ORIGINAL ARTICLE

Desensitizing Effect of Cancer Cachexia on Immune Checkpoint Inhibitors in Patients With Advanced NSCLC

Taichi Miyawaki, MD,[a,b] Tateaki Naito, MD, PhD,[a,*] Akihro Kodama, MD,[a] Naoya Nishioka, MD,[a] Eriko Miyawaki, MD,[a] Nobuaki Mamesaya, MD,[a] Takahisa Kawamura, MD, PhD,[a] Haruki Kobayashi, MD,[a] Shota Omori, MD,[a] Kazushige Wakuda, MD,[a] Akira Ono, MD, PhD,[a] Hirotsugu Kenmotsu, MD, PhD,[a] Haruyasu Murakami, MD, PhD,[a] Akifumi Notsu, PhD,[c] Keita Mori, PhD,[c] Hideyuki Harada, MD, PhD,[d] Masahiro Endo, MD, PhD,[e] Kazuhisa Takahashi, MD, PhD,[b] Toshiaki Takahashi, MD, PhD[a]

[a]*Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan*
[b]*Department of Respiratory Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan*
[c]*Division of Clinical Research Promotion Unit, Shizuoka Cancer Center, Shizuoka, Japan*
[d]*Radiation and Proton Therapy Center, Shizuoka Cancer Center, Shizuoka, Japan*
[e]*Division of Diagnostic Radiology, Shizuoka Cancer Center, Shizuoka, Japan*

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ABSTRACT

Introduction: Programmed cell death 1 (PD-1) inhibitors have become standard treatment for patients with advanced NSCLC. However, few studies have focused on the impact of cancer cachexia on the efficacy of PD-1 or programmed death-ligand 1 (PD-L1) inhibitors among patients with NSCLC.

Methods: We retrospectively reviewed medical records of patients with advanced NSCLC who received PD-1 or PD-L1 inhibitor monotherapy from May 2016 to December 2018. We defined cancer cachexia as unintentional weight loss

*Corresponding author.

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Address for correspondence: Tateaki Naito, MD, PhD, Division of Thoracic Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan. E-mail: t.naito@scchr.jp

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greater than 5% over 6 months and high PD-L1 as greater than 50% expression on tumor cells. We evaluated the objective response rates (ORRs) and progression-free survival (PFS).

Results: Among 108 patients, 52 had cancer cachexia. Patients with cachexia had a lower ORR (15% versus 57%, $p < 0.001$) and shorter PFS (2.3 mo versus 12.0 mo, $p < 0.001$) than those without cachexia. Patients with low PD-L1 expression had a lower ORR (14% versus 53%, $p < 0.001$) and shorter PFS (2.8 mo versus 10.8 mo, $p = 0.002$) than those with high PD-L1 expression. Multivariate analysis revealed cancer cachexia and low PD-L1 expression as independent negative predictors of PFS. Among patients with cachexia, there was no significant difference in the ORR ($p = 0.514$) or PFS ($p = 0.992$) on the basis of PD-L1 expression.

Conclusions: Our findings indicate that cancer cachexia might be a negative predictor of the efficacy of PD-1 or PD-L1 inhibitors and reduce the impact of PD-L1 expression on the effect of PD-1 or PD-L1 inhibitors in patients with advanced NSCLC. Further clinical and basic studies are needed.

Keywords: Non–small cell lung cancer; Cancer cachexia; Programmed death 1 inhibitors; Programmed death-ligand 1 inhibitors; PD-L1 tumor proportion score

Introduction

Cancer cachexia is a multifactorial syndrome characterized by the loss of body weight combined with a negative metabolic balance in energy and protein.[1] Cancer cachexia is observed in over half of patients with advanced lung cancer and is associated with poor prognosis.[2,3] Recently, anti-immune checkpoint molecule antibodies targeting programmed cell death 1 (PD-1) and programmed death-ligand 1 (PD-L1) have revolutionized the landscape of treatment for patients with NSCLC.[4-6] Increased PD-L1 expression on tumor cells is reportedly associated with increased overall survival (OS) and progression-free survival (PFS) in these patients.[7] However, the efficacy of immune checkpoint inhibitors may be hindered by cancer cachexia. A preclinical study revealed that antitumor immunity was attenuated by impaired nutritional status.[8] In addition, loss of body weight[9,10] or skeletal muscle,[11,12] a hallmark of cancer cachexia, was associated with decreased efficacy of PD-1 or PD-L1 inhibitors in patients with NSCLC. Most studies estimated the impact of cancer cachexia without adjustment for previously known predictors, including PD-L1 expression on tumors and the presence of driver oncogenes.[9-12] Therefore, whether cancer cachexia is associated with worse outcome independent of these known predictors is unknown.

Accordingly, this study aimed to evaluate whether the presence of cancer cachexia predicts the efficacy of PD-1 or PD-L1 inhibitor monotherapy regardless of confounding bias in patients with NSCLC.

Material and Methods

Patients

Our institutional ethics review board approved the study protocol. Between May 2016 and December 2018, a total of 286 consecutive patients with advanced NSCLC received PD-1 or PD-L1 inhibitor monotherapy at the Shizuoka Cancer Center. Nivolumab was administered intravenously at a dose of 3 mg/kg or 240 mg every 2 weeks. Pembrolizumab was administered intravenously at a dose of 200 mg every 3 weeks. Atezolizumab was administered intravenously at a dose of 1500 mg every 3 weeks. The patients' medical records were retrospectively reviewed to evaluate patient eligibility. The eligibility criteria were as follows: (1) histologically or cytologically proven stage III or IV NSCLC, including postoperative recurrence; (2) Eastern Cooperative Oncology Group performance status (PS) of 0 to 1; (3) weight loss during 6 months before initiating PD-1 or PD-L1 inhibitors; and (4) information regarding PD-L1 expression on tumor cells. Patients who had tumors harboring *EGFR/ALK/ROS1* genetic aberrations were excluded from this study.

Patient Enrollment and Timing of Data Collection

The first patient was enrolled in March 2016 and the last in December 2018. Body weight was measured to the nearest 0.1 kg, and body mass index (BMI; kg/m^2) was subsequently calculated. Tumor biopsy specimens were subjected to immunohistochemical staining using a monoclonal antibody against PD-L1 (22C3 pharm Dx assay, Agilent Technologies, Santa Clara, CA). PD-L1 expression on tumor cells was categorized by tumor proportion score (TPS), which was defined as the percentage of tumor cells with membranous PD-L1 staining. Patients with a PD-L1 TPS greater than or equal to 50% were considered potentially sensitive to PD-1 or PD-L1 inhibitors on the basis of the results of previous studies.[4,13] We stratified patients into high PD-L1 TPS and low PD-L1 TPS groups according to this threshold. The disease stage was determined according to the eighth edition of the TNM classification for lung cancer.[14] Objective tumor responses were assessed according to

the Response Evaluation Criteria for Solid Tumors version 1.1. The data cutoff date was August 10, 2019.

Definition of Cancer Cachexia

We defined cancer cachexia as unintentional weight loss greater than 5% during 6 months before initiation of PD-1 or PD-L1 inhibitors according to the international consensus criteria for the diagnosis of cancer cachexia.[1] A patient's weight during the previous 6 months was obtained by interviewing the patient and family members. We did not include skeletal muscle mass or BMI in the definition of cancer cachexia.

Statistical Analysis

Chi-square or Fisher's exact tests were used to compare categorical variables. PFS and OS were defined from the start of PD-1 or PD-L1 inhibitor monotherapy and were estimated by the Kaplan-Meier method and compared using the log-rank test. The end of the follow-up period was August 10, 2019. Potential predictors were assessed using logistic regression analysis for objective tumor response and the Cox proportional hazards model for PFS and OS. For the univariate analyses, the covariates included cancer cachexia, age ($\geq$75 y versus $<$75 y), sex, smoking status, PS (0 versus 1), histology (nonsquamous versus squamous), BMI ($\geq$25 kg/m^2 versus $<$25 kg/m^2), and PD-L1 TPS ($\geq$50% versus $<$50%). Factors with univariate p values less than 0.05 were subjected to multivariate analyses. Odds ratios and hazard ratios for cancer cachexia were adjusted by PD-L1 TPS and potentially confounding factors retained in the univariate analysis. Subgroup analysis was used to assess correlation between cancer cachexia and PD-L1 TPS. For all analyses, p values less than 0.05 were considered significant. All analyses were performed using STATA software (version 14.0; Stata Corp., College Station, TX).

Results

Patient Characteristics

Of the 286 consecutive patients who had advanced NSCLC and received PD-1 or PD-L1 inhibitor monotherapy from December 2015 to December 2018 in our institution, a total of 108 patients were finally included in the analyses. We excluded 36 patients with *EGFR/ALK/ROS1* alterations and 35 patients with an Eastern Cooperative Oncology Group PS of greater than or equal to 2, who were less sensitive to PD-1 or PD-L1 inhibitors.[7] We also excluded 85 patients with unknown PD-L1 status, which is a predominant predictor for PD-1 or PD-L1 inhibitors (Fig. 1).[4-7,13,14] The median age was 67 (range, 33–84) years, and most of the patients were smokers, men, and had nonsquamous tumor histology (Table 1). All patients received PD-1 or PD-L1 inhibitors

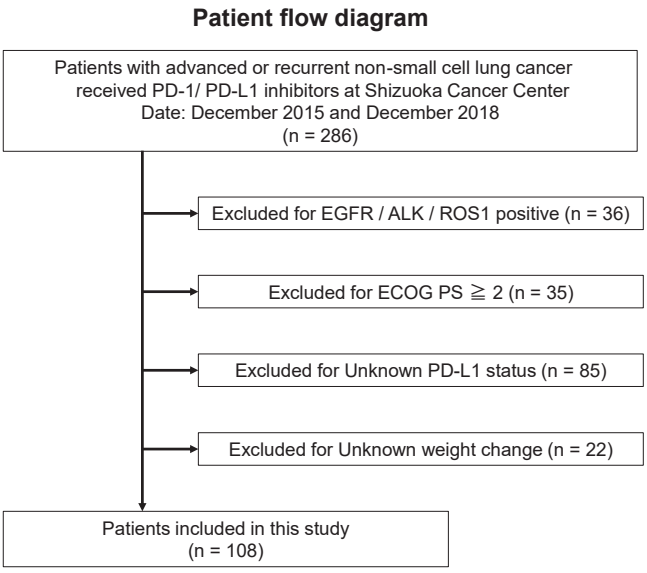

Figure 1. Study flowchart. ECOG, Eastern Cooperative Oncology Group; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; PS, performance status.

for the first time during this study period. The PD-1 or PD-L1 inhibitors prescribed included pembrolizumab in 75 patients (69%), nivolumab in 18 patients (17%), and atezolizumab in 15 patients (14%). All PD-1 or PD-L1 inhibitors were administered as monotherapy. The PD-L1 TPS was greater than or equal to 50% in 59 patients (55%) and greater than 50% in 49 patients (45%). A total of 52 patients (48%) had experienced greater than or equal to 5% weight loss within 6 months before initiation of PD-1 or PD-L1 inhibitor treatment and were diagnosed as having cancer cachexia. Patients with cachexia had a lower BMI (20 kg/m^2 versus 22 kg/m^2, $p < 0.001$) and were less likely to be overweight (BMI $\geq$ 25) than those without cancer cachexia (10% versus 29%, $p = 0.013$).

Impact of Cancer Cachexia on Objective Tumor Response

The objective response rate (ORR) for all patients was 35% (95% confidence interval [CI]: 26–44). Patients with low PD-L1 TPS had a lower ORR than those with high PD-L1 TPS (14% versus 53%, $p < 0.001$). Patients with cancer cachexia had a lower ORR than those without cancer cachexia (15% versus 57%, $p < 0.001$). In the multivariate logistic regression model including these two variables, the odds ratios for the presence of cancer cachexia and low PD-L1 TPS were 0.13 (95% CI: 0.04–0.35, $p < 0.001$) and 0.12 (95% CI: 0.04–0.35, $p < 0.001$), respectively (Table 2). There was no other predictor of ORR among the patient characteristics, including BMI, age, sex, smoking status, histologic subtype, and PS.

Table 1. Characteristics of Patients

Characteristics	Total ($n = 108$)	Cachexia ($n = 52$)	Noncachexia ($n = 56$)	p
Age (range)	67 (33-84)	67 (53-84)	66 (33-84)	0.846
Sex				
Male	82 (80%)	40 (77%)	42 (75%)	0.815
Female	26 (20%)	12 (23%)	14 (25%)	
ECOG-PS				
0	15 (14%)	6 (12%)	9 (16%)	0.496
1	93 (86%)	46 (88%)	47 (84%)	
Smoking status				
Ever	94 (87%)	48 (90%)	46 (82%)	0.116
Never	14 (13%)	4 (10%)	10 (18%)	
Histology				
Nonsquamous	91 (84%)	43 (83%)	48 (86%)	0.667
Squamous	17 (16%)	9 (17%)	8 (14%)	
PD-L1 TPS				
<50%	49 (45%)	28 (54%)	21 (38%)	0.088
≥50%	59 (55%)	24 (46%)	35 (62%)	
BMI				
BMI ≥ 25	21 (19%)	5 (10%)	16 (29%)	**0.013**
BMI < 25	87 (81%)	47 (90%)	40 (71%)	
PD-1 or PD-L1 inhibitor				
Pembrolizumab	75 (69%)	34 (65%)	41 (73%)	0.575
Nivolumab	18 (17%)	9 (17%)	9 (16%)	
Atezolizumab	15 (14%)	9 (17%)	6 (11%)	
Treatment line				
1st	40 (37%)	18 (35%)	22 (39%)	0.616
2nd or later	68 (63%)	34 (65%)	34 (61%)	

Significant p value is shown in bold type.
ECOG, Eastern Cooperative Oncology Group; PS, performance status; PD-L1, programmed death-ligand 1; PD-1, programmed cell death 1; TPS, tumor proportion score; BMI, body mass index.

Impact of Cancer Cachexia on PFS

Among the 108 patients, 76 patients (70%) had disease progression at the cutoff date. The median follow-up period was 19.7 months (95% CI: 15.9–23.2). The median PFS for all patients was 5.8 months (95% CI: 3.7–9.9). Patients with cancer cachexia had shorter PFS than those without cachexia (2.3 mo versus 12.0 mo, log-rank test $p < 0.001$, Fig. 2*A*). Patients with low PD-L1 TPS had significantly shorter PFS than those with high PD-L1 TPS (2.8 mo versus 10.8 mo, log-rank test $p = 0.002$, Fig. 2*B*). In the multivariate Cox proportional hazards model for PFS, the hazard ratios for the presence of cancer cachexia and low PD-L1 TPS were 4.2 (95% CI: 2.2–8.4, $p < 0.001$) and 3.0 (1.5–6.6, $p = 0.002$), respectively (Table 3). There was no other predictor for PFS among the patient characteristics, including BMI, age, sex, smoking status, and PS, except for histologic subtype.

Table 2. Predictor for Efficacy in PD-1 or PD-L1 Inhibitors

	Univariate Analysis			Multivariate Analysis		
ORR	OR	95% CI	p Value	OR	95% CI	p Value
Cachexia vs. noncachexia	0.14	0.05-0.34	<0.001	0.13	0.04-0.35	<0.001
PD-L1 TPS < 50% vs. ≥ 50%	0.13	0.05-0.34	<0.001	0.12	0.04-0.35	<0.001
BMI ≥ 25 vs. BMI < 25	1.37	0.51-3.57	0.539			
Age ≥ 75 vs. < 75 y	1.77	0.70-4.50	0.230			
Male vs. female	1.15	0.46-2.89	0.769			
Smoking yes vs. no	0.76	0.24-2.36	0.630			
Nonsquamous vs. squamous	1.50	0.48-4.62	0.480			
ECOG-PS 0 vs. 1	1.59	0.53-4.77	0.408			

ORR, objective response rate; OR, odds ratio; PD-L1, programmed death-ligand 1; PD-1, programmed cell death 1; TPS, tumor proportion score; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; PS, performance status; CI, confidence interval.

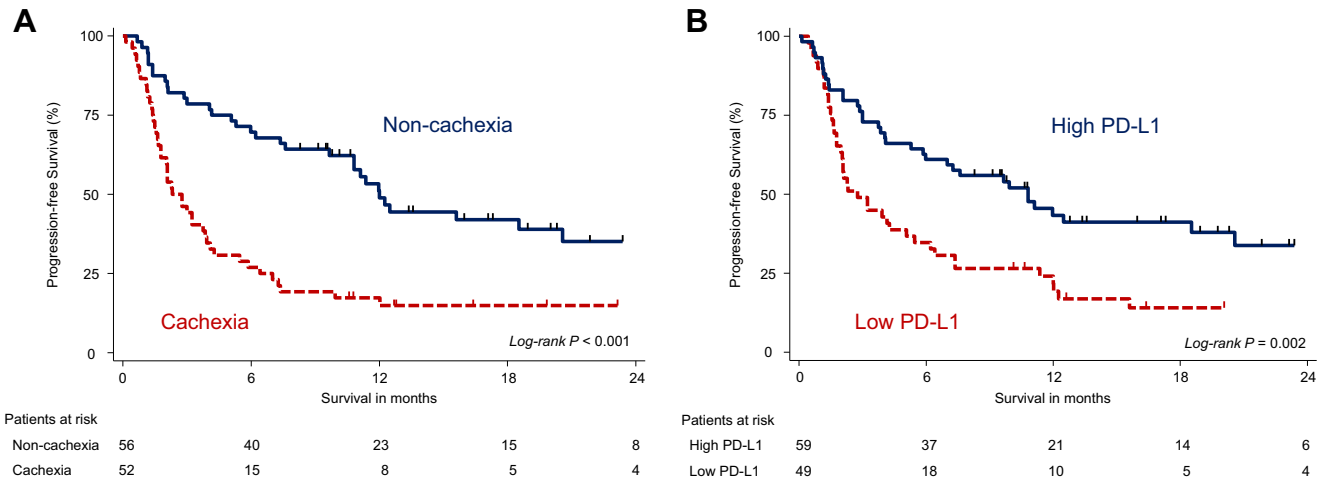

Figure 2. Kaplan-Meier curves for progression-free survival by PD-L1 TPS (≥50% versus <50%) (*A*) and by cachectic status (noncachexia versus cachexia) (*B*). The *p* values were calculated using the log-rank test. PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

Impact of Cancer Cachexia on OS

Among the 108 patients, 51 (47.2%) had died at the cutoff date. The median follow-up period was 18.1 months (95% CI: 14.0–21.8). The median OS for all patients was 21.9 months (95% CI: 13.5–26.9). Patients with low PD-L1 TPS had significantly shorter OS than those with high PD-L1 TPS (13.0 mo versus 27.3 mo, log-rank test $p = 0.004$). Patients with cancer cachexia had shorter OS than those without cachexia (12.9 mo versus 27.3 mo, log-rank $p < 0.001$). The adjusted hazard ratios of OS for the presence of cancer cachexia and low PD-L1 TPS were 2.77 (95% CI: 1.51–5.06, $p = 0.001$) and 1.66 (95% CI: 0.33–1.08, $p = 0.090$), respectively, after adjustment by PS (0 versus 1) and histology (nonsquamous versus squamous).

Desensitizing Effect of Cancer Cachexia on Potentially Sensitive Patients

In the subset of 52 patients with cancer cachexia, 24 (46%) and 28 (54%) had high and low PD-L1 TPS, respectively. In the subset of 56 patients without cancer cachexia, 35 (63%) and 21 (37%) had high and low PD-L1 TPS, respectively. The distribution of characteristics among patients with high and low PD-L1 TPS was similar in those with and without cancer cachexia, although among patients with cachexia, those with high PD-L1 TPS were older than those with low PD-L1 TPS (Supplementary Table 1).

Among patients with cancer cachexia, there was no significant difference in the ORR (13% versus 7%, $p = 0.514$) or PFS (2.8 mo versus 2.2 mo, log-rank test $p = 0.992$) among patients with high PD-L1 TPS and those with low PD-L1 TPS (Fig. 3*A*). Among patients without cachexia, those with high PD-L1 TPS had a higher ORR (77% versus 23%, $p < 0.001$) and longer PFS (20.5 mo versus 5.1 mo, log-rank test $p < 0.001$) than those with low PD-L1 TPS (Fig. 3*B*).

Discussion

To our knowledge, this is the first study to measure the unfavorable impact of cancer cachexia on the efficacy

Table 3. Predictor for Efficacy in PD-1 or PD-L1 Inhibitors

	Univariate Analysis			Multivariate Analysis		
PFS	OR	95% CI	*p* Value	OR	95% CI	*p* Value
Cachexia vs. noncachexia	2.74	1.72-4.37	<0.001	2.46	1.52-3.98	<0.001
PD-L1 TPS < 50% vs. ≥ 50%	2.00	1.28-3.23	0.002	1.62	1.01-2.58	0.044
BMI ≥ 25 vs. BMI < 25	0.87	0.49-1.56	0.539			
Age ≥ 75 vs. < 75 y	0.67	0.36-1.22	0.193			
Male vs. female	0.68	0.41-1.13	0.142			
Smoking yes vs. no	0.86	0.44-1.67	0.655			
Nonsquamous vs. squamous	0.51	0.28-0.92	0.026	0.50	0.28-0.91	0.023
ECOG-PS 0 vs. 1	0.74	0.38-1.44	0.380			

OR, odds ratio; PFS, progression-free survival; PD-L1, programmed death-ligand 1; PD-1, programmed cell death 1; TPS, tumor proportion score; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; PS, performance status; CI, confidence interval.

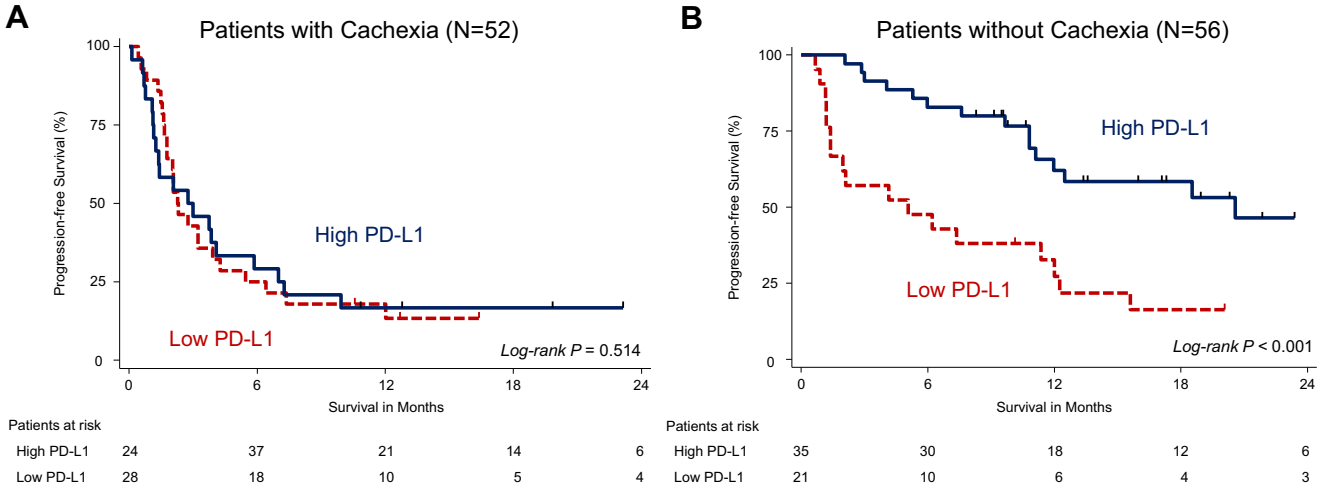

Figure 3. Kaplan-Meier curves for progression-free survival by PD-L1 TPS (≥50% versus <50%) in patients with cancer cachexia (*A*) and in patients without cancer cachexia (*B*). The *p* values were calculated using the log-rank test. PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

of PD-1 or PD-L1 inhibitors after adjusting for other clinical factors, including PD-L1 TPS. We found that the pretreatment diagnosis of cancer cachexia was strongly associated with reduced efficacy of PD-1 or PD-L1 inhibitors, regardless of other clinical confounding factors. Our analyses also indicated a desensitizing effect of cancer cachexia on the effect of PD-1 or PD-L1 inhibitors among potentially sensitive patients, that is, those with high PD-L1 expression on tumor cells. These results suggest that cancer cachexia is not only a prognostic factor but also a crucial predictor of efficacy of PD-1 or PD-L1 inhibitors.

Several previous studies have reported negative associations between cancer cachexia or sarcopenia and the efficacy of PD-1 or PD-L1 inhibitors.[9-12] However, these previous studies had considerable limitations, including small sample sizes and patient heterogeneity regarding the status of driver oncogenes, PS, and PD-L1 expression on tumor cells. To assess the specific impact of cancer cachexia, our studies included exclusively patients who had PS of 0 to 1, no *EGFR/ALK/ROS1* gene mutations, and no missing value for PD-L1 TPS. Furthermore, previous studies measured the effect of cancer cachexia without adjustment for PD-L1 expression on tumor cells. The PD-L1 expression on tumor cells is important as a predictor of efficacy of PD-1 or PD-L1 inhibitors in patients with advanced NSCLC.[4,13,15] Therefore, it is imperative to adjust for PD-L1 TPS as a confounding factor in the evaluation of new predictors of response to PD-1 or PD-L1 inhibitors. Our study overcame these limitations by multivariate and subgroup analyses and revealed a clear relationship between cancer cachexia and efficacy of PD-1 or PD-L1 inhibitors.

Although the precise mechanisms of desensitization of tumors to immunotherapy in patients with cancer cachexia are not known, some basic and clinical studies may support our hypothesis. Several cachexia-associated mediators, including interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF)-α, have been reported to suppress tumor-infiltrating lymphocytes (TILs), a key regulator of PD-1 or PD-L1 targeted therapy, resulting in decreased antitumor immunity.[2,8,16-20] The negative effect of IL-6 on outcomes in patients treated with PD-1 inhibitors was reported in a clinical study of patients with melanoma.[16] IL-6 suppresses hepatic ketogenesis and raises serum glucocorticoid levels, which may blunt the proliferation and infiltration of $CD8^+$ T cells within the tumor and reduce the efficacy of PD-1 or PD-L1 inhibitors.[8,17] TNF-α compromises $CD8^+$ TILs and reduces the expression of PD-L1 on tumor cells in a murine model of melanoma, which results in decreased efficacy of PD-1 inhibitors.[18,19] IL-1β also suppresses TILs and adversely enhances tumor-infiltrating myeloid-derived suppressor cells.[20]

The suppression of immunopotentiators is another possible mechanism of desensitization. Increased serum leptin level in obese mice enhances PD-1 expression on $CD8^+$ TILs and is associated with increased antitumor activity of PD-1 inhibitors.[21] A positive effect of obesity on PD-1 or PD-L1 inhibitors in human studies supports these findings.[21,22] Serum leptin levels are decreased in patients with cancer cachexia and may be associated with decreased sensitivity to PD-1 or PD-L1 inhibitors.[23] Although PD-L1 expression on tumor cells is associated with sensitivity to PD-1 or PD-L1 inhibitors, the presence of $CD8^+$ TILs is essential for antitumor activity.[17,24,25] Therefore, multiple mechanisms exist to decrease $CD8^+$

TILs in the tumor, which may explain the desensitizing effect of cachexia on PD-1 or PD-L1 inhibitors in patients with NSCLC.

The resolution of cancer cachexia is essential for optimizing the response to PD1 or PD-L1 inhibitors. Recent studies have shown that novel pharmacologic interventions, including anamorelin hydrochloride[26] and enobosarm,[27] and multidrug[28] and multimodal interventions combining nutritional and exercise interventions[29] may reverse cachectic status and improve nutritional status in patients with cancer cachexia. Furthermore, activation of the ghrelin pathway[30] and physical exercise[31] have been shown to decrease systemic inflammation, which promotes an immunosuppressive tumor microenvironment. Treatment strategies that combine anticachectic treatments and PD-1 or PD-L1 inhibitors might attenuate the desensitizing effect of cancer cachexia and enhance efficacy of PD-1 or PD-L1 inhibitors. We need further basic and clinical studies to test this hypothesis.

There were some limitations in our study. First, our analysis was limited by its retrospective nature and our inability to eliminate biases for unknown confounders. Second, we did not evaluate inflammatory cytokines, including IL-1, IL-6, and TNF-α, that are known to be associated with cancer cachexia. Third, a small population in a single Japanese cancer center limits the generalizability of our results to other populations. Fourth, our study might have bias because of the heterogeneous population. Finally, this study had a deficiency in the clinical assessment of skeletal muscle mass, a critical component of cachexia.[2] Further prospective studies with a large number of patients are required to validate our findings.

In conclusion, cancer cachexia is an independent predictor for the antitumor effect of PD-1 or PD-L1 inhibitors. In addition, cancer cachexia might have a desensitizing effect on PD-1 or PD-L1 inhibitors in potentially sensitive patients with high PD-L1 expression.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2020.100020.

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