Original Article

Effectiveness and safety of opioids for dyspnea in patients with lung cancer: secondary analysis of multicenter prospective observational study

Yoshihiko Taniguchi[1]^, Yoshinobu Matsuda[2]^, Masanori Mori[3], Madoka Ito[4], Tomoo Ikari[5]^, Akihiro Tokoro[2], Sayo Aiki[6]^, Shunya Hoshino[7], Daisuke Kiuchi[8,9], Kozue Suzuki[10]^, Yuko Igarashi[11], Takuya Odagiri[12]^, Kiyofumi Oya[13]^, Emi Kubo[14]^, Takashi Yamaguchi[11]^

[1]Department of Internal Medicine, National Hospital Organization Kinki-Chuo Chest Medical Center, Sakai, Japan; [2]Department of Psychosomatic Internal Medicine, National Hospital Organization Kinki-Chuo Chest Medical Center, Sakai, Japan; [3]Division of Palliative and Supportive Care, Seirei Mikatahara General Hospital, Hamamatsu, Japan; [4]Department of Palliative Care, Konan Medical Center, Kobe, Japan; [5]Department of Palliative Medicine, Tohoku University School of Medicine, Sendai, Japan; [6]Department of Palliative Care, National Hospital Organization Osaka National Hospital, Osaka, Japan; [7]Department of Palliative Medicine, Teikyo University School of Medicine, Tokyo, Japan; [8]Department of Palliative Medicine, National Cancer Center Hospital, Tokyo, Japan; [9]Department of Palliative Care, Center Hospital of the National Center for Global Health and Medicine, Tokyo, Japan; [10]Department of Palliative Care, Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital, Tokyo, Japan; [11]Department of Palliative Medicine, Kobe University Graduate School of Medicine, Kobe, Japan; [12]Department of Palliative Care, Komaki City Hospital, Komaki, Japan; [13]Peace Home Care Clinic, Otsu, Japan; [14]Department of Palliative Medicine, National Cancer Center Hospital East, Kashiwa, Japan

Contributions: (I) Conception and design: Y Taniguchi, Y Matsuda, T Yamaguchi; (II) Administrative support: Y Matsuda, T Yamaguchi; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: Y Taniguchi, Y Matsuda; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Yoshihiko Taniguchi, MD. Department of Internal Medicine, National Hospital Organization Kinki-chuo Chest Medical Center, 1180 Nagasone-cho, Kita-ku, Sakai City, Osaka 591-8555, Japan. Email: taniguchi.yoshihiko.ny@mail.hosp.go.jp.

Background: Patients with lung cancer are more likely to have comorbidities [e.g., interstitial lung disease (ILD)], chronic obstructive pulmonary disease) and metastases that may affect dyspnea and the effectiveness and safety of opioids for dyspnea than other cancer types. Therefore, this study examined the effectiveness and safety of opioids for dyspnea, among the patients with lung cancer.

Methods: The present study is a secondary analysis of a multicenter prospective observational study examining the effectiveness and safety of opioids for dyspnea in patients with cancer in Japan. For this secondary analysis, patients with lung cancer with a documented dyspnea Numerical Rating Scale (NRS) at baseline were included. The primary outcome was dyspnea NRS, and Integrated Palliative care Outcome Scale/Support Team Assessment Schedule (IPOS/STAS) scores change between baseline and 24 hours after baseline. As secondary outcomes, we investigated the predictors of opioid effectiveness for dyspnea improvement and adverse events (nausea, somnolence, and delirium).

Results: This study analyzed 124 patients with lung cancer with known dyspnea NRS at baseline. The median age was 74, and the Eastern Cooperative Oncology Group performance status of 107 patients were 3–4. Both NRS and IPOS/STAS score of dyspnea significantly improved 24 hours after opioid initiation [−1.64, 95% confidence interval (CI): −2.12 to −1.17, P<0.001; −1.03; 95% CI: −1.21 to −0.85, P<0.001; respectively]. Moreover, the improvement of NRS score was greater than the minimal clinically important difference of 1 point. In the multivariate logistic regression analysis, ILD was significantly associated with

^ ORCID: Yoshihiko Taniguchi, 0000-0001-6387-3683; Yoshinobu Matsuda, 0000-0001-5092-9377; Tomoo Ikari, 0000-0003-3441-5768; Sayo Aiki, 0000-0001-9222-0438; Kozue Suzuki, 0000-0002-1959-772X; Takuya Odagiri, 0000-0002-6488-5595; Kiyofumi Oya, 0000-0002-8614-8449; Emi Kubo, 0000-0001-9369-2824; Takashi Yamaguchi, 0000-0003-3060-0245.

a better improvement [(hazard ratio (HR): 3.39, 95% CI: 1.34–11.09, P=0.043]. Somnolence was the most common grade 3–4 adverse event (n=16), followed by delirium (n=9).

Conclusions: Opioids were effective and safe for treating dyspnea in patients with lung cancer. Furthermore, lung cancer patients with ILD may benefit more from opioids.

Keywords: Lung cancer; opioid; dyspnea; morphine; interstitial lung disease (ILD)

Submitted Jul 08, 2022. Accepted for publication Nov 12, 2022.
doi: 10.21037/tlcr-22-512
View this article at: https://dx.doi.org/10.21037/tlcr-22-512

Introduction

Dyspnea is one of the most prevalent and deteriorating symptoms in patients with cancer, especially those with lung cancer. Approximately 54–84% of patients with lung cancer present with some form of dyspnea, which are especially exacerbated in the terminal stages of the disease (1-7).

Patients with lung cancer can have interstitial lung disease (ILD), chronic obstructive pulmonary disease (COPD), and other lung diseases (8-10). Pleural effusion, pleural dissemination and lung metastasis are common in patients with lung cancer (11). Radiation pneumonitis and drug-induced pneumonia may also affect dyspnea.

Opioids are considered the first choice of pharmacological treatment for cancer-induced dyspnea (12-17). Considering these, dyspnea in patients with lung cancer may be different from dyspnea in those with other cancer (i.e., may be mainly caused by lesions in the thoracic cavity. Moreover, patients with concomitant COPD are at risk for hypercapnia. However, few studies have evaluated the effectiveness and safety of opioids, in the real world, in patients with lung cancer. Therefore, this study examined the effectiveness and safety of opioids for dyspnea in patients with lung cancer and identified factors that influence their efficacy. We present the following article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-512/rc).

Methods

The present study is a secondary analysis of a multicenter prospective observational study that primarily aimed to evaluate the effectiveness and safety of opioids for dyspnea caused by cancer in Japan. Patients were enrolled between December 2019 and June 2021. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of National Hospital Organization Kinki-Chuo Chest Medical Center (approval number 2019-042). Informed consent was waived in this study because usual clinical practices, including treatments and assessments, were observed. We used an opt-out method so patients and families could refuse to participate in the study.

Patients

The participating sites were 12 institutions in Japan. The original research was a registry study on opioid therapy for dyspnea in cancer. The eligibility criteria for the original study are hospitalized adult patients with cancer starting regular opioid (morphine, oxycodone, hydromorphone, or fentanyl) administration (new, increased, switched, or combined with different opioids already administered) for dyspnea, and dyspnea on the Integrated Palliative Care Outcome Scale (IPOS) of ≥2 in the past 24 hours at baseline. Cases in which patients were already using opioids for other symptoms were included. Exclusion criteria are patients scheduled for therapeutic intervention for dyspnea due to conditions not directly related to cancer (e.g., antibiotics for bacterial pneumonia, or bronchodilator and corticosteroid for asthma attack or exacerbation of COPD) within 3 days of enrollment. In addition, patients scheduled to undergo an intervention within 3 days of enrollment that could cause a change in symptoms of dyspnea in a short period (e.g., chest drainage for pleural effusion, stenting for airway stenosis or superior vena cava stenosis). We included only patients with lung cancer who could document dyspnea Numerical Rating Scale (NRS) at baseline in the secondary analysis.

Procedure and measurements

We collected clinical data, including patients' sociodemographic data [age, sex, primary tumor, site of metastasis, main cause

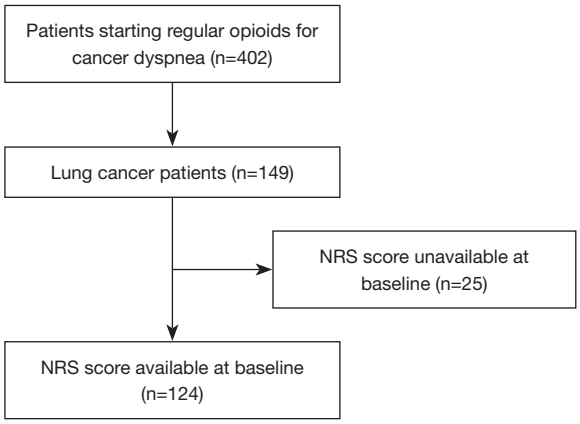

Figure 1 Study flowchart. NRS, Numerical Rating Scale.

of dyspnea as estimated by the treating physician, prognosis as estimated by the physician, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), smoking history], comorbid lung disease (COPD, ILD) diagnosed based on clinical diagnosis, laboratory values (Cr, AST, ALT, T-Bil), type and morphine oral equivalent dose of previously administered opioids, concomitant interventions at study entry (benzodiazepines, corticosteroids). Furthermore, the dyspnea and anxiety scores of the IPOS for the previous 24 h and the dyspnea scores of current NRS, vital signs (respiratory rate, SpO_2, oxygen dose), adverse events (nausea, drowsiness, delirium) assessed by Common Terminology Criteria for Adverse Events (CTCAE) ver. 5.0, type of opioid administered, and morphine oral equivalent dose of opioid. At the baseline (T0), we collected clinical data, including patients' sociodemographic data, anxiety (IPOS), comorbid lung disease and laboratory values within 1 month of study entry, type and dose of previously administered opioids, concomitant interventions at study entry, dyspnea score of IPOS and NRS, vital signs, adverse events, type of opioid administered and morphine oral equivalent dose of opioid at start of regular dosing. In the 24 (±12) (T1), 48 (±12) (T2) and 72 (±12) (T3) hours following the start of opioid treatment for dyspnea, we collected the dyspnea scores of the IPOS and NRS, vital signs, adverse events, type of opioid administered and morphine oral equivalent dose of opioid. IPOS is a 5-point objective symptom scale ranging from 0 (not at all) to 4 (overwhelmingly). NRS is a 11-point subjective symptom scale ranging from 0 (none) to 10 (worst).

Statistical analysis

Wilcoxon's signed rank test with Bonferroni correction was used to compare NRS and IPOS/SATS scores over time. In sensitivity analysis, we imputed missing data with the last observational carried forward (LOCF) method. Univariate logistic regression analysis was performed with 1 or greater improvement in NRS score of dyspnea, which is Minimal Clinically Important Difference (MCID) of 1 point, (18) as dependent variable and age (≥75), sex, PS (≥3), smoking history, metastases, comorbidities, prognostic predictors, NRS score of dyspnea at baseline (≥7), IPOS anxiety score and opioid type as independent variables. Multivariate logistic regression analysis was performed with 1 or higher improvement in NRS score of dyspnea as dependent variable and age (≥75), sex, PS (≥3), smoking history, metastases, comorbidities, prognostic predictors, NRS score of dyspnea at baseline (≥7) and IPOS anxiety score as independent variables. Each independent variable was binarized if it was a continuous variable. Age and NRS score of dyspnea at baseline were binarized using the median. A P value <0.05 was considered statistically significant. All analyses were performed using JMP statistical software program (14th version, SAS Institute Inc., Cary, NC)

Results

Among the 402 patients who participated in the original study, 149 with lung cancer were extracted. Twenty-five patients without NRS score of dyspnea at baseline were excluded, and 124 were included in the analysis (*Figure 1*).

The median age at the time of opioid treatment was 74 years, and 84 patients (68%) were male, 107 (86%) had a PS score of 3–4, 78 (62.9%) had pleural effusion, and 60 (48.4%) had pleural dissemination. The major causes of dyspnea were lung tumor (n=57, 46.0%) and pleural effusion (n=30, 24.2%). Thirty-eight patients (30.6%) had COPD, and 21 (16.9%) had ILD. Fifty-nine patients (47.6%) were opioid-tolerant, and the median previous opioid's morphine equivalent dose was 30 mg. The median NRS score of dyspnea was 6, and the median IPOS/STAS score of dyspnea was 3. Morphine was the most common opioid for dyspnea, with oxycodone second. The median opioid starting dose for opioid-naïve and opioid-tolerant patients were 12 mg and 32 mg, respectively (*Table 1*).

Both NRS and IPOS/STAS dyspnea scores significantly improved after 24 h of opioid initiation (mean difference: −1.64, 95% CI: −2.12 to −1.17; mean difference: −1.03, 95% CI: −1.21 to −0.85, respectively) (*Table 2*). Moreover, this improvement persisted even after correction by LOCF (Table S1).

Table 1 Patient characteristics

Characteristics	Value (N=124)
Median age [range], years	74 [40–90]
Sex: male/female, n	84/40
Median body weight [range], kg	50.9 [32–80]
Smoking history: Yes/No/Unknown, n	91/32/1
Performance status: 0–2/3–4, n	17/107
Metastatic site, n (%)	
Lung metastasis: Yes	63 (50.8)
Pleural effusion: Yes	78 (62.9)
Pleural dissemination: Yes	60 (48.4)
Liver metastasis: Yes	11 (8.9)
Main etiologies of dyspnea, n (%)	
Lung tumor: Yes	57 (46.0)
Pleural effusion: Yes	30 (24.2)
Cachexia/respiratory muscle fatigue: Yes	1 (0.8)
Respiratory infection: Yes	9 (7.3)
expectoration difficulty: Yes	1 (0.8)
Anemia: Yes	0 (0)
Carcinomatous lymphangitis: Yes	14 (11.3)
Unidentifiable/others: Yes	12 (9.7)
COPD: Yes	38 (30.6)
Interstitial lung disease: Yes	21 (16.9)
Concomitant medications, n (%)	
Benzodiazepine: Yes	10 (8.1)
Corticosteroid: Yes	55 (44.4)
Previous opioid, n (%)	
None	65 (52.4)
Morphine	11 (8.9)
Oxycodone	16 (12.9)
Hydromorphone	8 (6.5)
Fentanyl	16 (12.9)
Tapentadol	8 (6.5)
Tramadol	1 (0.8)
Codeine phosphate	1 (0.8)
Median previous opioid dose [range], mg	30 [6–384]
Opioid for dyspnea: increase dose/switching/ new start, n	18/37/69
Baseline status	
Median NRS score of dyspnea, n	6
Median IPOS/STAS score of dyspnea, n	3
Median respiratory rate [range], min	20 [12–46]
Median SpO_2 [range], %	95 [79–100]
Median oxygen flow [range], L	3 [0–50]
Opioid type: morphine/oxycodone/ hydromorphone/fentanyl, n	77/29/16/3
Median opioid dose for opioid naive [range], mg	12 [6–72]
Median opioid dose for opioid-tolerant [range], mg	32 [6–384]

COPD, chronic obstructive pulmonary disease; NRS, Numerical Rating Scale; IPOS, Integrated Palliative Care Outcome Scale; STAS, Support Team Assessment Schedule.

Table 2 Changes from baseline in NRS and IPOS/SATS score of dyspnea

Score	Mean difference (95% CI)	P value
NRS score of dyspnea		
24±12 hours (n=100)	−1.64 (−2.12 to −1.17)	<0.001*
48±12 hours (n=85)	−1.86 (−2.32 to −1.40)	<0.001*
72±12 hours (n=74)	−2.22 (−2.84 to −1.60)	<0.001*
IPOS/STAS score of dyspnea		
24±12 hours (n=113)	−1.03 (−1.21 to −0.85)	<0.001*
48±12 hours (n=103)	−1.14 (−1.32 to −0.97)	<0.001*
72±12 hours (n=90)	−1.19 (−1.39 to −0.99)	<0.001*

*, P<0.05. CI, confidence interval; NRS, Numerical Rating Scale; IPOS, Integrated Palliative Care Outcome Scale; STAS, Support Team Assessment Schedule.

In the univariate logistic regression analysis of factors associated with NRS −1 or higher after 24 h, pleural dissemination was a response factor [odds ratio (OR): 2.71, 95% confidence interval (CI): 1.39–5.27, P=0.003], with poor effect in patients with physician prognosis of days (OR: 0.39, 95% CI: 0.20–0.77, P=0.007) (*Table 3*). In the multivariate logistic regression analysis of factors associated with NRS −1 or higher after 24 h, ILD was an independent and significant determinant (adjusted OR: 3.39, 95% CI: 1.34–11.09). Pleural dissemination tends to increase

Table 3 Univariate logistic regression analysis of factors associated with NRS –1 or higher after 24 hours

Variables	Effective case (%)	OR	95% CI	P value
Age ≥75 years (n=61)	33 (54.1)	1.01	0.50–2.04	0.988
Male (n=84)	45 (53.6)	0.85	0.42–1.70	0.639
Performance status: 3–4 (n=107)	57 (53.3)	0.53	0.19–1.48	0.228
Respiratory rate ≥21 (n=59)	30 (46.2)	0.87	0.41–1.69	0.603
History of smoking (n=91)	48 (52.8)	0.73	0.35–1.55	0.416
Lung metastasis (n=63)	35 (55.6)	1.09	0.57–2.09	0.786
Pleural dissemination (n=60)	40 (66.7)	2.71	1.39–5.27	0.003*
Pleural effusion (n=78)	48 (61.5)	1.88	0.95–3.74	0.072
COPD (n=38)	21 (55.3)	1.42	0.69–2.91	0.345
Interstitial lung disease (n=21)	14 (66.7)	1.70	0.72–4.05	0.227
Physician prognosis of days (n=49)	21 (42.9)	0.39	0.20–0.77	0.007*
NRS score of dyspnea at baseline ≥7 (n=53)	31 (58.5)	1.37	0.67–2.81	0.390
IPOS with anxiety (n=117)	64 (54.7)	1.99	0.49–8.02	0.333

*, P<0.05. OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; NRS, Numerical Rating Scale; IPOS, Integrated Palliative Care Outcome Scale.

effectiveness (adjusted OR: 2.35, 95% CI: 0.95–5.79, P=0.064) and possibly less effective with physician prognosis of days (adjusted OR: 0.44, 95% CI: 0.18–1.07, P=0.071), however, they were not significant (*Table 4*).

Regarding adverse events throughout the entire period, somnolence was the most common grade 3–4 adverse event (n=16, 12.9%), followed by delirium (n=9, 7.3%) (*Table 5*).

There were 31 deaths during the observation period.

Discussion

To the best of our knowledge, this is the report with the largest sample size to clarify the effectiveness and safety of opioids for dyspnea in patients with lung cancer in real-world practice. Moreover, opioids may be more effective in patients with lung cancer with ILD and pleural dissemination and may be less effective in patients with a physician prognosis of days.

Most importantly, we demonstrated the effectiveness of opioids on dyspnea caused by lung cancer. Takahashi *et al.* have reported the effects of oral morphine on dyspnea in patients with cancer in a multicenter study, 90% of which were patients with lung cancer. Nevertheless, the sample size was small (n=80), and only morphine was used (13). Compared with their study, we observed the effectiveness of multiple opioids in 124 patients with lung cancer in this multicenter study. For dyspnea assessment, we used the NRS subjective scale and the IPOS/STAS clinician-rated scale. NRS score of dyspnea decreased by 1.64 points, greater than the MCID of 1 point (18). The effectiveness of opioids for dyspnea was also demonstrated in IPOS/STAS. In addition, the results were maintained in a sensitivity analysis. Therefore, opioids are considered effective for dyspnea in lung cancer.

Opioids were more effective in patients with lung cancer with ILD. ILD often presents with dyspnea, which is difficult to control. Efficacy of opioids for dyspnea in ILDs is controversial (19,20). A phase II study is planned to validate the results (21). Okabayashi *et al.* investigated whether concomitant ILD affects palliative pharmacotherapy for end-stage symptom relief in patients with lung cancer (22). They have reported that opioid dosage for patients with lung cancer did not change with or without ILD, but concomitant use of continuous midazolam and opioid was higher in patients with lung cancer with ILD, which means that dyspnea in patients with lung cancer and ILD may be more difficult to treat than dyspnea in those with lung cancer alone. This was inconsistent with our results. The number of patients with ILD in our study was only 21, therefore, further studies are warranted to reveal

Table 4 Multivariate logistic regression analysis of factors associated with NRS –1 or higher after 24 hours

Variables	Adjusted OR	95% CI	P value
Age ≥75 years (n=61)	0.82	0.35–1.95	0.660
Male (n=84)	1.43	0.51–4.00	0.498
Performance status: 3–4 (n=107)	1.15	0.33–3.95	0.826
Respiratory rate ≥21 (n=59)	0.61	0.26–1.42	0.250
History of smoking (n=91)	0.92	0.28–3.00	0.889
Lung metastasis (n=63)	1.13	0.49–2.56	0.774
Pleural dissemination (n=60)	2.35	0.95–5.79	0.064**
Pleural effusion (n=78)	1.97	0.80–4.87	0.142
COPD (n=38)	1.04	0.39–2.80	0.938
Interstitial lung disease (n=21)	3.39	1.34–11.09	0.043*
Physician prognosis of days (n=49)	0.44	0.18–1.07	0.071**
NRS score of dyspnea at baseline ≥7 (n=53)	1.80	0.79–4.11	0.161
IPOS with anxiety (n=117)	1.00	0.16–6.44	0.999

*, P<0.05; **, P<0.10. OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; NRS, Numerical Rating Scale; IPOS, Integrated Palliative care Outcome Scale.

Table 5 Adverse events

Adverse events	Grade 1–2	Grade 3–4
Nausea	10	4
Somnolence	43	16
Delirium	24	9

whether the coexistence of ILD affects the effectiveness of opioids for dyspnea in patients with lung cancer.

Opioids tended to be more effective for dyspnea in patients with lung cancer with pleural dissemination. In a survey among palliative care physicians to investigate physician-perceived predictive factors for the effectiveness of opioids in the treatment of cancer dyspnea, a high proportion of physician participants reported expecting opioids to be effective for treating dyspnea in patients with pleural lesions (23). This result is in line with our result. Opioids might modulate mismatch between the intended respiratory motor output set and the ventilatory output accomplished. In addition, a previous study reported that pain was associated with dyspnea in patients with lung cancer (24). Opioids may decrease pain from pleural lesions, making deep breathing possible, and might lead to improvement of dyspnea.

There was a trend for opioids to be less effective for dyspnea in patients with a physician prognosis of days. The aforementioned survey among palliative care physicians has also shown that 81% of physicians reported expecting opioids to be effective for the treatment of dyspnea in patients with ECOG PS 0–2 (23). As the disease progresses, the intensity of dyspnea increases, impairing the patient's quality of life (2-7,25). It has been postulated that the principal cause of dyspnea is due to peripheral and respiratory muscle dysfunction, cardio-respiratory system disorder, and neuro-hormonal abnormalities (26). Various factors contribute to worsening dyspnea in patients with terminal lung cancer, including cachexia, multiple metastases to the chest, and worsening interstitial pneumonia. This combination of factors may make the treatment of dyspnea difficult in patients with lung cancer with a prognosis of days.

The percentage of grade 1–2 nausea, somnolence and delirium are 8%, 35% and 19%, respectively. Furthermore, the percentage of grade 3–4 nausea, somnolence and delirium are 3%, 13% and 7%, respectively. These were higher than in previous reports (12,13,15), but this may be because the previous studies were conducted at fixed doses or with small doses. Conversely, in this study, they were administered at the discretion of the attending physician.

This study has some limitations. First, this subgroup

analysis was not preplanned. Therefore, the number of patients may not be sufficient for the analysis of patients with lung cancer. Second, due to the poor prognosis of the patient group, it was not possible to assess patient-reported dyspnea intensity over time for all patients. Third, the influence of non-opioid treatments such as benzodiazepines and oxygen administration cannot be ruled out because we did not assess these treatments to increase the feasibility. Fourth, placebo effect may influence the improvement of dyspnea. Fifth, we are only able to evaluate over 72 h. Sixth, we did not diagnose COPD and ILD with standard diagnostic criteria. Seventh, we evaluated only the presence of pleural effusion and not the volume of the effusion. Finally, due to the small number of cases, no comparison was made between patients already receiving opioids and those not receiving opioids.

In conclusion, opioids were effective for dyspnea in patients with lung cancer and safe. Further, opioids may be more effective in patients with lung cancer with ILD and pleural dissemination and may be less effective in patients with a physician prognosis of days.

Acknowledgments

We wish to thank JORTC for their assistance with this study. We wish to thank Editage (www.Editage.jp) for English language editing.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-512/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-512/dss

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-512/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-512/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of National Hospital Organization Kinki-Chuo Chest Medical Center (approval number 2019-042). Informed consent was waived in this study because usual clinical practices, including treatments and assessments, were observed. We used an opt-out method so patients and families could refuse to participate in the study.

References

1. Dudgeon DJ, Kristjanson L, Sloan JA, et al. Dyspnea in cancer patients: prevalence and associated factors. J Pain Symptom Manage 2001;21:95-102.
2. Tanaka K, Akechi T, Okuyama T, et al. Prevalence and screening of dyspnea interfering with daily life activities in ambulatory patients with advanced lung cancer. J Pain Symptom Manage 2002;23:484-9.
3. Reuben DB, Mor V. Dyspnea in terminally ill cancer patients. Chest 1986;89:234-6.
4. Bruera E, Schmitz B, Pither J, et al. The frequency and correlates of dyspnea in patients with advanced cancer. J Pain Symptom Manage 2000;19:357-62.
5. Chiu TY, Hu WY, Lue BH, et al. Dyspnea and its correlates in taiwanese patients with terminal cancer. J Pain Symptom Manage 2004;28:123-32.
6. Lorenz KA, Lynn J, Dy S, et al. Quality measures for symptoms and advance care planning in cancer: a systematic review. J Clin Oncol 2006;24:4933-8.
7. Skaug K, Eide GE, Gulsvik A. Prevalence and predictors of symptoms in the terminal stage of lung cancer: A community study. Chest 2007;131:389-94.
8. Ogura T, Takigawa N, Tomii K, et al. Summary of the Japanese Respiratory Society statement for the treatment of lung cancer with comorbid interstitial pneumonia.

Respir Investig 2019;57:512-33.
9. Turner MC, Chen Y, Krewski D, et al. Chronic obstructive pulmonary disease is associated with lung cancer mortality in a prospective study of never smokers. Am J Respir Crit Care Med 2007;176:285-90.
10. Koshiol J, Rotunno M, Consonni D, et al. Chronic obstructive pulmonary disease and altered risk of lung cancer in a population-based case-control study. PLoS One 2009;4:e7380.
11. Clive AO, Jones HE, Bhatnagar R, et al. Interventions for the management of malignant pleural effusions: a network meta-analysis. Cochrane Database Syst Rev 2016;(5):CD010529.
12. Navigante AH, Cerchietti LC, Castro MA, et al. Midazolam as adjunct therapy to morphine in the alleviation of severe dyspnea perception in patients with advanced cancer. J Pain Symptom Manage 2006;31:38-47.
13. Takahashi K, Kondo M, Ando M, et al. Effects of Oral Morphine on Dyspnea in Patients with Cancer: Response Rate, Predictive Factors, and Clinically Meaningful Change (CJLSG1101). Oncologist 2019;24:e583-9.
14. Mori M, Morita T, Matsuda Y, et al. How successful are we in relieving terminal dyspnea in cancer patients? A real-world multicenter prospective observational study. Support Care Cancer 2020;28:3051-60.
15. Mori M, Kawaguchi T, Imai K, et al. How Successful Is Parenteral Oxycodone for Relieving Terminal Cancer Dyspnea Compared With Morphine? A Multicenter Prospective Observational Study. J Pain Symptom Manage 2021;62:336-45.
16. Luo N, Tan S, Li X, et al. Efficacy and Safety of Opioids in Treating Cancer-Related Dyspnea: A Systematic Review and Meta-Analysis Based on Randomized Controlled Trials. J Pain Symptom Manage 2021;61:198-210.e1.
17. Hui D, Bohlke K, Bao T, et al. Management of Dyspnea in Advanced Cancer: ASCO Guideline. J Clin Oncol 2021;39:1389-411.
18. Johnson MJ, Bland JM, Oxberry SG, et al. Clinically important differences in the intensity of chronic refractory breathlessness. J Pain Symptom Manage 2013;46:957-63.
19. Matsuda Y, Maeda I, Tachibana K, et al. Low-Dose Morphine for Dyspnea in Terminally Ill Patients with Idiopathic Interstitial Pneumonias. J Palliat Med 2017;20:879-83.
20. Kronborg-White S, Andersen CU, Kohberg C, et al. Palliation of chronic breathlessness with morphine in patients with fibrotic interstitial lung disease - a randomised placebo-controlled trial. Respir Res 2020;21:195.
21. Matsuda Y, Morita T, Oyamada S, et al. Study protocol for a randomised, placebo-controlled, single-blind phase II study of the efficacy of morphine for dyspnoea in patients with interstitial lung disease (JORTC-PAL 15). BMJ Open 2021;11:e043156.
22. Okabayashi H, Kitamura H, Ikeda S, et al. Impact of interstitial pneumonia complications on palliative medication for terminal lung cancer: A single-center retrospective study. Respir Investig 2021;59:859-64.
23. Matsuda Y, Matsunuma R, Suzuki K, et al. Physician-Perceived Predictive Factors for the Effectiveness of Drugs for Treating Cancer Dyspnea: Results of a Nationwide Survey of Japanese Palliative Care Physicians. Palliat Med Rep 2020;1:97-102.
24. Tanaka K, Akechi T, Okuyama T, et al. Factors correlated with dyspnea in advanced lung cancer patients: organic causes and what else? J Pain Symptom Manage 2002;23:490-500.
25. Gupta D, Lis CG, Grutsch JF. The relationship between dyspnea and patient satisfaction with quality of life in advanced cancer. Support Care Cancer 2007;15:533-8.
26. Clemens KE, Quednau I, Klaschik E. Use of oxygen and opioids in the palliation of dyspnoea in hypoxic and non-hypoxic palliative care patients: a prospective study. Support Care Cancer 2009;17:367-77.

Cite this article as: Taniguchi Y, Matsuda Y, Mori M, Ito M, Ikari T, Tokoro A, Aiki S, Hoshino S, Kiuchi D, Suzuki K, Igarashi Y, Odagiri T, Oya K, Kubo E, Yamaguchi T. Effectiveness and safety of opioids for dyspnea in patients with lung cancer: secondary analysis of multicenter prospective observational study. Transl Lung Cancer Res 2022;11(12):2395-2402. doi: 10.21037/tlcr-22-512

Supplementary

Table S1 Changes in NRS and IPOS/SATS score of dyspnea (Last Observational Carried Forward)

	Mean difference (95% CI)	P value
NRS score of dyspnea		
24±12 hours (n=100)	−1.30 (−1.70 to −0.90)	<0.001*
48±12 hours (n=85)	−1.34 (−1.74 to −0.94)	<0.001*
72±12 hours (n=74)	−1.54 (−2.02 to −1.06)	<0.001*
IPOS/STAS score of dyspnea		
24±12 hours (n=113)	−0.78 (−0.95 to −0.61)	<0.001*
48±12 hours (n=103)	−0.88 (−1.05 to −0.71)	<0.001*
72±12 hours (n=90)	−1.11 (−1.32 to −0.90)	<0.001*

*, P<0.05. CI, confidence interval; NRS, Numerical Rating Scale; IPOS, Integrated Palliative care Outcome Scale; STAS, Support Team Assessment Schedule.

https://dx.doi.org/10.21037/tlcr-22-512