

Patients with End-stage Interstitial Lung Disease may have More Problems with Dyspnea than End-stage Lung Cancer Patients

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ABSTRACT

Introduction: Patients with end-stage interstitial lung disease (ILD) do not appear to receive adequate palliative care despite apparent suffering before death. The aim of this study was to evaluate their signs, symptoms, and treatment received before death.

Methods: Patients with ILD and lung cancer (LC) who were hospitalized and died in our hospital were enrolled retrospectively. Signs and symptoms and treatments at 7 days, 3 days, and 1 day before death were evaluated and compared between the two groups of patients.

Results: A total of 23 patients with ILD and 59 patients with LC group were eligible for participation. Significantly more LC patients had loss of consciousness than ILD patients on 7 days (ILD: LC = 1 [5.6%]:24 [41%], $P = 0.013$), 3 days (1 [5.6%]:33 [56%], $P < 0.001$). Significantly more ILD patients had dyspnea than LC patients on 3 days (16 [89%]:38 [64%], $P = 0.047$) 1 day before death (21 [91%]:33 [56%], $P = 0.001$). On 1 day before death, significantly more LC patients received morphine than ILD patients (2 [8.7%]: 14 [24%], $P = 0.015$). More ILD patients received sedation (11 [48%]: 11 [19%], $P = 0.007$).

Conclusions: End-stage ILD patients may experience dyspnea more frequently than terminal LC patients, and they need sedation. Morphine should be administered to ILD patients who have dyspnea. Additional prospective studies are needed.

Key words: Dyspnea, Interstitial lung disease, Morphine, Palliative care

INTRODUCTION

Interstitial lung disease (ILD), especially idiopathic pulmonary fibrosis (IPF), is a fatal disease with a poor prognosis, and the therapeutic options are limited.^[1-3] The mean survival time of patients with IPF in Japan is 61 months.^[4] Moreover, most end-stage patients with ILD have dyspnea, hypoxemia, and cough.^[5] These signs

and symptoms, in the end, stage are similar to those of patients with lung cancer (LC). ILD patients generally do not receive adequate palliative care in Japan. Less ILD patients receive morphine even if they suffer from dyspnea than LC patients.^[5,6] In addition, the guidelines

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from the Japanese Respiratory Society (JRS) only contain recommendations on the diagnosis and treatment of ILD, which may account for why ILD patients are infrequently provided palliative care.^[7] By contrast, there are guidelines on palliative care for ILD patients based on collaboration between several medical societies.^[8,9] Moreover, the current view in the United Kingdom is that access to palliative care should be based on patients' needs instead of a diagnosis.^[10,11] While the patients with ILD cannot be admitted to the palliative care units because only malignancy and advanced immunodeficiency syndrome patients can admit to these facilities in Japan, 8.5% of the patients with lung disease who admitted to hospice have noncancer in the US,^[12] and both patients with ILD as well as patients with LC receive palliative care in Western countries.

To the best of our knowledge, there have not been any studies comparing the signs and symptoms of end-stage ILD and LC patients during the last few days of life, although physicians realize that patients with end-stage ILD have distress as often as patients with LC. The aim of this study was to evaluate the signs, symptoms, and treatments of patients with ILD before death. This study found that end-stage ILD patients had the same signs and symptoms as end-stage LC patients.

METHODS

Patients

This retrospective study was performed at Komatsu Municipal Hospital (340-bed community hospital). Patients with a diagnosis of ILD who were admitted to and died in this hospital from January 2007 to September 2013 were enrolled in this study. ILD was defined based on the American Thoracic Society/European Respiratory Society/JRS/Latin American Thoracic Association idiopathic interstitial pneumonia (IIPs) consensus guidelines 2002^[13] and 2013.^[14] ILD associated with collagen-vascular disease was included. Data from surgical lung biopsies were not required. Patients with LC who were admitted to and died in our hospital during the same period were also enrolled in this study. All patients were admitted to receive palliative care only. Therefore, patients receiving specific antitumor-specific treatment such as chemotherapy and radiation therapy were excluded. The types of LC included pathologically proven small cell and nonsmall cell carcinoma. The study protocol was approved by the Institutional Review Board of Komatsu Municipal Hospital.

Factors analyzed

Clinical data were collected from electronic medical records. Signs and symptoms at 7 days, 3 days, and 1 day before death was examined for both groups of patients. The frequencies of the following signs and symptoms were determined: Level of consciousness, cough, sputum, fatigue, delirium, dyspnea, appetite loss, and pain. Loss of consciousness was defined as more than one point of the Japanese Coma Scale.^[15] Causes of loss of consciousness were then researched. Nurses assessed these symptoms and recorded on the medical record. We could not evaluate the relationship between laboratory findings and several symptoms because only six patients underwent laboratory testing of blood samples and arterial blood gas analysis during the study period.

The following treatments received by the patients were investigated: Sedation, intubation, nonintubated ventilation, supplemental oxygen, opioids, and antimicrobials and glucocorticoids based on clinical condition. Sedation was evaluated if a patient received it to reduce subjective dyspnea. Patients who received morphine for analgesia were excluded from the study. Patients who were administered morphine for dyspnea were included this study.

Statistical analysis

The signs, symptoms, and treatments of ILD and LC patients were compared. Continuous variables with a normal distribution were compared using the Student's *t*-test. The Wilcoxon rank sum test was used for variables with a nonnormal distribution. The Chi-square statistic or Fisher exact test was used to compare categorical variables. Differences were assumed to be significant for $P < 0.05$. Analyses were performed using SPSS for Windows, version 20.00 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

Patient characteristics are shown in Table 1. There were 23 ILD patients and 59 LC patients with 5 (22%), and 26 (44%) female patients, respectively. The respective mean ages were 75 ± 9.7 years and 74 ± 10 years. There were no significant differences in the ages and numbers of each gender between ILD and LC patients. The duration of hospitalization of the LC patients was significantly longer than for the ILD patients (42 ± 40 days versus 21 ± 27 days, respectively; $P = 0.008$). Five ILD patients died within 2 days from the date of admission, whereas only one LC patient died within 7 days from admission.

Diabetes mellitus, dyslipidemia, chronic obstructive pulmonary disease (COPD), and chronic heart failure were significantly more common in patients with ILD. Fifty LC patients (85%) had metastatic disease when admitted, including 25 patients (42%) with brain metastasis and two patients (3.4%) with leptomeningeal carcinomatosis.

Signs and symptoms

The signs and symptoms of patients are shown in Table 2. Significantly more LC than ILD patients were not conscious at 7 days (26 [45%] vs. 2 [11%] respectively; *P* = 0.012) and 3 days (37 [63%] vs. 4 [22%], respectively; *P* = 0.003) before death. Anorexia was also more frequent in LC patients than in ILD patients at 7 and 3 days before

death. Patients with LC had pain more frequently than ILD patients on days 7–1 before death. Significantly more ILD patients than LC patients felt dyspnea at 1 day (21 [91%] vs. 33 [56%], respectively; *P* = 0.001) and 3 days before death (16 [89%] vs. 38 [64%], respectively; *P* = 0.047).

Medications and care

The medications and types of care received by study patients are shown in Table 3. Each physician decided whether to administer any sedative agents. More ILD than LC patients received sedation on day 1 before death (*P* = 0.007). There were more ILD patients who received morphine to reduce dyspnea in LC patients than ILD patients throughout 1–7 days before death. Midazolam was more frequently administered to ILD patients than LC patients 1 day before death (*P* = 0.031). Two patients at 1 day before death, one patient at 3 days before death and one patient at 7 days before death received midazolam for sedation. The remaining patients received midazolam to relieve distress. There were no patients who received midazolam as an anti-anxiety agent. Antimicrobials were more frequently administered to ILD than LC patients on days 7–1 day before death. Intubation and urethral catheterization were used more frequently for ILD than LC patients on days 7–1 day before death. Advanced directives were discussed with all LC patients, their families, and medical staff. On the other hand, three ILD patients (13%) did not make a decision for advance directive at 1 day before death.

Causes of loss of consciousness

Causes of loss of consciousness is described in Table 4. Receiving sedative agents was most commonly seen in ILD patients at 7 days, 3 days, and 1 day before death. On the other hand, disease progression was most commonly seen

Table 1: Characteristics of patients with interstitial lung disease and lung cancer

	ILD (n=23)	LC (n=59)	P
Age (years), mean±SD	75±9.7	74±10	
Female (sex), n (%)	5 (22)	26 (44)	
Duration of admission (days), mean±SD	21±27	42±40	0.008
Illness duration (days), median±SD			
Comorbidities, n (%)			
HT	10 (43)	15 (25)	
DM	9 (39)	4 (6.8)	0.001
Dyslipidemia	3 (13)	0	0.022
Asthma	0	2 (3.4)	
COPD	4 (17)	1 (1.7)	0.022
CKD	2 (8.7)	1 (1.7)	
Cerebrovascular disease	2 (8.7)	3 (5.1)	
Chronic heart failure	7 (30)	2 (3.4)	0.002
Home oxygen	9 (39)	0	< 0.001
Metastasis		50 (85)	
Brain metastasis		25 (42)	
Leptomeningeal carcinomatosis		2 (3.4)	

ILD: Interstitial lung disease; HT: Hypertension; DM: Diabetes mellitus; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; LC: Lung cancer

Table 2: Signs and symptoms of patients with interstitial lung disease and lung cancer at 7 days, 3 days, and 1 day before death

Symptoms	7 days before			3 days before			1 day before		
	ILD (n=18*), n (%)	LC (n=58**), n (%)	P	ILD (n=18*), n (%)	LC (n=59), n (%)	P	ILD (n=23), n (%)	LC (n=59), n (%)	P
Loss of consciousness	2 (11)	26 (45)	0.012	4 (22)	37 (63)	0.003	18 (78)	52 (88)	
Cough	10 (56)	30 (52)		11 (61)	35 (59)		13 (57)	30 (51)	
Sputum	9 (50)	28 (48)		11 (61)	33 (56)		12 (52)	35 (59)	
Fatigue	11 (61)	49 (84)		13 (72)	48 (81)		12 (52)	50 (85)	0.015
Delirium	2 (11)	9 (16)		1 (5.6)	15 (25)		2 (8.7)	15 (25)	
Insomnia	2 (11)	2 (3.4)		1 (5.6)	4 (6.8)		2 (8.7)	15 (25)	
Dyspnea	15 (83)	33 (57)		16 (89)	38 (64)	0.047	21 (91)	33 (56)	0.001
Anorexia	9 (50)	50 (86)	0.002	10 (56)	52 (88)	0.011	18 (78)	55 (93)	
Pain	0	32 (55)	<0.001	0	34 (58)	<0.001	0	40 (68)	<0.001

ILD: Interstitial lung disease; LC: Lung cancer. *Five patients died within 2 of admission in the ILD patients; **One patient died within 7 of admission in the LC patients

Table 3: Treatments used for patients with interstitial lung disease and lung cancer at 7 days, 3 days, and 1 day before death

Medications and care	7 days before			3 days before			1 day before		
	ILD (n=18*)	LC (n=58**)	P	ILD (n=18*)	LC (n=59)	P	ILD (n=23)	LC (n=59)	P
Advanced directives	17 (94)	58 (100)	0.02	17 (94)	59 (100)	0.02	20 (87)	59 (100)	0.02
Oxygen	17 (94)	46 (79)		16 (89)	52 (88)		23 (100)	55 (93)	
Intubation	1 (5.6)	0		1 (5.6)	0		3 (13)	0	0.02
NPPV	0	0		1 (5.6)	0		1 (4.3)	0	
Urethral catheter	12 (67)	21 (36)	0.045	11 (61)	21 (36)		21 (91)	28 (47)	<0.001
Antimicrobials	12 (67)	3 (5.2)	<0.001	11 (61)	5 (8.5)	<0.001	18 (78)	7 (12)	<0.001
Glucocorticoids	15 (83)	42 (72)		15 (83)	46 (78)		15 (65)	46 (78)	
Opioids	1 (5.6)	32 (55)	<0.001	1 (5.6)	33 (56)	<0.001	1 (4.3)	34 (58)	<0.001
Morphine	0	5 (8.6)	0.03	0	7 (12)	0.016	2 (8.7)	14 (24)	0.015
Sedation	2 (11)	3 (5.2)		3 (17)	4 (6.8)		11 (48)	11 (19)	0.007
Midazolam	1 (5.6)	3 (5.2)		3 (17)	4 (6.8)		7 (30)	5 (8.5)	0.031
Others	1 (5.6)	0		0	0		1 (4.3)	1 (1.7)	

ILD: Interstitial lung disease; LC: Lung cancer; DNR: Do not resuscitate; NPPV: Noninvasive positive-pressure ventilation. *Five patients died within 2 of admission in the ILD patients; **One patient died within 7 of admission in the LC patients

in LC patients. Furthermore, brain metastasis, delirium, hypercalcemia, and carcinomatous meningitis were also the reasons of loss of consciousness in LC patients. Patients who received sedative agent was less in LC patients than ILD patients at 7 days to 1 day before death.

DISCUSSION

Our study found that ILD patients have dyspnea more frequently than LC patients during the end stage of disease. LC patients needed to receive sedative agent more frequently than ILD patients because they suffered more distress and the other medication could not relieve these symptoms. This indicated that ILD patients may have more problems with dyspnea than LC patients. Arita *et al.* reported that 97% of ILD patients had dyspnea until 3 days before death,^[5] and Bajwah *et al.* reported that 93% of ILD patients had dyspnea during their last year of life.^[16] On the other hand, the prevalence of dyspnea in patients with advanced cancer ranges between 19% and 51%, and over 60% of advanced cancer patients with dyspnea have moderate to severe dyspnea.^[17] Although these studies evaluated patients during various stages of their disease and did not evaluate end-stage patients, the results of these studies and our study suggest that end-stage ILD patients may have more severe dyspnea than terminal LC patients.

Our study found that more ILD than LC patients were conscious on days 7–3 before death. Arita *et al.* reported that 45% of ILD patients had loss of consciousness 24–48 h before death,^[5] which is similar to our study findings. Moreover, loss of consciousness was not a finding in two case–control studies of ILD patients with acute exacerbation (AE), which is frequently fatal.^[18,19] Our

study found that 45–88% of LC patients developed loss of consciousness. Unlike ILD patients, there were several causes of loss of consciousness such as brain metastasis, delirium, hypercalcemia, and carcinomatous meningitis in LC patients. Patients with malignancy sometimes develop an altered level of consciousness, because of brain metastasis,^[20] leptomeningeal carcinomatosis,^[21] hypercalcemia due to pseudohyperparathyroidism,^[22] Hyponatremia,^[23] hypoxemia, hypercapnia,^[24] and delirium.^[25]

Morphine is commonly used to reduce dyspnea in palliative medicine.^[26] The effects of morphine, including suppression of respiratory center sensitivity in the brain stem, reduced oxygen consumption as a result of reduced respiratory rate, elevation of endogenous endorphin levels, central sedation, and improvement of heart failure, are thought to play roles in the relief of dyspnea.^[27] Results of two clinical studies indicate that morphine was an effective pharmacological agent for dyspnea in cancer patients.^[28,29] As shown in this study, morphine was not commonly used for dyspnea in ILD patients, however, Allen *et al.* found that subjective breathlessness, determined on a 100-mm visual analog scale, fell by a mean of 47 mm during the first 15 min after the first morphine injection of patients with IPF.^[30] Although nebulized morphine is a treatment used for dyspnea, it was not effective for improving the dyspnea of patients with ILD during exercise.^[31] A systematic review in the management of dyspnea reported that oral and parenteral opioids were more effective than nebulized opioids, and the data from the meta-analysis was insufficient for concluding whether nebulized opioids were effective.^[26] These studies were all performed in Western countries, and there have not been any Japanese studies. In fact, patients with nonmalignant disease do not tend to

Table 4: Causes of loss of consciousness in interstitial lung disease and lung cancer patients

	n (%)
7 days before death	
ILD (n=2)	
Sedation	1 (50)
Delirium	1 (50)
LC (n=26)	
Disease progression	13 (50)
Brain metastasis	5 (19)
Delirium	4 (15)
Sedation	2 (7.7)
Hypercalcemia	1 (3.8)
Carcinomatous meningitis	1 (3.8)
3 days before death	
ILD (n=4)	
Sedation	3 (75)
Delirium	1 (25)
LC (n=37)	
Disease progression	18 (49)
Delirium	8 (22)
Brain metastasis	6 (16)
Sedation	3 (8.1)
Hypercalcemia	1 (2.7)
Carcinomatous meningitis	1 (2.7)
1 day before death	
ILD (n=18)	
Sedation	12 (67)
Hypoxemia	3 (17)
Delirium	1 (5.6)
Sepsis	1 (5.6)
Hypoxic encephalopathy	1 (5.6)
LC (n=52)	
Disease progression	27 (52)
Sedation	9 (17)
Delirium	8 (15)
Brain metastasis	6 (12)
Hypercalcemia	1 (1.9)
Carcinomatous meningitis	1 (1.9)

ILD: Interstitial lung disease; LC: Lung cancer

receive opioids treatment even if they are suffering from dyspnea.^[4,5] In our study, there were only two patients (8.7%) with ILD, who received morphine for their dyspnea, and both patients had concomitant malignant disease.

In our study, most ILD patients were administered midazolam for sedation. Bajwah *et al.* reported that eight patients (18%) with ILD received benzodiazepines for dyspnea, which was effective in 7 (88%).^[16] Navigante *et al.* demonstrated that morphine was useful for controlling baseline levels of dyspnea in cancer patients, and dyspnea was improved when midazolam was used in addition to morphine.^[32] However, a review of several studies found

no evidence that benzodiazepines were effective in relieving breathlessness of patients with advanced cancer and COPD. Furthermore, there were no studies on the efficacy of benzodiazepines for ILD patients with dyspnea.^[33] Therefore, morphine should be administered not only for patients with LC, who have dyspnea but also for patients with ILD who have dyspnea.

It is difficult for physicians to recognize whether patients are end stage or not. The clinical presentation of many ILDs is insidious.^[34] Some ILD progress gradually, the other patients may present acutely because of AE or infection. The most common cause of death is AE in Japan.^[35] AE-ILD is a fatal and progressive disease. Several studies researched that age at the onset, respiratory status before the AE, low C-reactive protein and lactose dehydrogenase were prognostic factors for AE-ILD.^[36,37] These factors may be tools to recognize patients' prognosis. On the other hand, progressive breathlessness and respiratory failure are common natural history for the patients whose diseases progress slowly.^[34] These patients may be easily assessed end stage such as LC patients.

This study has several limitations. First, it was a retrospective analysis with a very small study population. Second, we could not objectively evaluate the signs and symptoms of any of the patients, because the electronic medical record did not include these descriptions. Third, our study patients with ILD had various types of disease. Finally, since this was a retrospective study, it is possible that selection bias was present. Therefore, additional prospective studies using objective assessments and enrolling more patients are needed to confirm and further clarify these results.

CONCLUSIONS

Terminal ILD patients may experience dyspnea more frequently than end-stage LC patients, and they need sedation. To relieve their distress, morphine should be used more frequently than its current practice, for ILD patients with dyspnea. Additional prospective studies using objective assessments and more patients are needed to accurately determine how morphine is used for terminal ILD patients.

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Conflicts of interest

There are no conflicts of interest.

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