahiro Hayashi and Shigeki Yamada belong, received a research grant from Sugi Holdings Co., Ltd.

Authors' Contributions

Takaki Kanie: Conceptualization, data curation, investigation, methodology, writing - original draft. Tomohiro Mizuno: Conceptualization, writing - original draft, Supervision. Takenao Koseki: Methodology, writing–review and editing. Aya Hanamoto: Data curation. Hiroko Sawano: Data curation. Masako Tomida: Data curation. Yukiko Kakumae: Data curation, methodology. Takahiro Hayashi: Writing - review and editing. Hiroshi Matsuoka: Methodology, writing - review and editing. Masanobu Usui: Writing - review and editing. Shigeki Yamada: Conceptualization, writing - review and editing.

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