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Research Article

Impact of Immune Checkpoint Inhibitor on the Survival in Elderly Patients with Non-Small Cell Lung Cancer

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ABSTRACT

Purpose: We analysed the relationship between a history of immune checkpoint inhibitor (ICI) and overall survival in elderly patients with non-small cell lung cancer (NSCLC).

Methods: We conducted a retrospective analysis of the data of patients with NSCLC aged ≥ 70 -year-old who had received systemic anticancer therapy between 2015 and 2019.

Results: The analysis included the data of a total of 63 patients. Multivariate analysis revealed a significant association between a history of treatment with ICI and the overall survival. A significant interaction was also observed between a history of treatment with an ICI and the tumor histology.

Conclusion: A significant association between history of ICI therapy and the overall survival was detected in elderly NSCLC patients aged ≥ 70 -year-old in a clinical practice setting. Our results also suggested that the impact of ICI therapy on the survival differed depending on the tumor histology.

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Introduction

In patients with advanced non-small cell lung cancer (NSCLC), systemic drug therapy is the standard of care. Recent studies have shown that treatment with immune checkpoint inhibitors (ICIs) yields a longer survival than treatment with cytotoxic agents in patients with advanced NSCLC [1-5]. In addition, although immune-related adverse events are problematic, ICI therapy has been shown to be associated with a lower frequency of severe adverse reactions as compared to cytotoxic chemotherapy, and ICIs are expected to be useful agents for the treatment of elderly patients with NSCLC [1-5].

Pooled analysis in the KEYNOTE study revealed the superiority of pembrolizumab over a cytotoxic agent in terms of the survival in elderly NSCLC patients, and a single-arm phase II study showed the efficacy and safety of pembrolizumab treatment in elderly NSCLC patients aged ≥ 75 -year-old [6, 7]. These clinical trials suggest that ICI therapy is effective even in elderly patients with NSCLC. We conducted this

retrospective study to analyse the effect of immune checkpoint inhibitor therapy on the overall survival in patients with NSCLC aged ≥ 70 -year-old in real-world setting.

Methods

I Clinical Information

We conducted a retrospective analysis of the data of patients with NSCLC who had received anticancer treatment at Toyama University Hospital. The patient inclusion criteria were as follows: 1) cytologically or histologically diagnosed NSCLC; 2) received systemic anticancer treatment, excluding adjuvant chemotherapy and chemoradiotherapy, between 2015 and 2019; 3) aged ≥ 70 years at the start of the systemic anticancer treatment. The exclusion criteria were as follows: 1) presence of tumor driver mutations; 2) synchronous multiple cancer; 3) history of treatment with an ICI as part of a clinical trial or of combined ICI therapy with cytotoxic agents. The disease stage was evaluated according to the

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8th edition of the UICC TNM classification and patients who had undergone surgery for NSCLC were re-classified based on the findings at the start of the systemic anticancer treatment. Information about the tumor PD-L1 status was retrieved from the medical charts, testing of which was commissioned to BML (Tokyo, Japan) and performed using 22C3 antibody. Any preexisting interstitial pneumonia was evaluated based on the findings of chest computed tomography and from the medical charts.

This study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects (Ministry of Health, Labour and Welfare of Japan), after obtaining approval from the Ethics committee, University of Toyama (Reference number: R2019146). We disclosed information about the study to the subjects but did not obtain written informed consent as it was a retrospective study.

II Statistical Analysis

Statistical analysis was performed using JMP ver. 14.0.2 (SAS, Cary, NC), and P value <0.05 was considered as being indicative of significance. Patients were divided into subgroups according to each of the clinical parameters and the overall survival (OS) among the groups were compared by the log-rank test. A Cox proportional hazards model was used to evaluate the association between clinical parameters, including history of treatment with ICIs, and the OS. We planned to include performance status (PS), disease stage, history of treatment with an ICI, history of treatment with a platinum doublet, and variables

identified by univariate analysis as being significant by the log-rank test with P values of <0.05 as independent variables.

A Cox proportional hazards model was also used to analyse the interaction between history of ICI therapy and the patient background characteristics for the OS. The model included history of ICI therapy (yes or no), each of the patient background characteristics, and interaction variables (product term of two variables) as independent variables.

Results

A total of 209 patients with NSCLC received systemic anticancer treatment between 2015 and 2019 at Toyama University Hospital. Of these, 79 patients with tumor driver mutations, 58 patients aged <70-year-old, and 9 other patients (reasons for exclusion indicated in the figure) were excluded. Finally, data of a total of 63 patients were included in the analyses (Figure 1).

Table 1 shows the patient characteristics. Twenty (31.7%) and 36 (57.1%) of the NSCLC patients were diagnosed as having squamous cell carcinoma and adenocarcinoma, respectively. Other histologic types included adenosquamous carcinoma, large cell neuroendocrine cell carcinoma, and NSCLC, not otherwise specified. In all, 36 patients (57.1%) had received treatment with ICIs. Thirteen (36.1%), 19 (52.8%), and 4 (11.1%) patients received ICI therapy as 1st, 2nd and 3rd line treatment, respectively, and 11 (30.6%), 21 (58.3%), and 4 (11.1%) patients received nivolumab, pembrolizumab and atezolizumab respectively.

Table 1: Patient characteristics.

		n (%)
Age (yr)	<75	30 (47.6%)
	≥75	33 (52.4%)
Sex	Male	52 (82.5%)
	Female	11 (17.5%)
Histology	Squamous	20 (31.7%)
	Adenocarcinoma	36 (57.1%)
	Others	7 (11.1%)
PD-L1 TPS	≥1%	27 (42.9%)
	<1%	22 (34.9%)
	Unknown	14 (22.2%)
History of surgery	Yes	26 (41.3%)
	No	37 (58.7%)
ILD	Yes	15 (23.8%)
	No	48 (76.2%)
Disease stage	≤III	17 (27.0%)
	IVA	37 (58.7%)
	IVB	9 (14.3%)
PS	0-1	53 (84.1%)
	≥2	10 (15.9%)
History of ICI therapy	Yes	36 (57.1%)
	No	27 (42.9%)
History of platinum therapy	Yes	32 (50.8%)
	No	31 (49.2%)

ICI: Immune Checkpoint Inhibitor; ILD: Interstitial Lung Disease; PD-L1: Programmed Death Ligand-1; PS: Performance Status; TPS: Tumor Proportion Score.

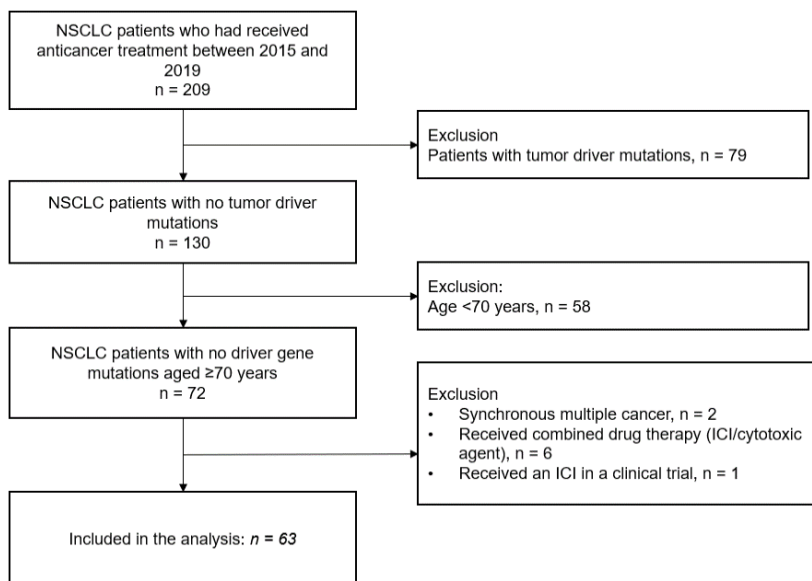


Figure 1: Patient selection.

Data of NSCLC patients aged ≥70-year-old with no tumor driver mutations were analysed.

Table 2: Association between the patient background characteristics and the overall survival (univariate analysis).

		OS (95% CI)	P
Age (yr)	<75	12.9 (9.2-27.4)	0.732
	≥75	11.0 (8.8-29.3)	
Sex	Male	12.8 (9.6-14.5)	0.953
	Female	17.2 (3.4-18.5)	
Histology	Squamous	9.6 (5.1-29.3)	0.354
	Adenocarcinoma	13.6 (10.7-NE)	
	Others	10.0 (2.7-NE)	
PD-L1 TPS	≥1%	27.4 (12.6-NE)	0.002
	<1%	12.9 (3.9-18.5)	
	Unknown	9.2 (4.2-9.8)	
History of surgery	Yes	14.4 (10.7-NE)	0.262
	No	9.8 (8.4-17.2)	
ILD	Yes	12.8 (4.9-27.4)	0.832
	No	12.6 (9.5-18.5)	
Disease stage	≤III	13.6 (10.4-53.9)	0.007
	IVA	12.9 (8.8-29.3)	
	IVB	5.7 (2.7-11.0)	
	PS	12.9 (10.4-18.5)	
≥2	5.2 (2.7-53.9)		
History of ICI therapy	Yes	17.2 (10.7-34.1)	0.026
	No	9.8 (4.2-14.4)	
History of platinum therapy	Yes	13.6 (9.2-34.1)	0.323
	No	11.0 (9.6-17.2)	

ICI: Immune Checkpoint Inhibitor; ILD: Interstitial Lung Disease; OS: Overall Survival; PD-L1: Programmed Death Ligand-1; PS: Performance Status; TPS: Tumor Proportion Score.

Table 2 shows the association between the patient characteristics and the OS analysed by the log-rank test. Univariate analysis identified the tumor PD-L1 status, disease stage, and history of treatment with an ICI as being significantly associated with the OS. Figure 2 shows the Kaplan-Meier curve for the OS in the patients with and without a history of treatment with ICIs.

Table 3 shows the association between a history of treatment with an ICI and the OS evaluated using the Cox proportional hazards model. The PS, disease stage, history of treatment with an ICI, and history of treatment with a platinum doublet were selected as the independent variables. The tumor PD-L1 status was excluded, because there was a significant overlap between the tumor PD-L1 status and history of treatment with

an ICI, even though the tumor PD-L1 status was found to be significantly associated with the OS by the log-rank test. Analysis using the Cox

proportional hazards model revealed a significant association between history of treatment with an ICI and the OS.

Table 3: Association between the patient background characteristics and the overall survival (multivariate analysis).

		HR (95% CI)	P
PS	0-1	0.31 (0.12-0.83)	0.020
	≥2	1	
Disease stage	≤III	0.37 (0.13-1.05)	0.061
	IVA	0.44 (0.19-1.03)	0.059
	IVB	1	
History of ICI therapy	Yes	0.42 (0.20-0.86)	0.019
	No	1	
History of platinum therapy	Yes	0.63 (0.31-1.28)	0.202
	No	1	

ICI: Immune Checkpoint Inhibitor; PS: Performance Status.

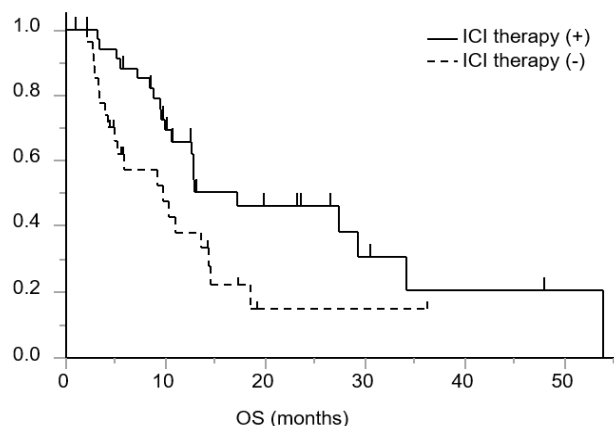


Figure 2: Kaplan-Meier curve for OS in patients who had and had not received ICI therapy.

Solid line: patients who had received treatment with an ICI; Dashed line: patients who had not received treatment with an ICI. Patients who had received treatment with an ICI showed a longer OS than those who had not received treatment with an ICI (p = 0.026, log-rank test).

Table 4 shows the results of a subset analysis in patients divided into subgroups by the patient background characteristics to assess the association between history of treatment with an ICI and the OS. There was a significant interaction between the tumor histology and history of treatment with an ICI on the effect, with the association between ICI therapy and OS not being seen in patients with adenocarcinoma, but evident in those with squamous cell carcinoma and carcinoma of other histologic types.

No significant differences in the OS were observed among patients who received ICI therapy as 1st (median: 12.6, 95% confidence interval: 5.5-NE months), 2nd (median: 29.3, 95% confidence interval: 12.8-53.9 months) and 3rd (median: 9.7, 95% confidence interval: 8.4-17.2 months) line treatment (p = 0.073, log-rank test). Furthermore, the OS was also not significantly different among patients who received ICI therapy (p=0.807, log-rank test), including treatment with nivolumab (median: 19.5, 95% confidence interval: 3.2-53.9 months), pembrolizumab (median: 27.4, 95% confidence interval: 10.7-NE months), and atezolizumab (median: 12.9, 95% confidence interval: 10.0-NE months).

Table 4: Subset analysis in patients divided into subgroups by the patient characteristics.

		OS (95% CI)		P (log-rank test)	P (Interaction)
		ICI (+)	ICI (-)		
Age (yr)	<75	27.4 (10.0-53.9)	9.5 (2.8-14.4)	0.060	0.620
	≥75	12.8 (9.5-34.1)	10.4 (3.9-18.5)	0.141	
Sex	Male	27.4 (10.7-34.1)	9.8 (4.2-13.6)	0.015	0.221
	Female	17.2 (3.2-17.2)	18.5 (3.4-18.5)	0.433	
Histology	Squamous	29.3 (7.2-53.9)	5.5 (3.3-10.4)	0.002	0.006
	Adenocarcinoma	12.9 (8.8-NE)	14.4 (4.9-NE)	0.686	
	Others	12.8 (3.4-NE)	2.8 (2.7-2.8)	0.008	
PD-L1 TPS	≥1%	27.4 (12.6-NE)	14.5 (5.1-NE)	0.467	0.983
	<1%	12.9 (3.2-34.1)	10.4 (2.8-NE)	0.667	
	Unknown	9.5 (5.1-29.3)	9.2 (3.3-11.0)	0.566	
History of surgery	Yes	12.9 (10.0-NE)	14.4 (3.3-18.5)	0.332	0.996
	No	17.2 (8.8-29.3)	9.2 (4.2-11.0)	0.085	
ILD	Yes	27.4 (7.2-53.9)	9.8 (3.3-14.5)	0.057	0.415
	No	12.9 (9.6-34.1)	10.4 (3.4-18.5)	0.158	
Disease stage	≤III	27.4 (12.6-53.9)	10.4 (3.3-NE)	0.065	0.647
	IVA	12.9 (8.8-NE)	14.4 (3.4-NE)	0.292	
	IVB	5.5 (3.4-17.2)	5.9 (2.7-11.0)	0.624	

PS	0-1	17.2 (12.6-34.1)	10.4 (5.1-14.5)	0.062	0.099
	≥2	7.2 (3.4-53.9)	3.4 (2.7-4.9)	0.031	
History of platinum therapy	Yes	27.4 (8.4-53.9)	10.4 (3.9-14.5)	0.110	0.844
	No	12.8 (9.5-29.3)	5.9 (2.1-18.5)	0.040	

ICI: Immune Checkpoint Inhibitor; ILD: Interstitial Lung Disease; OS: Overall Survival; PD-L1: Programmed Death Ligand-1; PS: Performance Status; TPS: Tumor Proportion Score.

Discussion

In the present study, multivariate analysis revealed a significant independent association between a history of treatment with an ICI and a longer OS in patients with NSCLC aged ≥70-year-old. However, because of the retrospective nature of the study, it was difficult to rule out the possible confounding effects of patient background factors on the results of the analyses. Especially, patients who showed long survival durations might have received ICI therapy in the late phase because they had survived for longer. Thus, we cannot draw any definitive conclusion about the causative relationship between history of treatment with an ICI and a longer OS in patients with NSCLC aged ≥70-year-old. However, the proportion of patients that received ICI therapy as 3rd line treatment was relatively low. Given that pooled analysis in the KEYNOTE study and a single-arm phase 2 study demonstrated the efficacy of treatment with an ICI in elderly patients with NSCLC, we believe that it is possible that treatment with an ICI contributed significantly to the longer survival in elderly patients with NSCLC [6, 7].

There was a significant interaction between ICI therapy and the histology for the OS, the association between ICI therapy and OS being stronger in patients with squamous cell carcinoma and carcinoma of other histologic types than in patients with adenocarcinoma. It has been reported that nivolumab is effective in patients with squamous cell carcinoma, regardless of the tumor PD-L1 expression, while was less effective in patients with non-squamous cell carcinoma with no tumor PD-L1 expression [1, 2]. A possible explanation for the interaction between ICI therapy and tumor histology in terms of the OS in the present study could be the lower lesser efficacy of ICI therapy against PD-L1-negative tumors in NSCLC patients with adenocarcinoma. The limitations of the present study were the retrospective nature of the study and the small sample size, which could have reduced the statistical power of the study; random errors and selection bias could also have influenced the results of the analysis. In addition, confounding factors might not have been fully adjusted for.

In conclusion, the present study demonstrated that NSCLC patients aged ≥70-year-old who had received ICI therapy showed a longer overall survival than those who had not received ICI therapy. The association was stronger in NSCLC patients with squamous cell carcinoma and other histologic types of carcinoma than in those with adenocarcinoma.

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