Cancer cachexia as a determinant of efficacy of first-line pembrolizumab in patients with advanced non-small cell lung cancer

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Abstract. Pembrolizumab, either as a type of monotherapy or in combination with cytotoxic anticancer agents, is effective in the treatment of advanced non-small cell lung cancer (NSCLC). However, the development of cancer cachexia may adversely affect anticancer drug therapy. The present study investigated the effect of cancer cachexia on clinical outcomes in patients with advanced NSCLC who received first-line pembrolizumab. The data of patients with advanced NSCLC receiving first-line monotherapy or combination therapy with pembrolizumab were retrospectively analyzed. The primary endpoint was time to treatment failure (TTF), and the secondary endpoints were overall survival (OS) and incidence of adverse events (AEs). Clinical outcome was compared between patients with and without cancer cachexia. A total of 53 patients were analyzed. Among all patients, median TTF and OS were significantly shorter in patients with cancer cachexia than in those without [TTF: 5.8 vs. 10 months; hazard ratio (HR): 2.13; 95% confidence interval (CI): 1.07-4.24; P=0.016; OS: 12.1 months vs. not reached; HR: 5.85; 95% CI: 2.0-17.1; P=0.001]. In addition, TTF in the pembrolizumab monotherapy group was significantly shorter in patients with cancer cachexia than in those without, but no significant difference was detected in patients receiving pembrolizumab combination therapy. The incidence of AEs did not significantly differ between patients with and without cancer cachexia, except with regard to hypothyroidism. In conclusion, although cancer cachexia is prognostic of a poor outcome in patients with advanced NSCLC who receive first-line pembrolizumab, cancer cachexia might not affect therapeutic efficacy in combination therapy with pembrolizumab and cytotoxic anticancer agents.

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide and the second-leading cause of new cases of cancer. Non-small cell lung cancer (NSCLC) is the most common type (1). In drug therapy for lung cancer, patients with stage IV NSCLC are treated with molecular-targeted drugs (2-9), immune checkpoint inhibitors (ICIs) (10-12) and cytotoxic anticancer drugs (13). In particular, in patients classified as driver gene mutation/rearrangement-positive, molecular-targeted drugs (kinase inhibitors) against epidermal growth factor receptor (EGFR) (2-4), anaplastic lymphoma kinase (ALK) (5), c-ROS oncogene 1 (ROS1) (6), v-raf murine sarcoma viral oncogene homologue B (BRAF) (7), and proto-oncogene cMET (8,9) have shown high therapeutic efficacy. In contrast, high efficacy with pembrolizumab monotherapy or platinum combination chemotherapy plus ICI, such as programmed cell death 1 (PD-1)/programmed cell death 1-ligand 1 (PD-L1) inhibitor, has been seen in patients with driver gene mutation/rearrangement negative disease (10-12).

The introduction of pembrolizumab as an ICI, has changed the outcome of treatment drastically, extending progression-free survival (PFS) and overall survival (OS) compared to the conventional platinum-based therapy (10). The addition of pembrolizumab to conventional platinum-based therapy has also been shown to be more effective than platinum-based therapy alone (11,12). While pembrolizumab monotherapy significantly extended PFS and OS only in patients with PD-L1 expression on at least 50% of tumor cells, pembrolizumab combined therapy showed efficacy even when PD-L1 expression was below 50% (11,12). Now, the main treatment of advanced NSCLC without a targetable mutation with PD-L1 expression of more than 50% is pembrolizumab, and pembrolizumab combined therapy when PD-L1 expression is less than 50% (13).

The efficacy of pembrolizumab and pembrolizumab combined therapy remains limited, however, and predictive markers of ICIs are important (14). Although tumor proportion score (TPS) is used to measure the expression of PD-L1 in tumor cells, its validity in predicting the effects of pembrolizumab and pembrolizumab combined therapy is also insufficient (15). Other biological features that predict high tumor expression include a high tumor mutational burden and the presence of tumor infiltrating CD8+ (16). Currently, however, only PD-L1 expression is used in routine practice, despite being an incomplete tool for prediction, as mentioned above, and new biomarkers to maximize the response of tumor regression and minimize immune-related adverse events (irAEs) are urgently needed.

Cancer cachexia is a feature of cancer that reflects the metabolic changes that occur with this condition (17). Cancer cachexia is defined as progressive skeletal muscle loss with or without weight loss that does not completely recover with conventional nutritional support and which leads to functional disability (18). The main symptom of cancer cachexia is involuntary weight loss. Cachexia is diagnosed when a weight loss greater than 5% occurs, or a weight loss greater than 2% occurs in individuals with a body mass index (BMI) below 20 or loss of skeletal muscle mass (sarcopenia) (18).

Roch *et al* reported that cancer sarcopenia, diagnosed by a decrease in the third lumbar vertebra skeletal muscle index (mSMI), is a useful determinant of disease control rate and survival in NSCLC patients receiving first- and second-line treatment with ICIs (19). They also reported that a body weight loss of 5% or more reduced disease control rate and OS. However, 87% of their patient population received second-line pembrolizumab monotherapy, with PD-L1 expression of 1% or more. It therefore remains unclear whether cancer cachexia predicts the efficacy of pembrolizumab in first-line treatment, in either mono- or combination therapy.

Here, we conducted a retrospective study to evaluate whether cancer cachexia is a determinant of treatment efficacy in patients receiving first-line pembrolizumab monotherapy and combined therapy.

Patients and methods

Patients. As a retrospective study, we collected data from medical records of NSCLC patients receiving first-line pembrolizumab treatment at our institution from April 2014 to June 2020. Eligibility was limited to patients treated with first-line treatment with pembrolizumab either alone or in combination with another agent.

Evaluation of cancer cachexia at the start of pembrolizumab therapy. Cancer cachexia is defined as progressive skeletal muscle loss with or without weight loss that does not completely recover by conventional nutritional support and leads to functional disability (18). Accordingly, we defined cancer cachexia as any of the following: i) weight loss greater than 5%; ii) weight loss greater than 2% in an individual with a BMI below 20; and iii) loss of skeletal muscle mass (sarcopenia) and weight loss greater than 2%. We compared weight with that 6 months prior to the day of therapy initiation as baseline. Sarcopenia was evaluated by tracing the outline

of the psoas major muscle at the L2-L3 position, performed by the same single operator for all cases. The sum of the right and left areas was calculated and a change rate in psoas major muscle area (PMMA) of more than 10% was defined as sarcopenia. Change rate was defined as follows: Change rate of PMMA (%)=(1-PMMA ICI initiation/PMMA before 6 months of ICI initiation) x100

These criteria are consistent with a study by Nishioka *et al* showing the association of sarcopenia and efficacy of ICI therapy in NSCLC (20).

Evaluation of pembrolizumab therapy efficacy. Time to treatment failure (TTF) was used as the primary endpoint of efficacy for pembrolizumab. We defined TTF as the time from the start of pembrolizumab therapy to the end of pembrolizumab therapy. Secondary endpoints were OS, tumor response and incidence rate of AEs. OS was defined from the start of pembrolizumab therapy to death by any cause.

Tumor response was assessed in four criteria in accordance with Response Evaluation Criteria in Solid Tumors guideline version 1.1 (21). Response rate was defined as complete response (CR) plus partial response (PR), and disease control rate as CR plus PR plus stable disease (SD).

Assessment of AEs. AEs were classified as pneumonitis, colitis, adrenal insufficiency, hypothyroidism, renal dysfunction, diabetes mellitus, hepatitis, severe skin toxicity and infusion-related reaction, and graded according to the Common Terminology Criteria for Adverse Events version 4.0 (22). Incidence rates of AEs were compared between patients with and without cancer cachexia.

Statistical analysis. Patient characteristics were summarized as medians with 25th and 75th percentiles for continuous variables, and frequencies and percentages for categorical variables. Differences in patient characteristics between the two groups were compared using the χ^2 test, Fisher's exact test or Mann-Whitney U-test. For the primary analysis, a Kaplan-Meier estimate and log-rank test were used to assess OS and TTF by development of cancer cachexia. Cox proportional hazards regression was used to evaluate the association between OS and cancer cachexia with adjustment for covariates. Categorical variables such as the incidence of AEs, tumor response and one-year survival were compared between patients with and without cancer cachexia using the χ^2 test. All analyses were conducted using IBM SPSS version 22 (IBM Japan Ltd.) and R software version 3.5.1 (www.r-project.org), with P<0.05 considered significant.

Results

Patient demographics. A total of 53 NSCLC patients were eligible. Among them, 55% (29/53) were diagnosed with adenocarcinoma and 32% (17/53) with squamous cell carcinoma. 32 patients were treated with pembrolizumab monotherapy and 21 with pembrolizumab combination therapy. Of these 21 patients, 10 patients received carboplatin plus pemetrexed, 9 received carboplatin plus nab-paclitaxel, and 2 received cisplatin plus pemetrexed other than pembrolizumab. There were 23 and 30 patients with and without cancer

Table I. Patient demographics and baseline characteristics in patients receiving pembrolizumab with or without cancer cachexia.

Characteristic	With cachexia (n=23)	Without cachexia (n=30)	P-value
Number of patients with combination of cytotoxic agents	10 (43.5%)	11 (36.7%)	0.615[a]
Sex, male/female	18/5	24/6	1.000[a]
Age, years	71.0 (67.5-76.5)	71.0 (67.2-76.7)	0.914[b]
Height, cm	164.9 (157.4-169.6)	162.2 (158.9-164.9)	0.290[b]
Body weight, kg	49.4 (45.4-56.5)	46.4 (43.4-58.3)	0.061[b]
Body mass index	20.9 (18.5-22.6)	22.2 (20.8-24.5)	0.002[b]
Albumin, mg/dl	3.5 (3.0-3.8)	4.0 (3.6-4.3)	0.007[b]
Aspartate aminotransferase, IU/l	24.0 (17.0-33.5)	20.0 (16.3-24.8)	0.254[b]
Alanine aminotransferase, IU/l	23.0 (12.0-40.5)	16.0 (12.0-26.0)	0.146[b]
Serum creatinine, mg/dl	0.64 (0.61-0.73)	0.79 (0.60-0.90)	0.068[b]
Total bilirubin, mg/dl	0.5 (0.5-0.65)	0.6 (0.5-0.7)	0.299[b]
C-reactive protein, mg/dl	3.1 (1.4-7.9)	0.43 (0.11-3.98)	0.004[b]
Neutrophils, /l	7,840 (5,342.5-9,185)	4,630 (3,800-5,597.5)	<0.001[b]
Lymphocytes, /l	1,210 (883.5-1,355.5)	1,393.5 (1,115.2-1,821.2)	0.032[b]
White blood cells, /l	9,880 (7,340-11,445)	7,315 (5,970-8,320)	0.006[b]
Hemoglobin, g/dl	11.6 (10.6-13.2)	13.0 (11.93-14.05)	0.042[b]
Platelets, 10^4/l	32.9 (24.3-39.4)	24.6 (19.9-28.8)	0.023[b]
Modified Glasgow prognostic score, 0/1/2	4/9/10	19/6/5	0.003[a]
Neutrophil-lymphocyte ratio	6.10 (5.01-8.23)	3.35 (2.52-4.58)	<0.001[b]
Carcinoembryonic antigen, U/ml	4.2 (2.1-19.9)	5.35 (1.6-36.8)	0.799[b]
Carbohydrate antigen 19-9, U/ml	6.0 (3.9-16.0)	2.6 (0.8-9.85)	0.095[b]
Squamous cell carcinoma antigen, ng/ml	2.2 (1.27-14.6)	1.4 (1.1-2.75)	0.274[b]
Number of metastatic organs/sites, 0/1/≥2	8/9/6	11/14/5	0.371[a]
Squamous cell carcinoma/Adenocarcinoma/Others	8/10/5	9/19/2	0.942[a]

Data indicate medians with 25th and 75th percentiles or number. [a]χ^2 test, [b]Mann-Whitney U-test.

cachexia, respectively (Table I), giving an overall incidence rate of cancer cachexia at the start of pembrolizumab of 43% (23/53). As shown Table I, BMI, albumin, lymphocytes and hemoglobin were significantly lower in patients with cachexia than in those without cachexia. On the other hand, C-reactive protein (CRP), neutrophils, white blood cells, platelets and neutrophil-lymphocyte ratio (NLR) were significantly higher in patients with cachexia than in those without. On evaluation for newly arising cancer cachexia, 13 patients had a weight loss of more than 5% and 10 with a BMI below 20 had a weight loss of more than 2%, meaning 23 patients met the criteria for cancer cachexia.

Efficacy of treatment. The relative dose intensity (RDI) of pembrolizumab in patients with and without cancer cachexia was 0.98 and 0.93, respectively. Median follow up was 13.6 months (interquartile range: 2.2-6.6). For all patients who received pembrolizumab, median TTF and median OS were 6.6 months [95% confidence interval (CI): 4.7-8.5] and 22.7 months (95% CI: 18-27).

Median TTF and OS were significantly shorter in patients with cancer cachexia than in those without [TTF: 5.8 vs. 10 months; hazard ratio (HR): 2.13; 95% CI: 1.07-4.24; P=0.016; OS: 12.1 months vs. not reached months; HR: 5.85; 95% CI: 2.0-17.1; P=0.001; Fig. 1].

In patients receiving pembrolizumab monotherapy, median TTF was shorter in patients with cancer cachexia than in those without. This result was not seen in patients receiving combination therapy including pembrolizumab (monotherapy: 4.2 vs. 19.4 months; HR: 3.56; 95% CI: 1.43-8.90; P=0.007; combination therapy: 6.5 vs. 7.3 months; HR: 1.35; 95% CI: 0.417-4.39; P=0.615; Fig. 2).

There was no significant difference between patients with and without cachexia in tumor response rate including response rate and disease control rate. One-year survival rate was lower in patients with cachexia than in those without (1-year survival: 26 vs. 60%; P=0.029) (Table II).

Incidence of AEs. Rates of pneumonitis, colitis, adrenal insufficiency, renal dysfunction, diabetes mellitus, hepatitis, severe skin toxicity and infusion-related reaction did not significantly differ between patients with and without cancer cachexia (Table III). In contrast, the rate of hypothyroidism was significantly lower in patients with cancer cachexia than in those without (P=0.048).

Discussion

In this study, we evaluated the impact of cancer cachexia in NSCLC patients receiving first-line treatment with
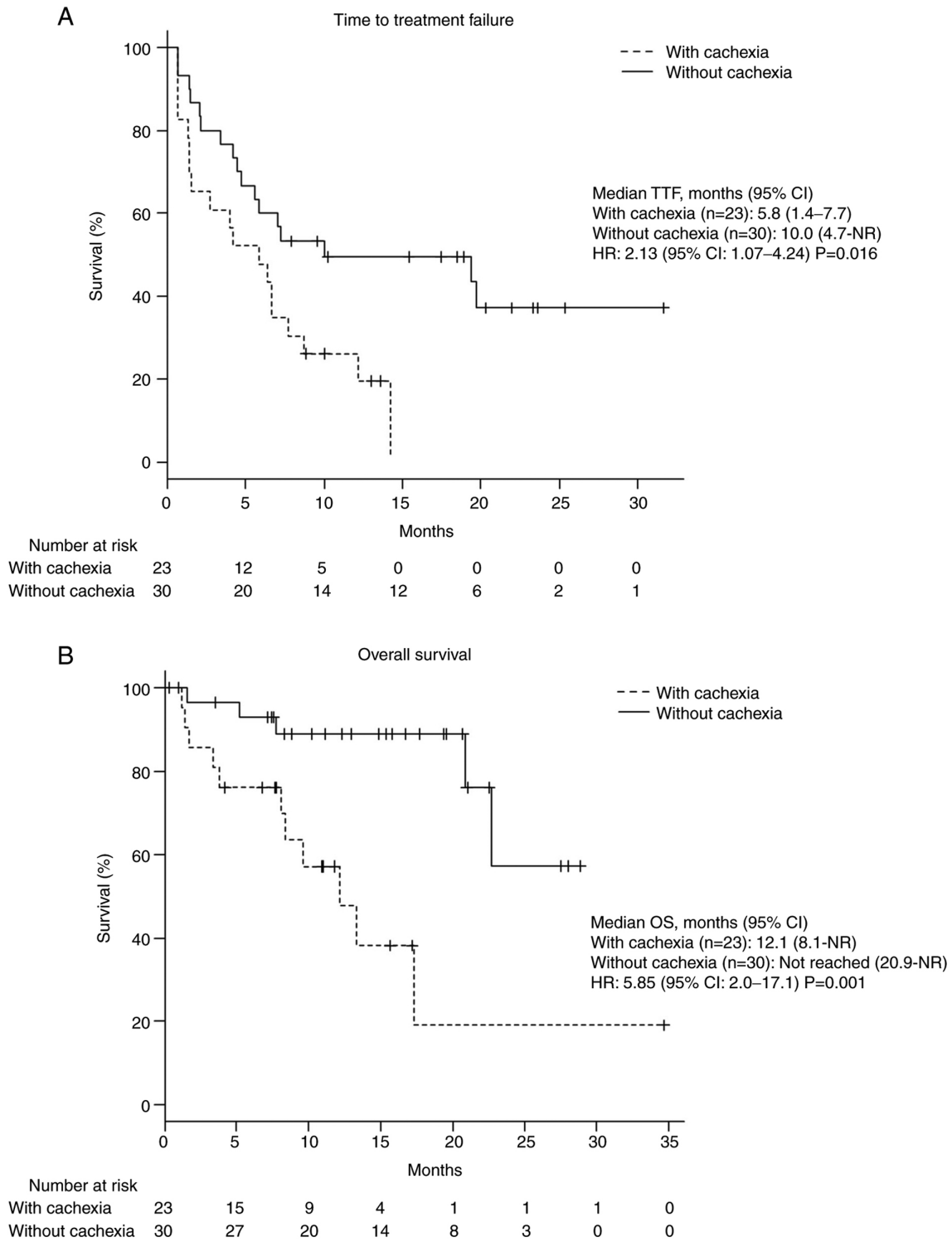
Figure 1. Kaplan-Meier curves comparing (A) time to treatment failure and (B) overall survival in patients with non-small cell lung cancer receiving pembrolizumab.

pembrolizumab. Cancer cachexia was found to be predictive in these patients, and was associated with significantly shortened TTF, OS, and 1-year survival. However, no association was seen between the first-line treatment effect of pembrolizumab combined with cytotoxic anticancer agents and cancer cachexia. These findings suggest that avoidance of cachexia will not result in a weakening of the therapeutic effect of pembrolizumab monotherapy in patients with NSCLC.

In our study, TTF in patients receiving pembrolizumab was 6.6 months. This finding is inconsistent with the KEYNOTE-024 trial of Reck *et al* (10), who reported a PFS of 10.3 months in 305 patients with advanced NSCLC receiving pembrolizumab. It is also inconsistent with the KEYNOTE-189 trial of Gandhi *et al* (11), who reported a PFS of 8.8 months in 410 patients with advanced NSCLC receiving pembrolizumab in combination with pemetrexed and a platinum-based drug.
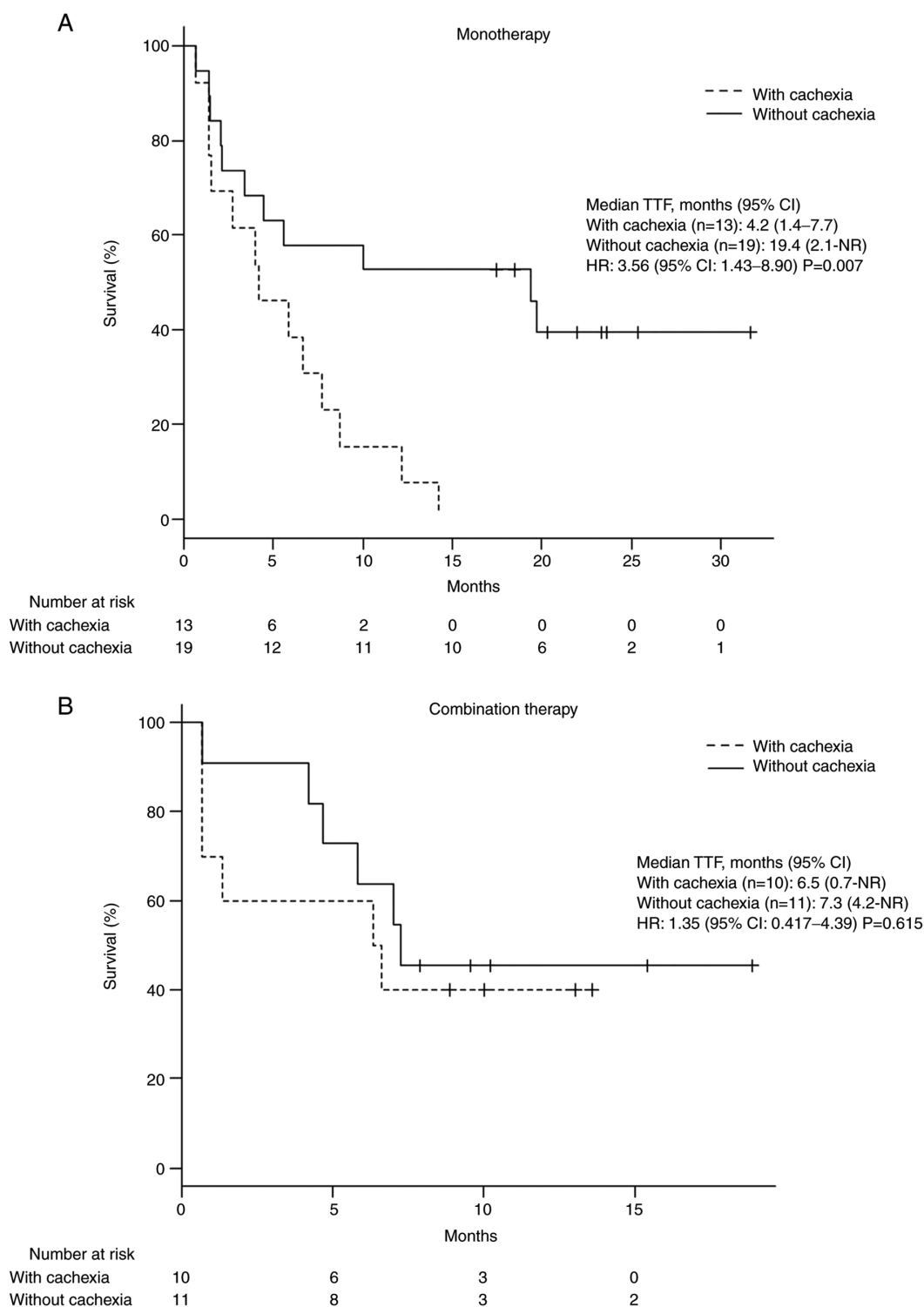
Figure 2. Kaplan-Meier curves comparing time to treatment failure in patients with non-small cell lung cancer receiving pembrolizumab (A) monotherapy and (B) combination therapy.

This difference in TTF might be ascribable to recruitment: The KEYNOTE-024 and KEYNOTE-189 trials were Phase 3 clinical trials which limited recruitment to patients having adequate organ function (10). In contrast, our present study recruited all patients who received pembrolizumab in real-world clinical practice, including those in poor general condition. In addition, we considered cachexia as a factor in some patients with poor condition, whereas these are typically excluded from clinical trials. Indeed, 43.4% of our patients had cachexia. Of note, the TTF of patients who did not have cachexia (10.0 months) was generally similar to that of the pembrolizumab group (10.3 months) in the KEYNOTE-024 trial (10).

In this study, significant differences were found in BMI, albumin, CRP, neutrophil count, white blood cell count, HGB, platelets, mGPS, and NLR. Since systemic inflammation is

Table II. Comparison of median time to treatment failure and disease control rate in patients with non-small cell lung cancer with or without cachexia.

Effect	With cachexia (n=23)	Without cachexia (n=30)	P-value
Tumor response rate (%)			
Response rate (CR + PR)	6 (26.1)	10 (33.3)	0.789[a]
Disease control rate (CR + PR + SD)	19 (82.6)	26 (86.7)	0.715[b]
One-year survival (%)	6 (26.1)	18 (60.0)	0.029[a]

[a]χ^2 test; [b]Fisher's exact test. CR, complete response; PR, partial response; SD, stable disease.

Table III. Comparison of incidence of adverse events between patients with non-small cell lung cancer with or without cachexia.

Adverse event	With cachexia (n=23)				Without cachexia (n=30)				P-value
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Overall	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Overall	
Pneumonitis	0.0	0.0	0.0	0/23	0.0	0.0	0.0	0/30	-
Colitis	4.3	0.0	0.0	1/23	0.0	0.0	0.0	0/30	0.434
Hypothyroidism	8.7	0.0	0.0	2/23	23.3	13.3	0.0	11/30	0.048
Adrenal insufficiency	0.0	0.0	0.0	0/23	0.0	0.0	0.0	0/30	-
Renal dysfunction	4.3	0.0	0.0	1/23	26.7	0.0	0.0	8/30	0.061
Pancreatitis	4.3	0.0	0.0	1/23	3.3	3.3	0.0	2/30	0.667
Hepatitis	26.1	4.3	4.3	8/23	40.0	3.3	0.0	13/30	0.524
Severe skin toxicity	21.7	21.7	0.0	10/23	33.3	20.0	0.0	16/30	0.642
Infusion-related reaction	4.3	0.0	0.0	1/23	0.0	0.0	0.0	0/30	0.434

Data were statistically analyzed by the χ^2 test.

present in cachexia patients (18), CRP, neutrophil count, white blood cell count, platelet count and NLR may have been higher in cachexia patients. Low BMI, albumin, lymphocytes, and hemoglobin in patients with cancer cachexia may also be due to reduced nutritional status.

Our finding that cancer cachexia is a predictor of worse clinical outcome is consistent with previous findings by Roch *et al* that evolving cancer sarcopenia as determined by third lumbar vertebra skeletal muscle index is associated with a shortened OS (19). It is also consistent with the finding of Shiroyama *et al* that sarcopenia determined by PMI can be used to predict a poor outcome of therapy (23).

Cancer cachexia also significantly shortened TTF in patients who received pembrolizumab monotherapy. In contrast, in patients who received combination therapy which included pembrolizumab, TTF did not significantly differ between patients with and without cachexia. It is widely known that the presence of cancer cachexia shortens OS (24). This corresponds to the finding of Sanders *et al* that NSCLC patients with early weight loss during chemoradiotherapy had shorter OS (25). Nevertheless, Ross *et al* reported that NSCLC patients with weight loss receiving chemotherapy did not have significantly shorter PFS than those without weight loss (26). This raises the possibility that cytotoxic treatment failure is

not associated with weight loss. Further investigation of the association between weight loss and chemotherapy failure is warranted.

Our findings indicate that cancer cachexia is strongly associated with pembrolizumab monotherapy failure. This may be the result of metabolic changes induced by cancer cachexia. The mechanism of weight loss is multifactorial, including decreased food intake, metabolic dysfunction and increased energy use (27). TNFα and IL-6 have been shown to cause weight loss (26). IL-1 causes protein breakdown in skeletal muscle (27). Flint *et al* reported that tumor-induced IL-6 causes hypoketonemia, which in turn triggers glucocorticoids and results in immune suppression (28). These inflammatory cytokines may downregulate the efficacy of pembrolizumab. Currently, the only pharmacological treatment showing promise against cancer cachexia is anamorelin (29). Further investigation of immunotherapy downregulation may reveal the pathophysiology of cancer cachexia and lead the way to promising treatments.

The incidence of hypothyroidism was significantly higher in patients without cancer cachexia. Osorio *et al* reported that median OS was significantly longer in those with thyroid dysfunction than in those without in patients with NSCLC who received pembrolizumab treatment (30). Median duration

to onset of hypothyroidism was 63 and 167 days in patients with and without cancer cachexia. It was considered that the incidence rate was lower in patients who did not have cancer cachexia due to a longer treatment period of chemotherapy including pembrolizumab.

Several limitations of our study warrant mention. It was conducted under a retrospective design at a single center. Further, the sample size was too small to allow precise consideration of confounding factors.

In conclusion, pembrolizumab monotherapy was associated with poor TTF and OS outcomes in NSCLC patients with cachexia compared to those without cachexia. Nevertheless, cachexia did not affect the clinical outcome in NSCLC patients receiving pembrolizumab plus cytotoxic anticancer agents. Improvement in cancer cachexia may improve clinical outcomes in patients with NSCLC treated with pembrolizumab monotherapy.

Acknowledgements

Availability of data and materials

All the datasets generated or analyzed during the present study are included in this published article.

Authors' contributions

HF and HI conceptualized this study. HF, AA and DKai acquired the clinical data. HF, AA and HI analyzed data. CH, MK, MY, JE, TI, KY, YS, TG, CS, DKaw, YK, MF, RK, YO and AS interpreted the data. YO and AS confirmed the authenticity of all the raw data. HF, AA and HI drafted the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study was carried out in accordance with the guidelines for human studies adopted by the Ethics Committee of Gifu University Graduate School of Medicine and the Japanese Government, and approved by the Medical Review Board of Gifu University Graduate School of Medicine (approval no. 2021-B050 Institutional Review Board). Informed consent was not obtained because this was a retrospective observational study. We posted information about the study and how patients could opt out on the website of the hospital.

Patient consent for publication

In view of the retrospective nature of the study, the need for informed consent from subjects was not mandated.

Competing interests

The authors declare that they have no competing interests.

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