Original Article

Chemotherapy for patients with advanced lung cancer receiving long-term oxygen therapy

Manabu Hayama, Hidekazu Suzuki, Takayuki Shiroyama, Motohiro Tamiya, Norio Okamoto, Ayako Tanaka, Naoko Morishita, Takuji Nishida, Takashi Nishihara, Tomonori Hirashima

Department of Thoracic Malignancy, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Habikino City, Japan

Contributions: (I) Conception and design: M Hayama; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: H Suzuki, T Shiroyama, M Tamiya, N Okamoto, A Tanaka, N Morishita, T Nishida, T Nishihara, T Hirashima; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Manabu Hayama, MD. Department of Thoracic Malignancy, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, 3-7-1, Habikino, Habikino City, Osaka 583-8588, Japan. Email: manabuhayama@gmail.com.

Background: Long-term oxygen therapy (LTOT) is sometimes prescribed for patients with advanced lung cancer who are potential candidates for chemotherapy. The aim of this study was to assess the usefulness of chemotherapy for patients with this disease who require LTOT.

Methods: The medical records of 40 patients with advanced lung cancer who received LTOT while undergoing systemic chemotherapy at our institution between January 2009 and December 2014 were retrospectively reviewed. Chemotherapy consisted of cytotoxic or molecular-targeted agents.

Results: Twenty-four patients had adenocarcinoma, 6 had squamous cell carcinoma, and 10 had small cell lung cancer (SCLC). The median survival time from the date of the first chemotherapy cycle performed in conjunction with LTOT was 194 days. In a multivariate analysis, the only factor significantly associated with better prognosis was the line (first or second) of the first chemotherapy with LTOT (hazard ratio =0.42; 95% confidence interval, 0.18 to 0.94). Among the 40 patients, 10 (25%) received chemotherapy during the last 30 days of their lives, 2 of whom died of chemotherapy-related adverse events.

Conclusions: Chemotherapy for patients with advanced lung cancer who receive LTOT may be acceptable if it is the first- or second-line treatment. However, we should be mindful of the potential overuse of chemotherapy and its negative impact on quality of life.

Keywords: Lung cancer; chemotherapy; comorbidity; long-term oxygen therapy (LTOT); performance status

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Introduction

Lung cancer is the leading cause of cancer-related death in the world (1). Because most lung cancers are unfortunately diagnosed at an advanced stage, systemic chemotherapy (including molecular-targeted therapy) or best supportive care is the only treatment choice (2,3). A meta-analysis showed that chemotherapy improves overall survival in patients with advanced lung cancer (4). Good responses in patients with advanced non-small lung cancer (NSCLC) were recently observed for chemotherapy regimens including epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) or anaplastic lymphoma kinase tyrosine kinase inhibitors (ALK-TKIs) (5-8). However, physicians often encounter lung cancer patients with severe comorbidities, including cardiovascular disease, chronic obstructive pulmonary disease (COPD), and interstitial lung disease (ILD), and the prognosis of these patients remains poor (9,10). These patients sometimes experience chronic respiratory failure, and physicians commonly prescribe

long-term oxygen therapy (LTOT) to support their daily activities (11).

In the 1980s, LTOT significantly improved the survival of patients with COPD and chronic hypoxemia (12,13). In Japan, LTOT has been increasingly prescribed for chronic respiratory diseases including lung cancer (14,15). Patients with advanced lung cancer who receive LTOT are sometimes in relatively good condition owing to their enhanced ability to perform daily activities. However, aggressive chemotherapy in patients receiving LTOT should be carefully considered by physicians because it has been associated with poor outcomes in patients with severe comorbidities (16). To our knowledge, no reports have addressed the use of chemotherapy in patients with advanced lung cancer who require LTOT. The aim of this study was to evaluate the effects of chemotherapy in such patients based on our clinical experience.

Methods

Study approval

This study was approved by the Institutional Review Board of the Osaka Prefectural Medical Center for Respiratory and Allergic Diseases. Because it was a retrospective chart review, informed consent was not required for approval. Written informed consent for chemotherapy was obtained from all eligible patients.

Patient selection

This study included patients with advanced lung cancer who received LTOT while undergoing at least 1 cycle of chemotherapy between January 2009 and December 2014 at our institution. Chemotherapy included cytotoxic agents, EGFR-TKIs, or ALK-TKIs. Patients receiving adjuvant or neoadjuvant chemotherapy were excluded from this study. All study participants were observed until death or April 30, 2015.

Indication for long-term oxygen therapy (LTOT)

Patients with a PaO_2 level ≤60 mmHg or a SpO_2 level ≤90% at rest or during exercise were indicated for LTOT. Non-hypoxemic patients receiving palliative oxygen therapy were excluded from this study. Oxygen was provided to patients via an oxygen concentrator (Hi-Sanso®, Teijin Pharma Ltd, Japan) and an oxygen cylinder. In patients with an underlying pulmonary disease (e.g., COPD or ILD), maximum medical therapy (e.g., use of bronchodilators or administration of inhaled or oral corticosteroids) was performed before prescribing LTOT. Oxygen rates were reevaluated every month. The first date of LTOT was defined as the date when continuous oxygen therapy was started in an outpatient or inpatient setting.

Treatment strategy

Treatments for lung cancer (e.g., surgery, radiotherapy, chemotherapy, or best supportive care) were determined via regular multidisciplinary team discussions at our institution. Moreover, board-certified oncologists and pulmonologists carefully considered the eligibility of each candidate for chemotherapy and selected the appropriate chemotherapy regimen (platinum-based, non-platinum-based, EGFR-TKI, or ALK-TKI).

Clinical review

The clinical history of the eligible patients was retrospectively reviewed. Baseline demographic information including age, sex, smoking status, underlying respiratory disease, histology, disease stage, and Eastern Cooperative Oncology Group performance status (PS) was obtained for each patient. Age and PS were determined at the beginning of the first chemotherapy cycle performed in conjunction with LTOT. Staging was based on the criteria of the seventh edition of the Tumor, Node, and Metastasis classification for lung cancer (17). The components and treatment line of the first chemotherapy regimen with LTOT, and the number of regimens performed with LTOT were also evaluated. Chemotherapy-related severe adverse events (non-hematological toxicity ≥ grade 3 or hematological toxicity ≥ grade 4) were examined during and immediately after the first chemotherapy regimen with LTOT.

Survival time from diagnosis was calculated as the duration from the date of diagnosis to the date of death or final follow-up. Survival time with LTOT was calculated from the date of the first chemotherapy cycle with LTOT to the date of death or final follow-up. For patients alive at the end of the study period, the final follow-up date was April 30, 2015.

Chemotherapy at the end of life

Because of the toxicity of aggressive chemotherapy in

Table 1 Patient characteristics

Variable	Total (n=40)
Age, median [range] (years)	69.5 [49–83]
Male, n (%)	32 (80.0)
Smoker, n (%)	34 (85.0)
Respiratory disease, n (%)	
COPD	14 (35.0)
ILD	10 (25.0)
None	16 (40.0)
Histology, n (%)	
NSCLC	30 (75.0)
Adenocarcinoma	24 (60.0)
Squamous cell carcinoma	6 (15.0)
SCLC	10 (25.0)
Stage, n (%)	
IIIA	3 (7.5)
IIIB	4 (10.0)
IV	28 (70.0)
Recurrent	5 (12.5)
PS, n (%)	
2	33 (82.5)
3	7 (17.5)

COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; PS, performance status.

Table 2 Chemotherapy with long-term oxygen therapy

Variable	Total (n=40)
First chemotherapy regimen, n (%)	
Platinum-based	12 (30.0)
Non-platinum-based	22 (55.0)
EGFR-TKI	5 (12.5)
ALK-TKI	1 (2.5)
Treatment line of the first chemotherapy, n (%)	
1st	17 (42.5)
2nd	10 (25.0)
3rd or 4th	8 (20.0)
5th to 8th	5 (12.5)
Number of regimens performed, n (%)	
1	28 (70.0)
2	6 (15.0)
3–6	6 (15.0)

EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; ALK-TKI, anaplastic lymphoma kinase tyrosine kinase inhibitor.

patients with comorbidities, whether chemotherapy is terminated at the appropriate time should be determined in patients receiving LTOT. In this study, we evaluated the composition of the final chemotherapy regimen, the survival time (time between the date of the final chemotherapy and death), and the cause of death in patients who received chemotherapy during the last 30 days of their lives.

Statistical analysis

Values are presented as frequency, percentage, or median (range). Survival time was assessed via Kaplan-Meier survival analysis. For survival time with LTOT, differences between survival curves were assessed by using the log-rank test. Variables with a P value <0.05 in a univariate analysis were included in a multivariate analysis using Cox's regression model to identify independent predictors of survival with LTOT. All analyses were conducted using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is the graphical user interface of the R foundation for Statistical Computing (Vienna, Austria). All comparisons with a P value <0.05 were considered statistically significant.

Results

Overall, 40 patients received at least 1 cycle of chemotherapy along with LTOT between January 2009 and December 2014 at our institution. Patient characteristics are summarized in *Table 1*. The study population had a median age of 69.5 years and mostly consisted of men. Most patients were smokers (n=34) and/or had underlying respiratory diseases including COPD (n=14) and ILD (n=10). Thirty patients had NSCLC, either adenocarcinoma (n=24) or squamous cell carcinoma (n=6), and 10 had small cell lung cancer (SCLC). There was an EGFR mutation in 5 of the 24 patients with adenocarcinomas and an ALK translocation in 2. The disease stage was IIIA in 3 patients, IIIB in 4 patients, IV in 28 patients, and recurrent after surgery in 5 patients. The PS at the beginning of the first chemotherapy cycle with LTOT was 2 in 33 patients and 3 in 7 patients.

The characteristics of the chemotherapy regimens performed in conjunction with LTOT are summarized in *Table 2*. The first chemotherapy regimen that was accompanied by LTOT was the first-line treatment in 17 patients, the second-line treatment in 10 patients, the third- or fourth-line treatment in 8 patients, and the fifth- to eighth-line treatment in 5 patients. It was platinum-based

Table 3 Univariate and multivariate analysis of survival time with long-term oxygen therapy

Variable	Univariate analysis			Multivariate analysis		
	N	Days[a]	P value	HR	95% CI	P value
Age (years)			0.74	–	–	–
<70	20	210.0				
≥70	20	177.5				
Sex			0.35	–	–	–
Male	32	196.0				
Female	8	123.0				
Respiratory disease			0.046	0.62	0.28–1.39	0.25
COPD or ILD	24	236.0				
None	16	134.0				
Histology			0.52	–	–	–
NSCLC	30	194.0				
SCLC	10	131.0				
Stage			0.17	–	–	–
III	7	347.0				
IV or recurrent	33	186.0				
PS			0.28	–	–	–
2	33	194.0				
3	7	134.0				
First regimen with LTOT: type			0.09	–	–	
TKI or platinum-based	18	236.0				
Non-platinum-based	22	124.0				
First regimen with LTOT: line			0.005	0.42	0.18–0.94	0.04
1st or 2nd	27	236.0				
3rd or more	13	111.0				

[a], median survival time with LTOT. HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; PS, performance status; TKI, tyrosine kinase inhibitor; LTOT, long-term oxygen therapy.

in 12 patients, non-platinum-based in 22 patients, and consisted of an EGFR-TKI in 5 patients and an ALK-TKI in 1 patient. Seven (58.3%) of the 12 patients receiving a platinum-based regimen, 4 (18.2%) of the 22 patients receiving a non-platinum-based regimen and 3 (50%) of the 6 patients receiving TKIs experienced chemotherapy-related severe adverse events. Most patients (n=28, 70%) received only 1 regimen during the study period.

The median survival time from diagnosis was 679 days (95% confidence interval, 327 to 968 days), while median survival time with LTOT was 194 days (95% confidence interval, 112 to 266 days). In univariate analyses of survival time with LTOT, prognosis was better when respiratory disease (COPD or ILD) was present (236 and 134 days with and without respiratory disease, respectively; P=0.046) (*Table 3*) and when the first chemotherapy regimen with LTOT was the first- or second-line treatment (236 and 111 days for first/second-line and third-line or higher, respectively; P=0.005) (*Table 3*, *Figure 1*). None of the other variables (age, sex, histology, stage, PS, and composition of the first chemotherapy regimen with LTOT) were associated with better prognosis. In a multivariate analysis of survival time with LTOT, the only factor significantly associated with better prognosis was the treatment line (first or second) of the first chemotherapy with LTOT (hazard ratio, 0.42; 95% confidence interval, 0.18 to 0.94) (*Table 3*).

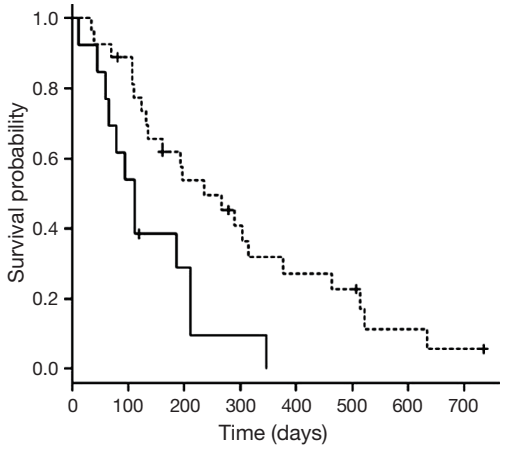

Figure 1 Kaplan-Meier curves showing the survival times with long-term oxygen therapy (LTOT). The dashed line represents the patients whose first chemotherapy regimen with LTOT was first- or second-line. The solid line represents the patients whose first chemotherapy regimen with LTOT was third-line or more. The median survival times with LTOT were 236 (first- and second-line) and 111 (at least third-line) days (P=0.005).

Ten patients (25%) received chemotherapy during the last 30 days of their lives (*Table 4*). The histological type was adenocarcinoma in 7 patients, SCLC in 2 patients, and squamous cell carcinoma in 1 patient. Survival time from the first chemotherapy with LTOT to death varied from 10 to 522 days, while survival time after the final chemotherapy to death varied from 3 to 23 days. The final chemotherapy regimen contained an EGFR-TKI in 4 patients and was platinum-based in 2 patients and non-platinum-based in 4 patients. It was third-line or more in 5 patients. Four patients received more than 1 regimen (2 to 6 regimens) with LTOT, and oxygen therapy was continued until death in all the patients. The cause of death was lung cancer in 7 patients and chemotherapy-related in 2 patients (ILD caused by the EGFR-TKI in 1 patient and febrile neutropenia in 1 patient). Sudden death at home presumably due to acute myocardial infarction occurred in 1 patient. In 1 of the 2 patients who died of chemotherapy-related adverse events, the final chemotherapy regimen administered was third-line.

Discussion

LTOT is sometimes prescribed for advanced lung cancer patients with chronic respiratory failure who might be candidates for chemotherapy. The present study describes our clinical experience with 40 advanced lung cancer patients who underwent systemic chemotherapy while receiving LTOT between January 2009 and December 2014. Two important clinical observations were made. First, chemotherapy with LTOT had an acceptable survival benefit, especially for patients for whom the first chemotherapy with LTOT was the first- or second-line treatment. Secondly, 10 of the 40 patients received chemotherapy during the last months of their lives, and chemotherapy-induced death was observed in 2 of the 40 patients (5%).

Patients with chronic respiratory failure requiring LTOT are usually ineligible for clinical trials; therefore, there is no standard chemotherapy regimen for these patients. The PS score at the start of chemotherapy with LTOT was 2 or 3 in our study population. Compared with lower values, PS scores ≥2 are associated with lower response rates to chemotherapy, shorter times to treatment failure, and shorter progression-free survival times (18,19). In recent clinical trials of patients with NSCLC with a PS of 2, overall survival ranged from 2.9 to 6.9 months (20-22). In the present study, the median survival time with LTOT was similar (194 days), suggesting that chemotherapy for patients with advanced lung cancer who receive LTOT might be beneficial.

Despite diversity in the tumor types, tumor stages, and chemotherapy regimens of the patients in our study, none of these variables significantly affected survival time with LTOT in univariate analyses. In the multivariate analysis, the treatment line (first or second) of the first chemotherapy with LTOT was the only factor associated with longer survival times. New effective therapeutic agents have been developed, especially for patients with NSCLC (6,7,23). First- and second-line chemotherapy with sufficient evidence of benefits may be acceptable even for advanced lung cancer patients receiving LTOT.

Although the eligible patients in the present study were carefully chosen via multidisciplinary team discussions, it has been reported that medical oncologists tend to overprescribe chemotherapy (24). Interestingly, the administration of chemotherapy to patients with advanced cancer at the end of their lives has increased recently (25,26). Twenty-five percent of the patients in our study received chemotherapy in their last month of life, 2 of whom died of chemotherapy-related adverse events. In the study by Näppä *et al.* (27), chemotherapy in the last month of life was associated with shorter survival, more hospital admissions,

Table 4 Clinical course of the 10 patients who received chemotherapy in their last 30 days

Patient No.	Age	Sex	Histology	Stage	PS	Final chemotherapy		Survival time, days		Cause of death
						Regimen	Line	From the first chemotherapy with LTOT	From the final chemotherapy	
1	63	Female	AD (EGFR+)	IV	2	GEF	1st	70	3	LC
2	79	Female	AD (EGFR+)	IV	3	ERL + BEV	3rd	106	17	LC
3	75	Male	AD (EGFR+)	IV	3	GEF	1st	304	5	ILD caused by GEF
4	64	Male	AD (EGFR+)	IV	2	AFA	7th	186	10	LC
5	70	Male	SQ	Recurrent	2	CBDCA + nab-PTX	3rd	289	8	FN
6	68	Male	AD	IV	2	CBDCA + PTX + BEV	7th	522	19	LC
7	68	Male	AD	IV	2	VNR	4th	10	10	CPA at home
8	49	Female	SCLC	IIIA	3	AMR	2nd	33	5	LC
9	81	Male	SCLC	IV	2	NGT	2nd	131	20	LC
10	68	Male	AD	IV	2	S1	2nd	236	23	LC

PS, performance status; LTOT, long-term oxygen therapy; AD, adenocarcinoma; EGFR, epidermal growth factor receptor; GEF, gefitinib; LC, lung cancer; ERL, erlotinib; BEV, bevacizumab; ILD, interstitial lung disease; AFA, afatinib; SQ, squamous cell carcinoma; CBDCA, carboplatin; nab-PTX nanoparticle albumin-bound paclitaxel; FN, febrile neutropenia; PTX, paclitaxel; VNR, vinorelbine; CPA, cardiopulmonary arrest; SCLC, small cell lung cancer; AMR, amrubicin; NGT, nogitecan.

and fewer deaths at home. We did not evaluate quality of life in this study; however, the quality of life in patients receiving chemotherapy at the end of their lives might decline considerably. Consistent with the results of the present study, late-line chemotherapy in NSCLC patients with a poor PS has been shown to be ineffective (28,29). We also found that the final chemotherapy was third-line in 1 of the 2 patients who died of chemotherapy-related adverse events. Chemotherapy should be withheld for advanced lung cancer patients receiving LTOT if it is third-line or greater.

This study had two limitations. First, it was a retrospective single-institution study with a small study population. Second, PaO_2 was not routinely checked; therefore, the indication for LTOT might be arbitrary. A prospective multicenter study is needed in the future.

In conclusion, chemotherapy for patients with advanced lung cancer who receive LTOT may be acceptable if it is the first- or second-line treatment. We should be mindful of the potential overuse of chemotherapy and its negative impact on quality of life.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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