Systemic Opioids for Dyspnea in Cancer Patients: A Real-world Observational Study

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Systemic opioids for dyspnea in cancer patients: A real-world observational study.

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Abstract

Context: Although Systemic opioids are recommended as a pharmacological treatment for cancer-related dyspnea, their effectiveness and safety needs to be investigated in a real-world context

Objectives: To evaluate the effectiveness and safety of systemic regular opioids for dyspnea in cancer patients, in the real-world palliative care practice.

Methods: This was a multicenter prospective observational study. We consecutively enrolled adult cancer patients starting regular opioids (morphine, oxycodone, hydromorphone, or fentanyl) for dyspnea from 12 palliative care services across Japan. We evaluated dyspnea intensity using the Numerical Rating Scale (NRS) and Integrated Palliative Outcome Scale (IPOS) every 24 hours until 72 hours after starting opioids (T1–T3). We also evaluated common opioid-related adverse events (AEs) and other severe AEs.

Results: We enrolled 402 cancer patients. The proportion of responders was 68.8% (95%confidence intervals (CI): 0.63–0.74) at T1, 75.7% (95%CI: 0.70–0.81) at T2, and 82.1% (95%CI: 0.76–0.87) at T3. The mean differences in dyspnea NRS from baseline were 1.73 (95%CI: 1.46–1.99) at T1, 1.99 (95%CI: 1.71–2.28) at T2, and 2.47 (95%CI:2.13–2.82) at T3. The most common treatment-emergent AE was somnolence with an incidence of the severe form of approximately 10% throughout the study period. In the multivariate analysis, baseline dyspnea NRS ≥6 had a positive correlation with dyspnea relief by systemic regular opioids, while liver metastasis, clinician-predicted survival days, and opioid tolerance had a negative correlation.

Conclusions: Regular systemic opioids were effective for dyspnea in real-world cancer patients.

Key Message: This study highlighted the effectiveness of various systemic opioids for dyspnea in cancer

patients in the real-world palliative care setting. The most prevalent adverse event was somnolence. Opioid naivety, the absence of liver metastases, longer life expectancy, and severe dyspnea intensity may predict systemic opioid response.

Key Words: dyspnea, cancer, opioid, palliative care, real-world

Running Title: Systemic opioids for cancer dyspnea

Introduction

Dyspnea is defined as 'a subjective experience of breathing discomfort'.[1] Dyspnea is common in patients with advanced cancer, with a reported prevalence of 54–76%.[2-5] Moreover, dyspnea is one of the most distressing symptoms for not only patients but also their families and caregivers. Therefore, dyspnea relief is important for the improvement of the quality of life in cancer patients and their families.

Systemic morphine is the only pharmacological therapy proven to be efficacious for cancer dyspnea in randomized controlled trials.[6-9] Clinical guidelines recommend systemic morphine as the first-line pharmacological treatment for dyspnea in cancer patients.[10-12] On the other hand, although there were several reports about other opioids, such as oxycodone[13], hydromorphone[14], or fentanyl[15-20], for dyspnea in cancer patients and some clinical guidelines suggested these opioids as an alternative to morphine for dyspnea in cancer patients,[12,21] there is still not enough evidence to support their use.

In the real-world palliative-care setting, many patients with advanced cancer have organ dysfunction. It was reported that the accumulation of active metabolites of morphine in patients with renal insufficiency increased the risk of adverse events (AEs), such as somnolence and myoclonus.[22,23] Also, it is not rare that opioids other than morphine are prescribed for dyspnea management in cancer patients in daily practice.[24]

For the first step to overcome this evidence-practice gap, the aim of this study was to evaluate the effectiveness and safety of various opioids for cancer-related dyspnea, in the real-world setting.

Methods

Study Design

This was a multicenter prospective observational study evaluating systemic opioid therapy for dyspnea in cancer patients. We conducted the study following the Declaration of Helsinki, and the Institutional Review Board (IRB) of Kinki-Chuo Chest Medical Center as well as IRBs of all participating sites approved the study protocol. Following the ethical guidelines for human research of the Ministry of Health, Labor, and Welfare in Japan, informed consent from the patients was waived due to the observational nature of the study. We registered the trial at UMIN-CTR (UMIN 000038918).

Participants

We consecutively enrolled adult patients with cancer who started regular opioids for dyspnea from 12 palliative care services (palliative care units or palliative care consultation teams) across Japan. Our main inclusion criteria was the Integrated Palliative Outcome Scale (IPOS) for dyspnea at the time of starting regular opioids of 2 or more. We chose the IPOS as the dyspnea cut-off for the inclusion criteria because it was widely used in routine practice in Japanese palliative care setting.[25] In addition, we chose this because we expected significant proportion of participants might be unable to rate the patient-reported outcomes due to cognitive or consciousness impairment. We excluded 1) patients starting treatment interventions for dyspnea etiology (i.e., antibiotics for pneumonia, or corticosteroid for COPD exacerbation) simultaneously with opioids, or 2) patients planning to undergo any interventions which might provide a short-term change in dyspnea intensity (i.e., drainage of pleural effusion or stent placement for airway obstruction) within three days after starting

opioid. We included any types of practice of opioid use. Regarding the types of opioids, we included morphine, oxycodone, hydromorphone, and fentanyl as regular systemic opioids for dyspnea. The participants were enrolled from December 2019 to August 2021.

Measurements

Dyspnea intensity: We evaluated dyspnea intensity using Numerical Rating Scale (NRS: 0-10; 0 indicates no dyspnea and 10 indicates the worst possible dyspnea) average over 24 hours as a patient-reported outcome.[26] We also evaluated dyspnea intensity using IPOS[27,28] for the previous 24 hours as a clinician-rated outcome. Dyspnea item of IPOS was a 5-point Likert scale (0 = not at all; 1 = slightly; 2 = moderately; 3 = severely; 4 = overwhelmingly).

Opioid treatments for dyspnea: We differentiated types of practice of opioid use for dyspnea as follows: “newly start opioid for opioid-naïve patients’” “opioid switching” ”Increase doses of baseline opioids” and ”the addition of another opioid to the baseline opioid (opioid combination)”. We also documented the types of opioids for dyspnea (morphine, oxycodone, hydromorphone, and fentanyl) and the dose amount of regular opioids for dyspnea by calculating to oral morphine equivalent daily dose.

Adverse events: We evaluated common opioid-related AEs (nausea, somnolence, and delirium) using the Japanese version of the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[29] We also evaluated any other AEs of grade 3 or more using CTCAE version 5.0.

Other measurements: We evaluated respiratory rate, SpO_2, and amount of supplemental oxygen as respiratory parameters. Demographic information, primary cancer site, presence or absence of metastases (lung, liver, and pleural dissemination) and pleural effusion, physician-perceived primary dyspnea etiology, comorbid respiratory diseases (COPD and interstitial lung disease), smoking history, clinician prediction survival (CPS: days, weeks, or month), Eastern Cooperative Oncology Group Performance Status (ECOG PS), current medication use (benzodiazepines and corticosteroids), and current opioid use (the type and amount) were obtained from medical charts.[30,31] We also obtained laboratory data (Creatinine, total bilirubin, AST, and ALT) and the body weight within one month of inclusion from medical charts. In addition, we evaluated the intensity of anxiety by IPOS at baseline.

Procedure

After enrollment, we evaluated dyspnea NRS, dyspnea IPOS, respiratory parameters, AEs, and the type and amount of regular opioids for dyspnea at baseline and every 24 hours until 72 hours after the start of regular opioids for dyspnea (T1: 24 hours, T2: 48 hours, and T3: 72 hours) or drop-out from follow-up (death, discharge, or stopping opioid for any reason), whichever came first.

This study was completely observational in nature. Thus, we did not apply concurrent treatment restrictions during the study period. Also, opioid dosing was followed by the primary physician's decision based on the domestic clinical guidelines.[12]

Statistical Analysis

Our primary endpoint was the proportion of responders. We defined responder as '1 or more points reduction in the dyspnea NRS from baseline because a 1-point reduction is considered a clinically meaningful change.[32,33] We also defined responder as 'dyspnea IPOS of 1 or less' for the secondary endpoint.[25] Other secondary endpoints were the mean difference in dyspnea NRS from baseline, the mean difference in dyspnea IPOS from baseline, and treatment-emergent AEs (TEAEs). TEAEs were defined as symptoms that appeared or worsened after evaluation at baseline.

We used paired t-test to assess the difference in dyspnea NRS and IPOS between baseline and each evaluation time point. We also determined the mean differences in dyspnea NRS from baseline at each evaluation time point with 95% confidence intervals (CIs). Then, we descriptively calculated the proportion of responders per NRS and IPOS definitions at each evaluation time points (T1-3) with 95% CIs. We used a binominal logistic regression analysis to explore the factors influencing the response to opioid for dyspnea defined as 1 or more reduction in NRS at any evaluation time points. We performed all statistical analyses using SPSS for Windows software, version 27.0 (IBM Japan Institute, Tokyo, Japan). A p-value of <0.05 was considered statistically significant in all analyses.

Results

We enrolled a total of 402 cancer patients who started regular systemic opioids for dyspnea (Figure 1). Baseline characteristics are shown in Table 1.the mean age was 79.4 (SD: 12.6) years, 54.7% were male, and the most common primary cancer site was lung. More than half (51.5%) had lung metastases and 63.2% were complicated with pleural effusion. The majority (59.7%) were ECOG PS 4 and 46.3% were given a CPS of "days". Opioid-naïve patients accounted for 55.7% of participants. For opioid-tolerant patients, the mean baseline opioid dose was 55.7 mg/day of oral morphine equivalent. The majority (83.3%) of participants used supplemental oxygen or high-flow nasal cannula.

Change in Dyspnea Intensity

The proportion of responders by NRS definition were 68.8% (95%CI: 0.63–0.74) at T1, 75.7% (95%CI: 0.70–0.81) at T2, and 82.1% (95%CI: 0.76–0.87) at T3 (Figure 2-a). The proportion of responders by IPOS definition were 42.5% (95%CI: 0.38–0.48) at T1, 52.4% (95%CI: 0.47–0.58) at T2, and 57.0% (95%CI: 0.51–0.63) at T3 (Figure 2-b).

In terms of dyspnea intensity, the mean dyspnea score for both NRS and IPOS decreased over time (Figure 3). The mean differences in dyspnea NRS from baseline were 1.73 (95%CI: 1.46–1.99) at T1, 1.99 (95%CI: 1.71–2.28) at T2, and 2.47 (95%CI:2.13–2.82) at T3, with a statistically significant difference at all three evaluation time-points (Table 2). Similarly, The mean differences in dyspnea IPOS from baseline were 0.97 (95%CI: 0.86–1.07) at T1, 1.16 (95%CI: 1.06–1.26) at T2, and 1.26 (95%CI: 1.14–1.37) at T3, with statistically significant differences at all three evaluation time points (Table 3).

AEs

Table 4 shows an overview of TEAEs. The most common TEAE was somnolence with an incidence of 25.9%, 30.3%, and 29.4% at T1, T2, and T3, respectively. Of those, the rates of severe AE (grade 3 or more) were 8.0%, 11.5%, and 12.6% at T1, T2, and T3, respectively. Approximately 5% and 15% of participants developed nausea and delirium respectively at each evaluation time points. Of those, the rates of severe were approximately 1% and 4%, respectively at each evaluation time points. Other severe AEs were found 4 (respiratory failure, hypoxemia, liver failure, and fracture, each for one case) at T1 and 3 (2 cases of respiratory failure and one apnea) at T2.

Factors Influencing the Response to Opioid for Dyspnea (Table 5)

In the univariate analysis, sex (female) had a positive correlation while liver metastasis, those giving a CPS of days, ECOG PS 4, tachypnea (≥25 breath/minutes), hypoxia (SpO2 <90%) and supplement oxygen use had negative correlations with the dyspnea relief by systemic regular opioids. Then, multivariate analyses revealed that baseline dyspnea NRS ≥6 had a positive correlation, and liver metastasis, those giving a CPS of days, and opioid-tolerant had negative correlations with the dyspnea relief by systemic regular opioids.

Discussion

This large-scale observational study described the real-world effectiveness and safety of regular systemic opioids for dyspnea in cancer patients. This study had several major findings. First, dyspnea intensity decreased over time after the start of systemic opioids. This decrease was consistent when evaluating patient-reported outcomes (NRS) as well as clinician-rated outcomes (IPOS), and this was statistically significant and clinically meaningful. This result was similar to previous real-world observational study of opioids for dyspnea in patients with non-malignant respiratory diseases.[34] Participants of both our study (mean NRS at baseline was 6.4) and previous study in patients with non-malignant respiratory diseases (> 90% were modified Medical Research Council score of 4) had moderate/severe dyspnea. Based on these results, systemic opioids may be widely effective in the real-world cancer and non-cancer patients with severe dyspnea. Despite the paucity of evidence regarding the effectiveness of opioids other than morphine, nearly half of participants were prescribed oxycodone or hydromorphone in this study. Moreover, this study included the population who were usually excluded from randomized control trials, such as the super elderly (96 participants were 80 years or older in this study) and renal impairment (29 participants had serum Cr >2 mg/dl). Thus, this result suggested the effectiveness of systemic opioid therapy which includes not only morphine but also oxycodone or hydromorphone for cancer dyspnea in real-world practice. Second, somnolence was the most prominent TEAE of opioid therapy for cancer dyspnea. More than one-fourth of the participants of this study developed somnolence and nearly half of them developed severe (grade 3 or more) form. Since dyspnea development is a known predictor of poor survival,[35,36] cancer patients who developed dyspnea tended to be fragile. In fact, the majority of participants in this study were ECOG PS 4 and had a CPS of days. Thus, we have to beware

of somnolence when prescribing opioids for dyspnea in advanced cancer patients. Also we should consider discussing the trade-off between dyspnea relief and somnolence development with patients and their families, as recommended in a previous study.[37] Except for somnolence, severe TEAEs were not common throughout the study period. Third, we found the factors related to the response of dyspnea improvement by systemic opioids were opioid-naïve, the absence of liver metastasis, CPS of weeks or months, and severe levels of dyspnea (NRS ≥6). These findings may reflect the fact that systemic opioid for cancer dyspnea is more effective in patients with relatively good general conditions and/or severe dyspnea. Thus, we should proactively prescribe systemic opioids to these patients without unnecessary hesitation. At the same time, we have to explore or develop an effective treatment strategy for dyspnea in less effective populations, such as dying phase or opioid-tolerant patients.

This study had several limitations. First, this study was observational in nature. So, we did not restrict concurrent treatments such as oxygen supplementation. The modification of these concurrent therapies might influence dyspnea intensity. Second, we did not correct the data about what kinds of formulation of opioids were used. There may be a difference in response among formulations. We should investigate this point in future research. Third, we did not prepare a control group (placebo or no treatment) in this study. Thus, we could not confirm the efficacy of systemic opioid therapy. Fourth, in this analysis, we did not compare the effectiveness between different types of opioids and did not explore the difference in response of opioids for dyspnea among different types of practices of opioid use. Thus, we should explore these aspects in future secondary analyses of this study.

Despite these limitations, this study included the highest number of patients ever among studies that

evaluate the effectiveness of systemic opioids for dyspnea in cancer patients. In addition, this study evaluated the patient-reported outcome (NRS) as the primary outcome and half of the participants could report NRS until the end of the study period. These were the strengths of this study and they may increase the reliability of the findings of this study.

In conclusion, regular systemic opioids were effective for dyspnea in real-world cancer patients under palliative care. We should pay attention to somnolence and discuss the trade-off between dyspnea relief and somnolence development in particular cases when we use systemic opioids for cancer dyspnea. As opioid-naïve, the absence of liver metastases, longer life expectancy, and severe dyspnea intensity may predict the response, we should proactively consider prescribing systemic opioid when cancer patients who have these features develop dyspnea.

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Author contributions

Conception and design: Takashi Yamaguchi, Yoshinobu Matsuda, Keisuke Ariyoshi, Kota Kihara ,Masanori Mori.
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Data analysis and interpretation: Takashi Yamaguchi, Ryo Matsunuma, Junichi Tasaki, Shunsuke Oyamada.
Manuscript writing: All authors
Final approval of manuscript: All authors

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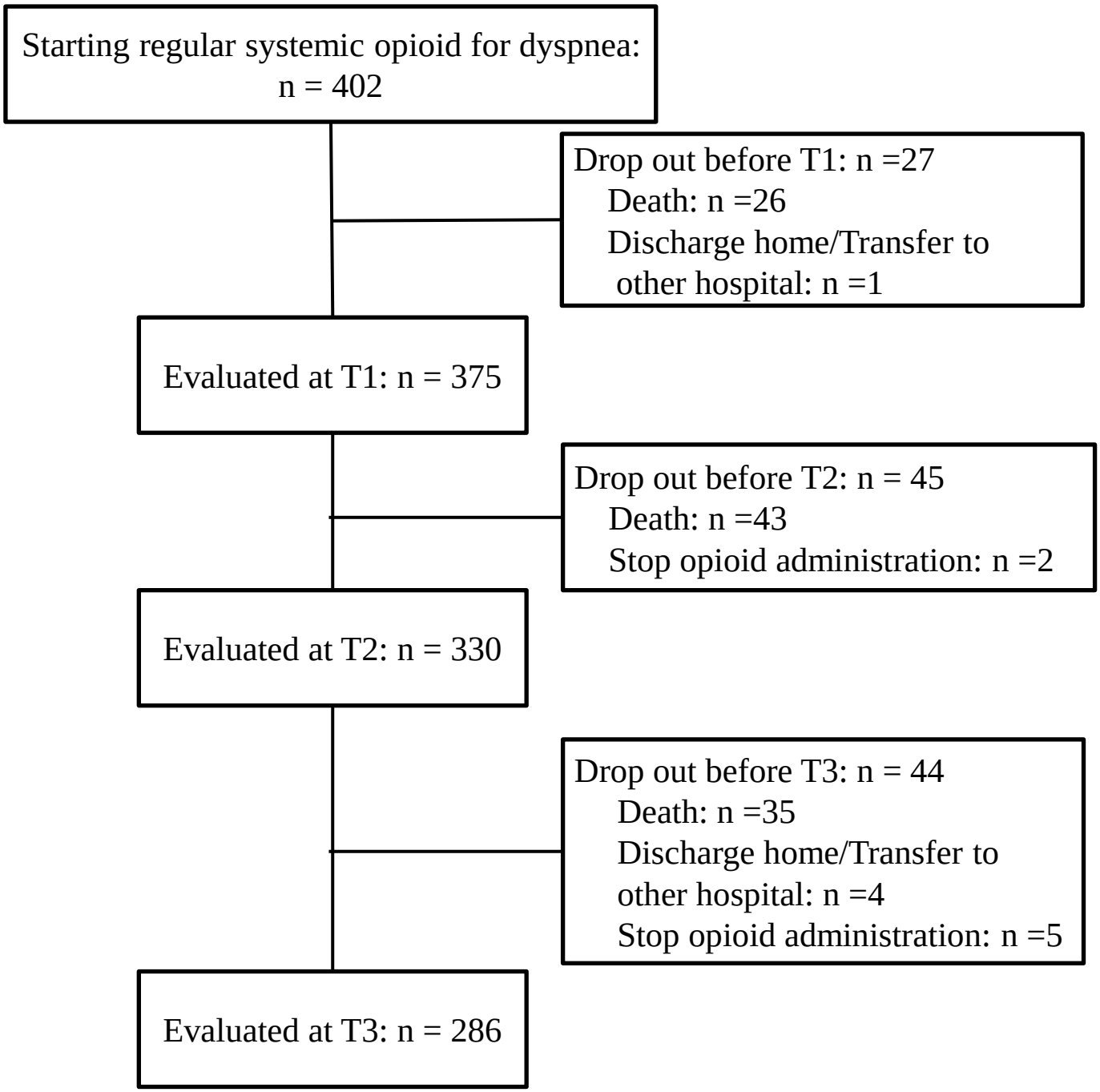
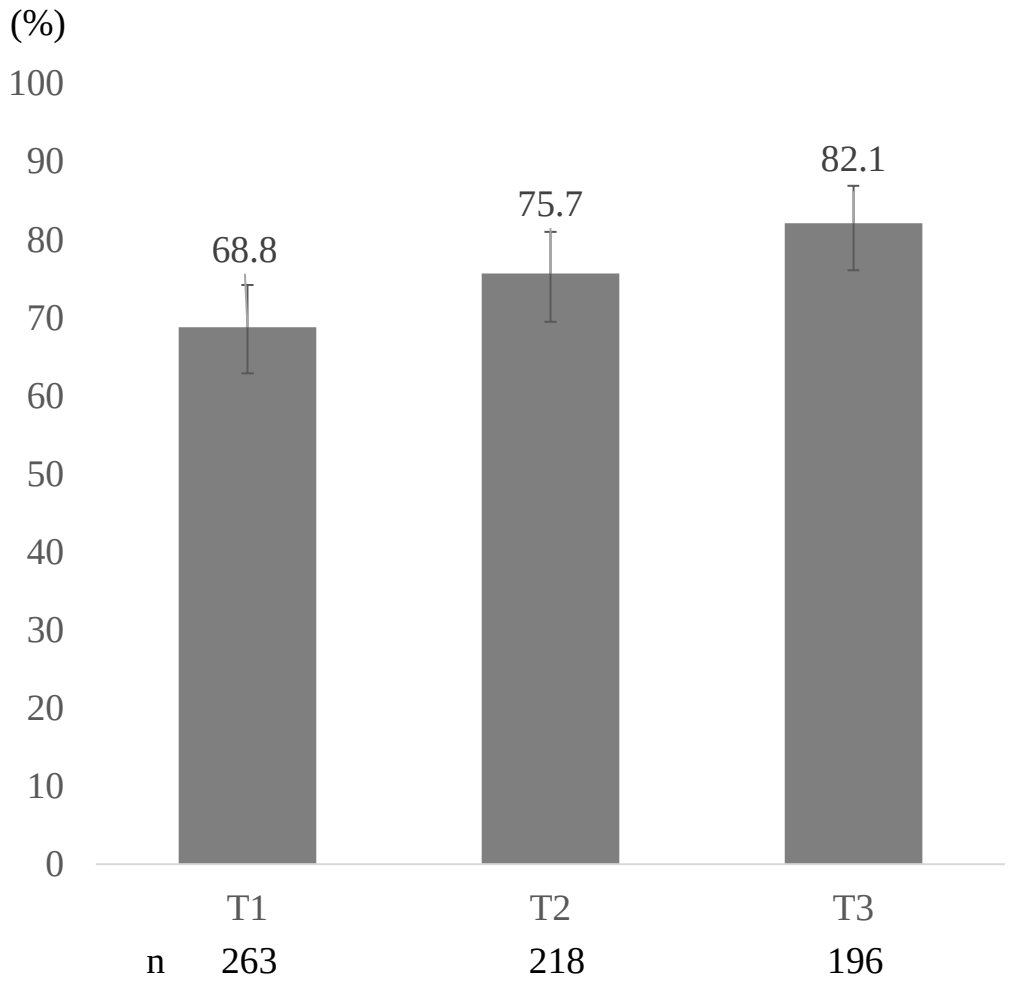


Figure 1. Recruitment flow of participants.

Figure 2. Proportion of Responders with time.

a) NRS definition



b) IPOS definition

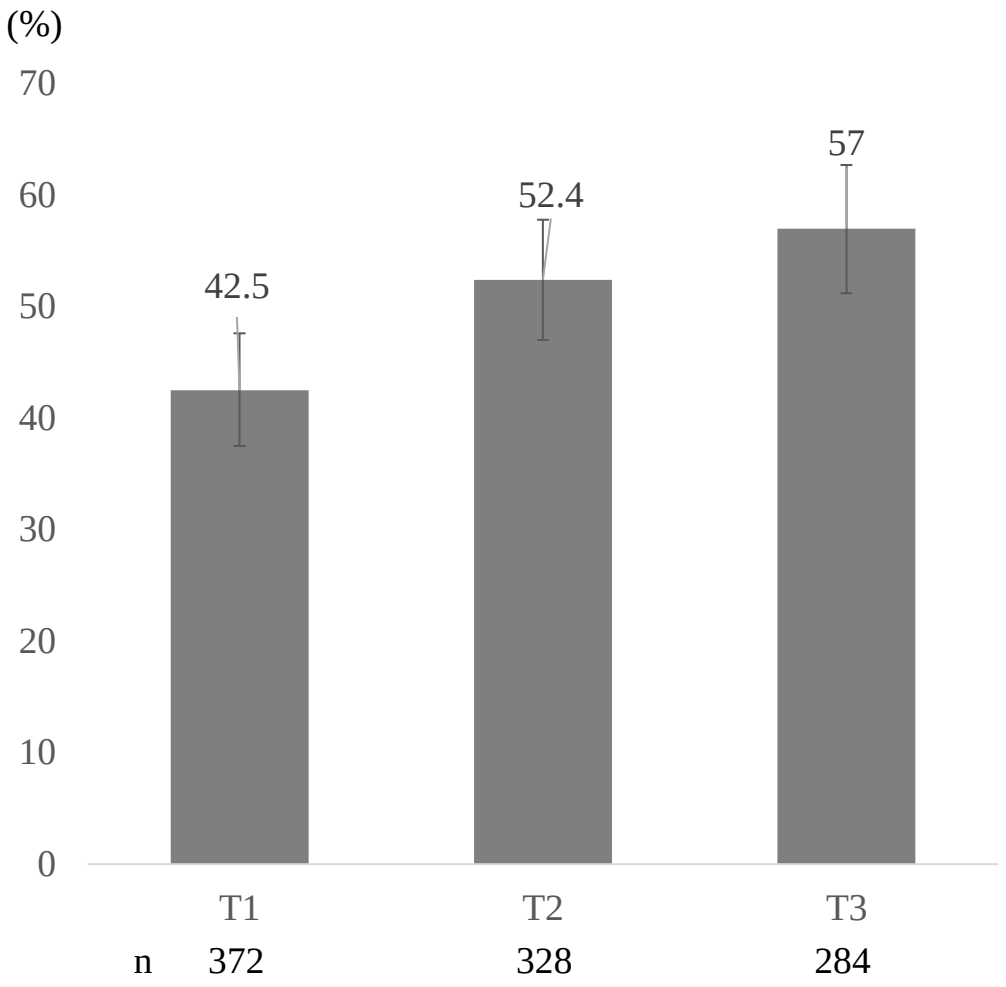
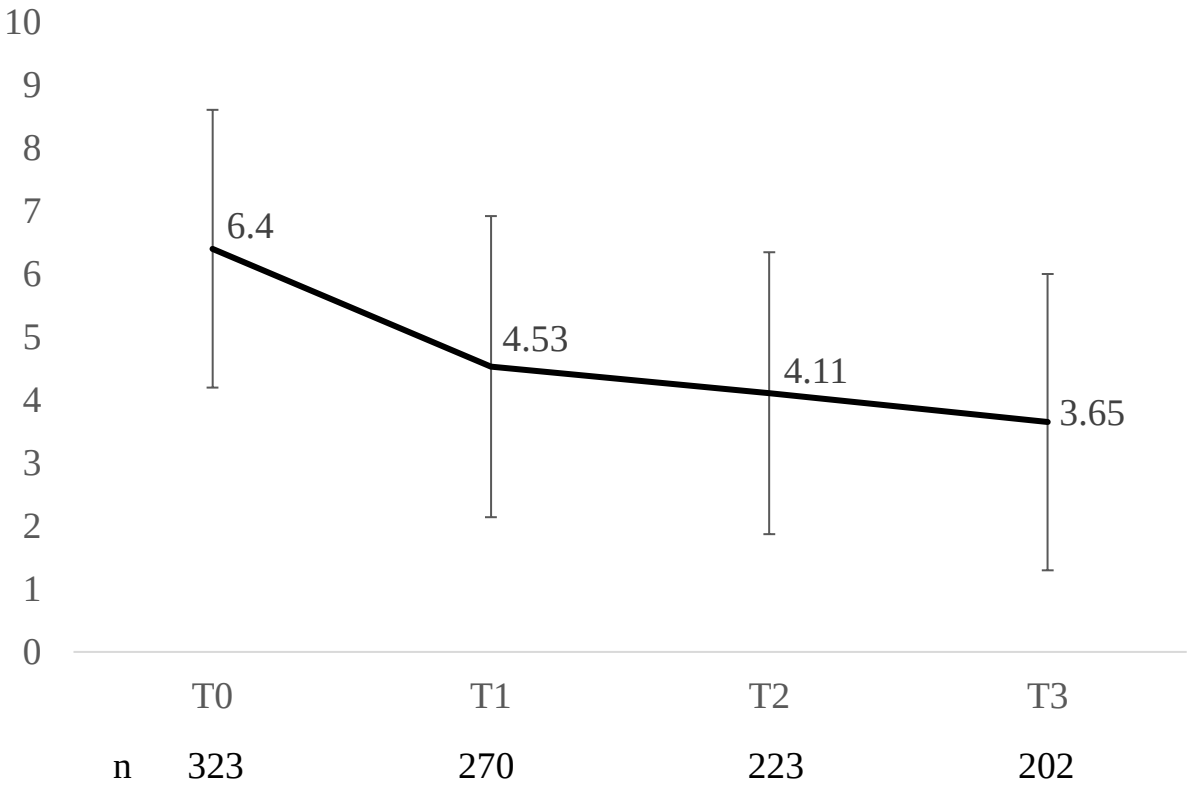


Figure 3. Change in dyspnea intensity with time.

a) Dyspnea NRS



b) Dyspnea IPOS

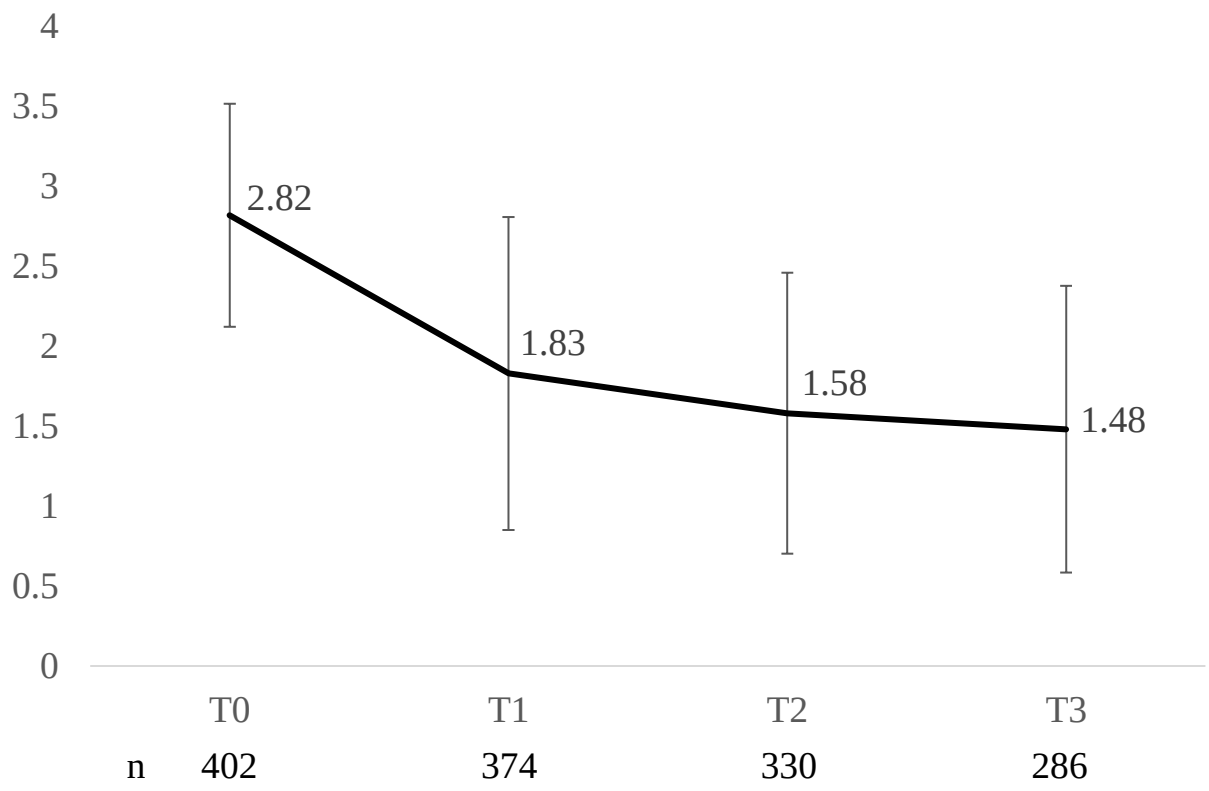


Table 1 Baseline Characteristics of Participants (n = 402).

	Values [n (%)]
Age (years, mean ± SD)	70.4 ± 12.6
Sex (Male)	220 (54.7%)
Primary cancer site	
Lung	149 (37.1%)
Breast	39 (9.7%)
Colon/Rectum	29 (7.2%)
Gynecological	29 (7.2%)
Pancreas/Bile duct	28 (7.0%)
Esophagus	22 (5.5%)
Urological	21 (5.2%)
Others	85 (21.1%)
Metastasis/Pleural effusion	
Lung metastasis	207 (51.5%)
Liver metastasis	82 (20.4%)
Pleural dissemination	144 (35.8%)
Pleural effusion	254 (63.2%)
Primary etiology of dyspnea	
Lung tumor (primary or metastatic)	125 (31.1%)
Pleural effusion	118 (29.4%)
Lymphangitis carcinomatosa	46 (11.4%)
Respiratory tract infection	25 (6.2%)
Others	78 (19.4%)
Not specified	10 (2.5%)
Coexisting Lung disease	
COPD	52 (12.9%)
ILD	37 (9.2%)
Smoking history	
Current smoker	31 (7.7%)
Ex-smoker	173 (43.3%)
Never smoke	194 (48.3)
Clinician's prediction of survival	
Days	186 (46.3%)
Weeks	174 (43.3%)
Months	42 (10.4%)
ECOG performance status	
0-2	42 (10.4%)

3	120 (29.9%)
4	240 (59.7%)
Anxiety (IPOS 2-4)	223 (55.5%)
Concurrent medication	
Benzodiazepine	47 (11.7%)
Corticosteroid	140 (34.8%)
Baseline opioid use	178 (44.3%)
Morphine	28 (7.0%)
Oxycodone	52 (12.9%)
Hydromorphone	24 (6.0%)
Fentanyl	55 (13.7%)
Others	22 (5.5%)
Baseline opioid dose [OMEDD, mg/day, mean ± SD (n 178)]	55.7 ± 67.1
Baseline oxygen use	
Nasal/Face mask	328 (81.6%)
High flow nasal cannula	7 (1.7%)
Baseline respiratory parameters	
Dyspnea NRS [0-10, mean ± SD (n 323)]	6.40 ± 2.20
Dyspnea IPOS [0-4, mean ± SD (n 402)]	2.82 ± 0.70
Respiratory rate [breath/minutes, mean ± SD (n 396)]	22.3 ± 6.4
SpO2 [%, mean ± SD (n 402)]	94.5 ± 5.4
Baseline laboratory data	
Cr [mg/dl, mean ± SD (n 396)]	1.06 ± 2.60
AST [IU/ml, mean ± SD (n 395)]	65.4 ± 129.2
ALT [IU/ml, mean ± SD (n 395)]	39.6 ± 93.2
Total bilirubin [mg/dl, mean ± SD (n 390)]	1.31 ± 2.90
Type of opioid for cancer dyspnea	
Morphine	209 (52.0%)
Oxycodone	109 (27.1%)
Hydromorphone	68 (16.9%)
Fentanyl	16 (4.0%)
Type of practice of opioid for cancer dyspnea	
Newly start for opioid naïve	224 (55.7%)
Opioid switching	106 (26.4%)
Increase dose of baseline opioid	61 (15.2%)
Add another opioid on baseline opioid (combination)	11 (2.7%)

Table 2. Change in dyspnea intensity (NRS)

	T0, mean (SD)	T1, mean (SD)	*p*	Difference from baseline (95% CI)
n = 263	6.24 (2.11)	4.52 (2.38)	< 0.001	1.73 (1.46 – 1.99)
	T0, mean (SD)	T2, mean (SD)		
n = 218	6.12 (2.11)	4.13 (2.24)	< 0.001	1.99 (1.71 – 2.28)
	T0, mean (SD)	T3, mean (SD)		
n = 196	6.14 (2.11)	3.66 (2.38)	< 0.001	2.47 (2.13 – 2.82)

Table 3. Change in dyspnea intensity (IPOS)

	T0, mean (SD)	T1, mean (SD)	*p*	Difference from baseline (95% CI)
n = 374	2.79 (0.69)	1.83 (0.98)	< 0.001	0.97 (0.86 – 1.07)
	T0, mean (SD)	T2, mean (SD)		
n = 330	2.74 (0.68)	1.58 (0.88)	< 0.001	1.16 (1.06 – 1.26)
	T0, mean (SD)	T3, mean (SD)		
n = 286	2.73 (0.66)	1.48 (0.90)	< 0.001	1.26 (1.14 – 1.37)

Table 4. Treatment-emergent adverse events.

	T1 (n = 375) [n (%)]	T2 (n = 330) [n (%)]	T3 (n = 286) [n (%)]
Nausea	20 (5.3%)	17 (5.2%)	14 (4.9%)
Grade 1	13 (3.5%)	5 (1.5%)	6 (2.1%)
Grade 2	5 (1.3%)	8 (2.4%)	5 (1.7%)
Grade 3	2 (0.5%)	3 (0.9%)	3 (1.0%)
Grade 4	0 (0%)	1 (0.3%)	0 (0%)
Somnolence	97 (25.9%)	100 (30.3%)	84 (29.4%)
Grade 1	34 (9.1%)	36 (10.9%)	26 (9.1%)
Grade 2	33 (8.8%)	26 (7.9%)	22 (7.7%)
Grade 3	22 (5.9%)	28 (8.5%)	26 (9.1%)
Grade 4	8 (2.1%)	10 (3.0%)	10 (3.5%)
Delirium	45 (12.0%)	47 (14.2%)	45 (15.7%)
Grade 1	20 (5.3%)	18 (5.4%)	19 (6.6%)
Grade 2	12 (3.2%)	15 (4.5%)	13 (4.5%)
Grade 3	11 (2.9%)	11 (3.3%)	10 (3.5%)
Grade 4	2 (0.5%)	3 (0.9%)	3 (0.1%)
Other severe AEs	4 (1.1%)	3 (0.9%)	0 (0%)

Table 5. Related factors of effectiveness of opioid therapy for cancer dyspnea.

	Effective [n (%)]	In-effective [n (%)]	Univariate		Multivariate	
			p	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)
Age			0.72	0.92		
≧ 65 years old	62 (57.1)	46 (42.6)		(0.59-1.44)		
≦ 64 years old	163 (55.4)	131 (44.6)				
Sex			0.025	1.58	0.611	1.16
Male	112 (50.9)	108 (49.1)		(1.06-2.36)		(0.66-2.02)
Female	113 (62.1)	69 (37.9)				
Primary site			0.480	0.86	0.058	0.58
Lung	80 (53.7)	69 (46.3)		(0.77-1.68)		(0.33-1.02)
Others	145 (57.3)	108 (42.7)				
Lung metastasis			0.528	1.14	0.714	1.11
Yes	119 (57.5)	88 (42.5)		(0.77-1.68)		(0.64-1.92)
No	106 (54.4)	89 (45.6)				
Liver metastasis			0.027	0.58	**0.043**	**0.50**
Yes	37 (45.1)	45 (54.9)		(0.35-0.94)		**(0.26-0.98)**
No	188 (58.8)	132 (41.3)				
Pleural dissemination			0.121	1.39	0.244	1.44
Yes	88 (61.1)	56 (38.9)		(0.92-2.10)		(0.78-2.68)
No	137 (53.1)	121 (46.9)				
Pleural effusion			0.386	0.83	0.835	0.94
Yes	138 (54.3)	116 (45.7)		(0.55-1.26)		(0.52-1.70)
No	87 (58.8)	61 (41.2)				
COPD			0.244	1.43		
Yes	33 (63.5)	19 (36.5)		(0.78-2.61)		
No	192 (54.9)	158 (45.1)				

ILD			0.066	1.97		
Yes	26 (70.3)	11 (29.7)		(0.95-4.11)		
No	199 (54.5)	166 (45.5)				
Smoking history			0.627	0.91		
Ex/current smoker	114 (54.8)	94 (45.2)		(0.61-1.35)		
Never	111 (57.2)	83 (42.8)				
Clinician prediction of survival			< 0.001	0.28	**0.008**	**0.43**
Days	74 (39.8)	112 (60.2)		(0.19-0.43)		**(0.23-0.80)**
Weeks～Month	151 (69.9)	65 (30.1)				
ECOG PS			< 0.001	0.20	0.079	0.56
4	99 (41.3)	141 (58.8)		(0.13-0.32)		(0.30-1.07)
0-3	126 (56.5)	36 (22.2)				
Anxiety (IPOS ≧2)			0.810	1.05	0.644	1.14
Yes	126 (56.5)	97 (43.5)		(0.71-1.56)		(0.66-1.97)
No	99 (55.6)	80 (44.7)				
Benzodiazepine use			0.178	0.66		
Yes	22 (46.8)	25 (53.2)		(0.36-1.21)		
No	203 (57.2)	152 (42.8)				
Corticosteroid use			0.078	0.69		
Yes	70 (50.0)	70 (50.0)		(0.46-1.04)		
No	155 (59.2)	107 (40.8)				
Baseline opioid use			0.255	0.79	**0.037**	**0.55**
Opioid tolerant	94 (52.8)	84 (47.2)		(0.53-1.18)		**(0.31-0.96)**
Opioid naïve	131 (58.5)	93 (41.5)				
Tachypnea			<0.001	0.43	0.064	0.55
≧25/min	43 (40.8)	61 (59.2)		(0.26-0.67)		(0.29-1.04)
≦24/min	181 (61.8)	112 (38.2)				
Hypoxia			< 0.001	0.28	0.397	0.66

< 90%	9 (28.1)	23 (71.9)		(0.13-0.62)		(0.25-1.74)
≧90%	216 (58.4)	154 (41.6)				
Oxygen supplement			0.043	0.57	0.217	0.60
Yes	180 (53.7)	155 (46.3)		(0.33-0.99)		(0.26-1.36)
No	45 (67.2)	22 (32.8)				
Baseline dyspnea severity			0.554	1.16	**0.039**	**1.82**
NRS ≧6	141 (70.9)	58 (29.1)		(0.71-1.88)		**(1.03-3.22)**
NRS ≦5	84 (67.7)	40 (32.3)				