【 ORIGINAL ARTICLE 】

Relationship between Patient Characteristics and the Timing of Provision of Explanation about DNAR to Patients with Advanced Lung Cancer

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Abstract:

Objective The aim of the present study was to analyze the relationship between the patient characteristics and the timing of provision of an explanation about "Do Not Attempt Resuscitation (DNAR)" by attending physicians to advanced lung cancer patients.

Methods We conducted a retrospective analysis of patients with advanced or postoperative recurrent lung cancer in whom systemic therapy was initiated between 2015 and 2016.

Results The data of a total of 74 patients with lung cancer, including 59 patients with non-small cell lung cancer and 15 with small cell lung cancer were analyzed. The median overall survival of the patients was 10.0 months. Records of the explanation about DNAR by the physicians were available for 57 of the 74 (77.0%) patients. For 48 (64.9%) patients, the explanation was provided after the discontinuation of anticancer treatment, and for 9 (12.2%) patients, it was provided during the course of anticancer treatment. The provision of an explanation about DNAR during the course of treatment was associated with a poor performance status at the start of treatment (p=0.028), the tumor histology (p=0.037), the presence of driver gene mutation in the tumor (p=0.029), and shorter survival after the discontinuation of anticancer treatment (p<0.001).

Conclusion The results suggested that the timing of provision of an explanation about DNAR was associated with patient characteristics and the predicted prognosis.

Key words: advance care planning, Do Not Attempt Resuscitation, lung cancer, palliative care

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Introduction

Advances in therapies, such as the development of molecular-targeted therapies, including tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs), have led to prolongation of survival of patients with advanced lung cancer. However, it is still difficult to achieve a cure, and end-of-life care is an important part of lung cancer treatment. A previous study demonstrated that 70% of patients who needed to make end-of-life decisions lacked the ability to make decisions due to cerebrovascular disease or dementia. Among those who had prepared a living will, 96.2% indicated that they preferred palliative care and only 1.9% preferred all possible care (1). Indeed, it has been shown that the prognosis of patients with malignancy who receive cardiopulmonary resuscitation is poor (2-4), and resuscitation is not recommended for cancer patients with incurable widespread disease or a poor performance status (PS) (4).

Advance care planning is defined as a planning process that supports adults of any age or stage of health in under-

standing and sharing their personal values, life goals, and preferences regarding future medical care. The goal of advance care planning is to ensure that people receive medical care that is consistent with their values, goals and preferences when they develop serious and/or chronic illness (5). It has also been reported that the physical and psychosocial evaluation of patients and provision of information about the course of disease and palliative care can affect the clinical course of patients with lung cancer (6-8).

One of the problems with advance care planning is that the provision of advance directives at a time-point that is too far from or too close to death could lead to results that do not optimally reflect the patient's values and goals (9). The advanced lung cancer population is not a homogeneous population, and various factors, such as the tumor histology, tumor gene mutation status, and PS of the patient can affect the clinical course. Thus, the choice of timing for the provision of information regarding the patient prognosis and determination of advance directives should be based on the backgrounds of individual cases.

Do Not Attempt Resuscitation (DNAR) is a limited concept for dealing with cardiopulmonary arrest, but it is considered important in advance care planning. We conducted this retrospective observational study to evaluate the relationship between the patient characteristics and the timing at which the explanation about DNAR was provided by attending physicians to advanced lung cancer patients.

Materials and Methods

Patient and clinical information

The inclusion criteria for this study were as follows: 1) diagnosed with lung cancer by cytological and/or histological examinations, and 2) systemic anticancer treatment initiated between 2015 and 2016, including patients who had previously received radiotherapy or surgery. The exclusion criteria were as follows: 1) patients still undergoing anticancer treatment in 2019.

Clinical information, including the age and PS at the time of the initial diagnosis, sex, tumor histology, tumor gene mutation status, treatment history, outcomes, comorbidities (including chronic obstructive pulmonary diseases, interstitial lung disease, ischemic heart disease, and central nervous system disorders), and the timing of the provision of an explanation about DNAR were collected from the medical charts of the subject population. The timing of the provision of explanation about DNAR was classified into two timepoints: 1) during the course of anticancer treatment; or 2) after the discontinuation of anticancer treatment.

Overall survival (OS) was defined as the period from the initiation of systemic treatment to the date of death. Survival after the discontinuation of anticancer treatment was defined as the period from the last administration of drug therapy to death.

This study was conducted with the approval of the Ethics Committee of the University of Toyama, in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects by the Ministry of Health, Labour and Welfare, Japan. We conducted this study by disclosure of research information rather than after obtaining individual consent.

Statistical analysis

Survival was analyzed by drawing Kaplan-Meier curves, and the "event" was defined as death from any cause and was censored at the last visit for patients who remained alive at the end of the study period. Survival in different patient groups was compared by the log-rank test. The relationship between the patient characteristics and the timing of the provision of an explanation about DNAR was analyzed by Fisher's exact test.

All statistical analyses were performed using JMP Pro 14.0.2 (SAS Institute, Cary, USA). P values of <0.05 were considered to indicate statistical significance.

Results

Table 1 shows the patient characteristics. Between 2015 and 2016, 97 lung cancer patients, including 80 patients with non-small cell lung cancer (NSCLC) and 17 with small cell lung cancer (SCLC), received anticancer treatment. Among these, 23 patients, including 21 patients with NSCLC and 2 with SCLC, were still receiving treatment in 2019 and were excluded from the study. Finally, the data of a total of 74 patients with lung cancer, including 59 patients with NSCLC and 15 with SCLC, were analyzed. Of the 74 patients, 42 (56.8%) died in the hospital and 31 (41.9%) were transferred to other hospitals after the discontinuation of the anticancer treatment. One (1.4%) patient continued to visit our hospital, even though their anticancer treatment had been discontinued. Of the 31 patients who were transferred, the date of death could be confirmed for 16 patients. Therefore, information about the date of death was available for 58 (78.4%) patients (Fig. 1). Records of the explanation about DNAR were available for 57 of the 74 (77.0%) patients, including 34 of the 42 (81.0%) patients who died in the hospital and 23 of the 31 (74.2%) patients who were transferred. Of these, 48 (64.9%) patients and/or their families received the explanation after the discontinuation of anticancer treatment and 9 (12.2%) received the explanation during the course of anticancer treatment. All of these patients chose DNAR; there were no patients who received resuscitation.

The median survival time of the patients was 10.0 months. The median survival times of the patients who received the DNAR explanation while receiving anticancer treatment, patients who received the explanation after their anticancer treatment had been discontinued, and patients for whom a record of the explanation was not recorded were 12.8, 9.8, and 11.2 months, respectively (p=0.915, log-rank test).

Table 1. Patient Characteristics.

Number		74
Age	<70 years	38 (51.4%)
	≥70 years	36 (48.6%)
Gender	Male	55 (74.3%)
	Female	19 (25.7%)
Histology	NSCLC	59 (79.7%)
	SCLC	15 (20.3%)
Driver gene status	Positive	15 (20.3%)
	Negative/unknown	59 (79.7%)
PS (at the start of treatment)	0-1	55 (74.3%)
	≥2	19 (25.7%)
Treatment line	≤Second line treatment	53 (71.6%)
	≥Third line treatment	21 (28.4%)
Platinum-doublet	Yes	54 (73.0%)
	No	20 (27.0%)
TKI	Yes	15 (20.3%)
	No	59 (79.7%)
ICI	Yes	21 (28.4%)
	No	53 (71.6%)
COPD	Yes	7 (9.5%)
	No	67 (90.5%)
ILD	Yes	16 (21.6%)
	No	58 (78.4%)
IHD	Yes	7 (9.5%)
	No	67 (90.5%)
CNS disorder	Yes	7 (9.5%)
	No	67 (90.5%)

Treatment line refers to the total number of therapeutic regimens. Platinum-doublet, TKI, and ICI refer to the treatment history during the entire cancer trajectory in each patient. COPD: chronic obstructive pulmonary disease, CNS: central nervous system, ICI: immune check point inhibitor, IHD: ischemic heart disease, ILD: interstitial lung disease, NSCLC: non-small cell lung cancer, PS: performance status, SCLC: small cell lung cancer, TKI: tyrosine kinase inhibitor

Table 2 shows the relationship between the patient characteristics and the timing of provision of the explanation about DNAR. In patients with PS≥2 at the start of treatment (p= 0.028, Fisher's exact test) or patients treated with TKIs (p= 0.029, Fisher's exact test), the explanation was more likely to be provided during the course of the treatment. Significant overlap was observed between patients with PS≥2 and those with driver gene mutations in the tumor, with 8 of 15 (53.3%) patients with tumor driver gene mutations showing a PS of ≥2. Also, the proportion of patients with SCLC was higher among patients for whom no records on the provision of an explanation about DNAR were available (p=0.037, Fisher's exact test).

At the time that the patients received the DNAR explanation, the PS was ≥2 and ≥3 in 52 (91.2%) and 42 (73.7%) patients, respectively. While PS≥3 was recorded in 4 (44.4%) of the 9 patients who received the DNAR explanation while receiving anticancer treatment, PS≥3 was recorded in 38 of the 48 (79.2%) patients who received the DNAR explanation after their anticancer treatment had been discontinued (p=0.044, Fisher's exact test). The median (95% confidence interval) survival time from receiving the DNAR explanation to death was 1.0 (0.5-1.4) month overall, 2.8 (0.1-25.5) months in those who received the explanation while receiving anticancer treatment, and 0.8 (0.5-1.3) months in those who received the explanation after their anticancer treatment had been discontinued (p=0.090, log-rank test).

Table 3 shows the relationship between the patient characteristics and the period of survival after the discontinuation of anticancer treatment. The median survival time was 2.0 months and was not associated with any of the patient characteristics; it was, however, associated with the timing of the
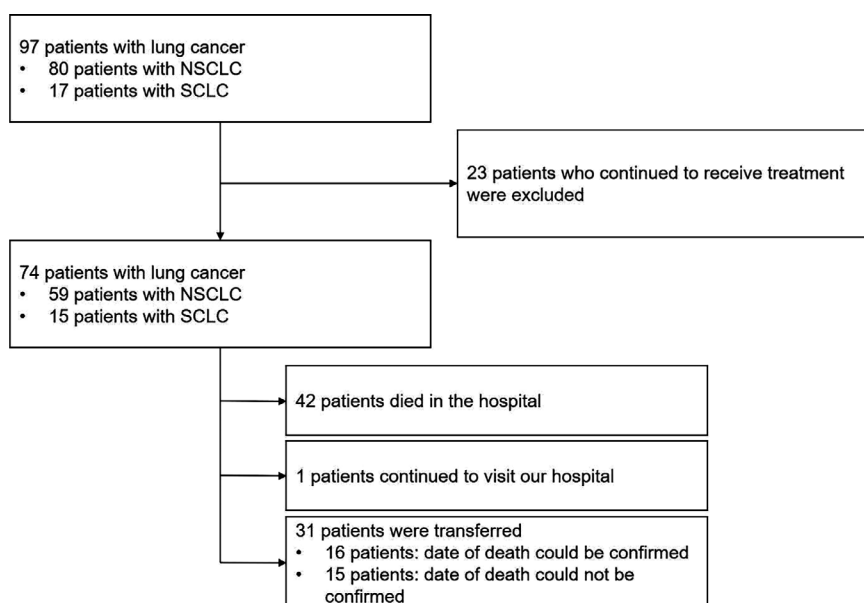

Figure 1. Patient selection. Data of a total of 74 patients with lung cancer were analyzed, including 42 patients who died in the hospital, 31 patients who were transferred to other hospitals, and 1 patient who continued to visit our hospital.

Table 2.   Relationship between the Patient Background Characteristics and the Timing of Provision of Explanation Regarding Resuscitation to the Patients/families by the Attending Physicians.

		During treatment 9 (12.2%)	After treatment 48 (64.9%)	No record 17 (23.0%)	p value
Age	<70 years	5 (13.2%)	24 (63.2%)	9 (23.7%)	1.000
	≥70 years	4 (11.1%)	24 (66.7%)	8 (22.2%)	
Gender	Male	5 (9.1%)	36 (65.5%)	14 (25.5%)	0.348
	Female	4 (21.1%)	12 (63.2%)	3 (15.8%)	
Histology	NSCLC	9 (15.3%)	40 (67.8%)	10 (17.0%)	0.037
	SCLC	0 (0%)	8 (53.3%)	7 (46.7%)	
PS (at the start of the treatment)	0-1	4 (7.3%)	40 (72.7%)	11 (20.0%)	0.028
	≥2	5 (26.3%)	8 (42.1%)	6 (31.6%)	
Treatment line	≤2nd line	4 (7.6%)	35 (66.0%)	14 (26.4%)	0.145
	≥3rd line	5 (23.8%)	13 (61.9%)	3 (14.3%)	
Platinum-doublet	Yes	5 (9.3%)	36 (66.7%)	13 (24.1%)	0.423
	No	4 (20.0%)	12 (60.0%)	4 (20.0%)	
TKI	Yes	5 (33.3%)	8 (53.3%)	2 (13.3%)	0.029
	No	4 (6.8%)	40 (67.8%)	15 (25.4%)	
ICI	Yes	5 (23.8%)	12 (57.1%)	4 (19.1%)	0.210
	No	4 (7.6%)	36 (67.9%)	13 (24.5%)	
COPD	Yes	0 (0%)	5 (71.4%)	2 (28.6%)	0.722
	No	9 (13.4%)	43 (64.2%)	15 (22.4%)	
ILD	Yes	1 (6.3%)	11 (68.8%)	4 (25.0%)	0.834
	No	8 (13.8%)	37 (63.8%)	13 (22.4%)	
IHD	Yes	1 (14.3%)	4 (57.1%)	2 (28.6%)	0.854
	No	8 (11.9%)	44 (65.7%)	15 (22.4%)	
CNS disorder	Yes	0 (0%)	3 (42.9%)	4 (57.1%)	0.095
	No	9 (13.4%)	45 (67.2%)	13 (19.4%)	

Treatment line refers to the total number of therapeutic regimens. Platinum-doublet, TKI, and ICI refer to the treatment history during the entire cancer trajectory in each patient. COPD: chronic obstructive pulmonary disease, CNS: central nervous system, ICI: immune check point inhibitor, IHD: ischemic heart disease, ILD: interstitial lung disease, NSCLC: non- small cell lung cancer, PS: performance status, SCLC: small cell lung cancer, TKI: tyrosine kinase inhibitor

provision of the explanation about DNAR. Fig. 2 shows the period of survival after the discontinuation of anticancer treatment in each group according to the timing of the provision of the DNAR explanation. Patient survival was shorter in the patient group that received the explanation during the course of anticancer treatment, and longest in the group for which no records on the DNAR explanation were available (p<0.001, log-rank test).

Discussion

The findings of the present study suggest that 75% of advanced lung cancer patients are given an explanation about DNAR. In most cases, the explanation was provided after the discontinuation of anticancer treatment, while in 12.2% of cases, the explanation was provided during the course of treatment. The timing of the provision of the explanation about DNAR was associated with the tumor histology, PS at the start of treatment, a history of TKI treatment, and the period of survival after the discontinuation of anticancer treatment.

Patients who had received the explanation about DNAR during the course of treatment had a poor PS at the start of treatment and shorter survival after the discontinuation of anticancer treatment. This suggests that prediction of a poor prognosis by the attending physician resulted in earlier provision of an explanation about DNAR. On the other hand, patients who had not received an explanation about DNAR showed a longer survival period after the discontinuation of anticancer treatment. The reason for this could be that the attending physician had predicted a relatively good prognosis in these patients. However, some patients who had not received an explanation about DNAR died early. Because this group had a higher proportion of patients with SCLC, it is possible that palliative care planning was difficult for this group due to the aggressive deterioration of the disease. In addition, there might have been cases that did not receive an explanation about DNAR in consideration of the characteristics of the patients and/or of the wishes of the patients and families.

The appropriate timing for providing an explanation about advance care planning depends on many factors, including religious, cultural, educational, and other factors, and no objective data to support the optimal timing of the provision of

Table 3. Relationship between the Patient Background Characteristics and Duration of Survival after the Last Day of the Anticancer Drug Therapy.

		Survival	p value
Age	<70 years	1.9 (1.2-2.4)	0.115
	≥70 years	2.2 (1.6-3.1)	
Gender	Male	2.1 (1.8-2.5)	0.276
	Female	1.6 (1.2-2.5)	
Histology	NSCLC	1.9 (1.6-2.5)	0.132
	SCLC	2.2 (1.6-NE)	
PS (at the start of treatment)	0-1	2.1 (1.6-2.5)	0.418
	≥2	1.9 (1.0-2.5)	
Treatment line	≤2nd line	2.2 (1.8-2.5)	0.285
	≥3rd line	1.6 (1.1-2.8)	
DNAR	During treatment	1.2 (0-1.6)	<0.001
	After treatment	2.1 (1.6-2.5)	
	No record	2.5 (1.8-6.1)	
Platinum-doublet	Yes	2.1 (1.6-2.5)	0.915
	No	1.9 (0.8-3.2)	
TKI	Yes	1.9 (0.2-4.1)	0.261
	No	2.2 (1.6-2.5)	
ICI	Yes	1.8 (1.2-3.0)	0.889
	No	2.1 (1.6-2.5)	
COPD	Yes	2.2 (0.8-NE)	0.115
	No	2.0 (1.6-2.5)	
ILD	Yes	2.2 (1.0-2.8)	0.422
	No	1.9 (1.6-2.4)	
IHD	Yes	1.9 (0.8-2.5)	0.476
	No	2.1 (1.6-2.5)	
CNS disorder	Yes	2.0 (0.7-2.5)	0.878
	No	2.1 (1.6-2.5)	

Treatment line refers to the total number of therapeutic regimens. Platinum-doublet, TKI, and ICI refer to the treatment history during the entire cancer trajectory in each patient. COPD: chronic obstructive pulmonary disease, CNS: central nervous system, DNAR: Do Not Attempt Resuscitation, ICI: immune check point inhibitor, IHD: ischemic heart disease, ILD: interstitial lung disease, NSCLC: non- small cell lung cancer, PS: performance status, SCLC: small cell lung cancer, TKI: tyrosine kinase inhibitor
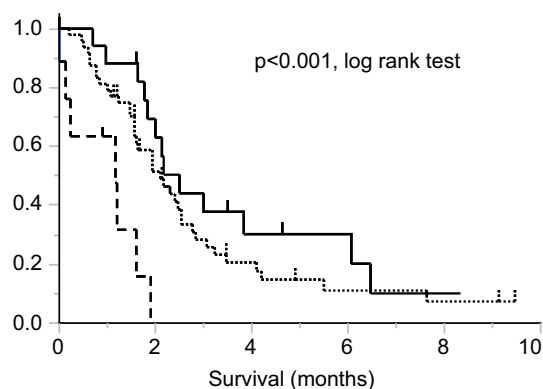

Figure 2. Survival after the discontinuation of the anticancer treatment. Solid line: Patients for whom no records on the DNAR explanation were available. Dotted line: Patients who received explanation about DNAR after the discontinuation of anticancer treatment. Dashed line: Patients who received an explanation about DNAR during anticancer treatment.

this explanation are available (9). In the present study, the median overall survival was 10 months and the median survival after receiving the DNAR explanation was 1 month in lung cancer patients. While 12.2% of the patients received the DNAR explanation during the time in which they were receiving anticancer treatment at our institution, in a previous study, 21.8% of patients received the DNAR explanation before they received first-line treatment or when they were still receiving chemotherapy (8). We cannot draw a definitive conclusion about the appropriate timing. However, the suggestion that the timing of the provision of the DNAR explanation should be based on the predicted prognosis (9) is considered reasonable.

The palliative prognostic index has been reported as an index for predicting the prognosis of patients with malignancy (10). We previously reported the usefulness of the palliative prognostic index for lung cancer, however, the sensitivity of the index for predicting death might be low in pa-

tients with SCLC (11). Although survival after the discontinuation of the anticancer treatment did not differ to a statistically significant extent depending on the tumor histology in the present study, differences in the clinical course associated with the tumor histology must be considered in clinical practice.

The present study was associated with several limitations. We could not collect information about the subject of the explanation regarding DNAR (i.e., whether it was given to the patients themselves or their families). Second, while we focused on the provision of the explanation about DNAR in this study, advance care planning does not refer to specific medical practice arrangements alone. Thus, the status of advance care planning implementation was not comprehensively evaluated in the present study. However, the provision of an explanation about DNAR is considered important in advance care planning, as it facilitates acceptance by the patient of the inevitability of death. Third, because the present study was conducted at a single center, it is not clear if the results can be generalized. In addition, the timing of provision of the DNAR explanation depended on the discretion of the attending physician. Although we considered that the predicted prognosis might affect the timing of the provision of the DNAR explanation (because patient characteristics and the clinical course are associated with the timing of provision of the explanation), we could not directly evaluate the attending physicians' reasons for the timing of the DNAR explanation.

In conclusion, the present study showed that the attending physicians provided an explanation about DNAR during the course of the anticancer treatment or after discontinuation of the anticancer treatment, and that the timing of the provision of the explanation was associated with patient characteristics, including the tumor histology and PS at the start of treatment. Our results suggest that palliative care planning is potentially difficult for patients who show aggressive deterioration and that the timing of the provision of the DNAR

explanation is affected by the patient's predicted prognosis.

The authors state that they have no Conflict of Interest (COI).

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