Predicting the efficacy of first-line immunotherapy by combining cancer cachexia and tumor burden in advanced non-small cell lung cancer

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Abstract

Background: Cancer cachexia and tumor burden predict efficacies of programmed cell death-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors and chemotherapy or pembrolizumab in non-small cell lung cancer (NSCLC). There are no predictive models that simultaneously assess cancer cachexia and tumor burden.

Methods: In the present retrospective study, we reviewed the medical records of patients with advanced NSCLC who received cancer immunotherapy as first-line systemic therapy. Clinical immune predictive scores were defined according to multivariate analysis of progression-free survival (PFS) and overall survival (OS).

Results: A total of 157 patients were included in the present study (75 treated with PD-1/PD-L1 inhibitors + chemotherapy; 82, pembrolizumab monotherapy). Multivariate analysis for PFS revealed that PD-L1 tumor proportion scores <50%, a total target lesion diameter ≥76 mm, and cancer cachexia were independently associated with poor PFS. Multivariate analysis for OS revealed that ≥4 metastases and cancer cachexia were significantly associated with poor OS. In the immune predictive model, the median PFS was 21.7 months in the low-risk group (N = 41); 7.6 in the medium-risk group (N = 64); and 3.0 in the high-risk group (N = 47). The median OS were not reached, 22.4 and 9.1 months respectively. Our immune predictive model was significantly associated with PFS (p < 0.001) and OS (p < 0.001).

Conclusion: We proposed the immune predictive model, including tumor burden and cancer cachexia, which may predict the efficacy and survival outcome of first-line immunotherapy in advanced NSCLC.

Keywords
cancer cachexia, immune checkpoint inhibitor, non-small cell lung cancer, predictive model, tumor burden

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INTRODUCTION

Recent advances in cancer immunotherapy have led to programmed cell death-1 (PD-1)/programmed death ligand-1 (PD-L1) inhibitors ± cytotoxic chemotherapy as the standard first-line therapy for patients with advanced non-small cell lung cancer (NSCLC). The overall response rate is approximately 30 to 50%; not all patients respond to first-line therapy with PD-1/PD-L1 inhibitors ± cytotoxic chemotherapy, and most patients still have progressive disease. There is an urgent need to determine the populations that do not benefit from first-line immunotherapy and to explore the potential for new treatment strategies for these populations. Meanwhile, there has been almost no research focusing on models for predicting therapeutic efficacy of first-line immunotherapy according to factors assessable in the clinical setting.

Cancer cachexia is a multifactorial disorder; it is a complex condition that includes weight loss, loss of muscle mass, and chronic inflammation. Several studies have demonstrated that cancer cachexia has a deleterious impact on the therapeutic efficacy of PD-1/PD-L1 inhibitors ± cytotoxic chemotherapy in patients with advanced NSCLC. Additionally, previous clinical studies have shown that higher tumor burden is associated with lower therapeutic efficacy of PD-1/PD-L1 inhibitor monotherapy in patients with advanced NSCLC.

Although cancer cachexia and tumor burden are reported to significantly contribute to the efficacy of cancer immunotherapy, the predictive models for therapeutic efficacy that include these factors have not been investigated. Therefore, we proposed a model for predicting the therapeutic efficacy of first-line immunotherapy in advanced NSCLC that integrates tumor burden and cancer cachexia; we also explored the clinical feasibility of the proposed model.

METHODS

Study population

Between December 2018 and December 2020, 216 patients with advanced NSCLC were treated with PD-1/PD-L1 inhibitors plus chemotherapy or pembrolizumab monotherapy as first-line therapy at the Shizuoka Cancer Center. We retrospectively examined the medical records of the applicable patients. We included patients receiving PD-1/PD-L1 inhibitor monotherapy as first-line therapy at the Shizuoka Cancer Center. We retrospectively examined the medical records of the applicable patients. We included patients receiving PD-1/PD-L1 inhibitor monotherapy as first-line systemic therapy, whose weight change during the 6-month period prior to the start of first-line systemic therapy. Patients or their families were interviewed about the patient’s weight change during the 6-month period prior to the start of the first-line systemic therapy. Skeletal muscle mass was not measured in clinical practice; therefore, it was not considered as a criterion for cancer cachexia in the present study.

Definition of cancer cachexia

We defined cancer cachexia as unintentional weight loss of ≥5% during the 6-month period prior to the start of first-line systemic therapy. Patients or their families were interviewed about the patient’s weight change during the 6-month period prior to the start of the first-line systemic therapy. Skeletal muscle mass was not measured in clinical practice; therefore, it was not considered as a criterion for cancer cachexia in the present study.

Evaluating tumor burden

All patients were assessed for lesions in the chest, abdomen, and intracranial region using computed tomography (CT) or magnetic resonance imaging (MRI) before the administration of first-line immunotherapy. Following previous studies, the sum of the target lesion diameters was evaluated by measuring the target lesions based on the Response Evaluation Criteria for Solid Tumors version 1.1 (RECIST 1.1), and the optimal cutoff value for distinguishing between high and low amounts was defined as 76 mm.

The baseline number of metastatic lesions was defined as any metastatic lesion identified on the baseline CT or MRI scan, including the target and nontarget lesions. Metastatic thoracic lymph nodes (N1–N3) are collectively considered a single metastatic lesion. Based on the oligometastatic disease criteria representing low tumor burden, patients with 1–3 metastases were considered to have few metastases, and patients with ≥4 metastases were considered to have multiple metastases.

Development of the immune predictive score

A factor significant in either multivariate analysis of progression-free survival (PFS) or overall survival (OS) was defined as a clinical immune predictive score of 1. We defined a significant factor of multivariate analysis for PFS and OS as a clinical immune predictive score of 2. Based on the sum of the clinical immune predictive scores of individual patients in the present study, the immune predictive scores were classified into low-, medium-, and high-risk groups.
Statistical analysis

Correlations with cancer cachexia, number of metastases, and total diameter of target lesions were evaluated separately with Spearman’s rank correlations. All categorical variables were compared using Chi-square or Fisher’s exact tests. The objective response of first-line immunotherapy was assessed according to RECIST 1.1. PFS and OS were assessed using the Kaplan–Meier method and compared using the log-rank test. The follow-up period ended on May 1, 2021.

Cox proportional hazards models were used to evaluate potential predictive/prognostic factors for PFS and OS. For univariate analyses, the covariates included cancer cachexia (cachexia vs. noncachexia), age (≥75 vs. <75 years), sex, smoking history, ECOG-PS (0 vs. 1), histology (non-squamous vs. squamous cell carcinoma), PD-L1 TPS (≥50% vs. <50% or unknown), the number of metastases (1–3 vs. ≥4), and sum of the target lesion diameters based on RECIST 1.1 (<76 mm vs. ≥76 mm). Factors with univariate p-values <0.1 were included in the multivariate analysis. The known prognostic and predictive factors, including PD-L1 TPS and ECOG-PS, were integrated into the multivariate analysis. For all analyses, p-values <0.05 were considered statistically significant. All analyses were conducted using the Stata software (version 14.0; Stata Corp.).

RESULTS

Patient characteristics

In total, 216 consecutive patients with advanced NSCLC were administered PD-1/PD-L1 inhibitor + chemotherapy or pembrolizumab monotherapy as the first-line therapy at our institution between December 2018 and December 2020; 152 patients were included in our analysis. We excluded 20 patients enrolled clinical trials, 18 patients with an unknown weight change before the start of treatment,
10 patients with ECOG-PS2, and 11 patients who were transferred during first-line systemic treatment (Figure 1).

The median age of patients was 71 years (range, 35–88 years), most of whom were male, had a history of smoking and nonsquamous cell carcinoma. Seventy-two (48%) patients received pembrolizumab monotherapy. Sixty-nine (45%) patients had cancer cachexia. Forty-eight patients (32%) had 1–3 metastases. Almost half of the target lesion diameters in patients were summed to be \( \geq 76 \text{ mm} \) (Table 1).

Correlation between cancer cachexia and tumor burden

As shown in Figure 2, there was no significant correlation between the number of metastases and tumor diameter or weight loss (Spearman’s \( \rho = 0.023, p = 0.772 \)) (Figure 2a). There was no strong correlation between the rate of weight loss and the number of metastases (Spearman’s \( \rho = 0.223, p = 0.005 \)) (Figure 2b) or between the rate of weight loss and the sum of tumor diameters (Spearman’s \( \rho = 0.307, p = 0.001 \)) (Figure 2c).

Predictive factors for the efficacy of first-line immunotherapy

Among the 152 patients, 113 (74%) showed disease progression or death at the cutoff date. The median follow-up time for this study was 23.4 months (range 4.8–48.5). The median PFS for all patients in the present study was 7.3 months (95% confidence interval [CI] 5.2–9.5).

Univariate analysis of PFS revealed that cancer cachexia (hazard ratio [HR] 1.9; 95% CI: 1.33–1.82, \( p = 0.005 \)), number of metastases \( \geq 4 \) (HR: 1.72; 95% CI: 1.13–2.60, \( p = 0.037 \)), and sum of the target lesion diameters \( \geq 76 \text{ mm} \) (HR: 1.82; 95% CI: 1.25–2.66, \( p = 0.0002 \)) were significantly associated with poor PFS, and PD-L1 TPS <50% (HR: 1.36; 95% CI: 0.94–1.99, \( p = 0.104 \)) tended to be associated with poor PFS (Table 2).

Multivariate analysis of PFS revealed that cancer cachexia (HR: 1.64; 95% CI: 1.10–2.45, \( p = 0.015 \)), PD-L1-TPS <50% (HR: 1.48; 95% CI: 1.10–2.16, \( p = 0.044 \)), and the total diameter of target lesions \( \geq 76 \text{ mm} \) (HR: 1.70; 95% CI: 1.15–2.49, \( p = 0.007 \)) were independently associated with poor PFS (Table 2).

Of the 152 patients who participated in this study, 76 (50%) were confirmed dead by the cut-off date. The median OS for all patients in the study was 22.4 months.

Univariate analysis of OS revealed that ECOG-PS1 (HR: 1.88; 95% CI: 1.03–3.42, \( p = 0.038 \)), cancer cachexia (HR: 2.83; 95% CI: 1.77–4.51, \( p < 0.001 \)), number of metastases \( \geq 4 \) (HR: 2.17; 95% CI: 1.26–3.74, \( p < 0.001 \)), and sum of the target lesion diameters \( \geq 76 \text{ mm} \) (HR: 1.97; 95% CI: 1.23–3.14, \( p = 0.004 \)) along with PD-L1 TPS <50% (HR: 1.32; 95% CI: 0.83–2.09, \( p = 0.106 \)) were significantly associated with poor OS (Table 3).

**Figure 2** (a) Correlation between sum of the longest diameters of the target lesions and number of metastatic lesions based on Spearman’s rank correlation. (b) Correlation between rate of weight loss and number of metastatic lesions based on Spearman’s rank correlation. (c) Correlation between rate of weight loss and sum of the longest diameters of the target lesions based on Spearman’s rank correlation.
Multivariate analysis of OS revealed that cancer cachexia (HR: 2.32; 95% CI: 1.43–3.77, p = 0.001) and number of metastases ≥4 (HR: 1.79; 95% CI: 1.03–3.11, p = 0.037) were independently associated with poor OS (Table 3).

### Clinical immuno-predictive score

The clinical immune predictive scores were constructed based on the HR in the multivariate analysis of PFS or OS. Based on the multivariate analysis of PFS or OS, the score of cancer cachexia was 2 points. PD-L1 TPS >50%, sum of target lesion diameters ≥76 mm, and number of metastases ≥4 were scored as 1 point. The median score was 3 points (range 0–5), and we classified scores 0–1 as the low-risk group, scores 2–3 as the medium-risk group, and scores 4–5 as the high-risk group in the clinical immuno-predictive model (Figure 3). Cancer cachexia and tumor burden combined with the number of metastases and sum of target lesion diameters were equally valued in the clinical immuno-predictive score.

Among the patients in the present study, 41 (27%), 64 (42%), and 47 (31%) patients were in the low-, medium-, and high-risk groups, respectively.

The objective response rate was significantly associated with the clinical immuno-predictive model according to this classification (63, 50, and 19% for the three groups, respectively; p < 0.001).

As shown in Figure 4a, the median PFS were 21.7 months (95% CI: 9.8 to not reached [NR]) in the low-risk group, 7.6 months (95% CI: 4.8–10.6) in the medium-risk group, and 3.0 months (95% CI: 2.0–5.5) in the high-risk group. Patients in the low-risk group had significantly better PFS than those in the medium-risk (HR: 0.44; 95% CI: 0.26–0.73, p = 0.002) and high-risk groups (HR: 0.31; 95% CI: 0.18–0.53, p < 0.001). There was a trend towards better PFS with decreasing risk based on the clinical immuno-predictive model.
As shown in Figure 4b, the median OS were NR (95% CI: NR - NR) in the low-risk group, 22.4 months (95% CI: 17.3 – 33.2) in the medium-risk group, and 9.1 months (95% CI: 7.4 – 15.8) in the high-risk group; the 24-month OS rates were 81.0%, 44.2%, and 25.1%, respectively. Patients in the low-risk group had significantly better OS than patients in the medium-risk (HR: 0.35; 95% CI: 0.16 – 0.72, \( p = 0.004 \)) and high-risk groups (HR: 0.17; 95% CI: 0.08 – 0.35, \( p < 0.001 \)). The trend towards better OS was demonstrated by a decrease in the clinical immuno-predictive score risk.

In the subanalysis of patients who were treated with PD-1/PD-L1 inhibitors plus chemotherapy, the median PFS was 18.5 months (95% CI: 3.2 – NR) in the low-risk group, 7.3 months (95% CI: 4.1 – 10.6) in the medium-risk group, and 3.8 months (95% CI: 2.3 – 8.3) in the high-risk group (Figure 5a). The median OS was NR (95% CI: 23.7 – NR) in the low-risk group, 20.7 months (95% CI: 14.9 – NR) in the medium-risk group, and 10.5 months (95% CI: 7.4 – 15.9) in the high-risk group. In the subanalysis of PD-1/PD-L1 inhibitors plus chemotherapy, the trend towards improved PFS and OS was also demonstrated by a decrease in the clinical immuno-predictive score risk.

In the subanalysis of patients who were treated with pembrolizumab monotherapy, the median PFS was 21.7 months (95% CI: 6.5 – NR) in the low-risk group, 7.6 months (95% CI: 4.0 – 18.3) in the medium-risk group, and 1.6 months (95% CI: 1.0 – 3.0) in the high-risk group (Figure 6a). The median OS was NR (95% CI: 25.5 – NR) in the low-risk group, 22.4 months (95% CI: 17.3 – NR) in the medium-risk group, and 8.3 months (95% CI: 7.4 – 15.8) in the high-risk group. In the subanalysis of pembrolizumab monotherapy, the trend towards improved PFS and OS was also demonstrated by a decrease in the clinical immuno-predictive score risk.

**DISCUSSION**

To the extent that we review the previous studies to date, this is the first study to demonstrate the value of a clinical immune predictive model for first-line immunotherapy in advanced NSCLC, including cancer cachexia and tumor burden. Subanalysis by therapeutic setting revealed a similar trend to the main analysis, further confirming validity of the clinical immune predictive model for first-line immunotherapy. Previous studies proposed a predictive model including sex, ECOG-PS, and the neutrophil/lymphocyte ratio (NLR) for PD-1/PD-L1 inhibitors in patients with advanced NSCLC. Another study proposed a predictive model including lactate dehydrogenase, NLR, albumin, PD-L1-TPS, and ECOG-PS for PD-L1 inhibitors in patients with advanced NSCLC. Although cancer cachexia and tumor burden have been shown to be crucial in predicting the efficacy and prognosis of PD-1/PD-L1 inhibitors and/or PD-1/PD-L1 inhibitors plus chemotherapy, the predictive models that include these factors have not yet been explored. In this study, we proposed a predictive model for initial immunotherapy combining cancer cachexia and tumor burden; we believe that it will contribute to establishing a new predictive model for immunotherapy in patients with advanced NSCLC. Our clinical immuno-predictive model could be evaluated through an interview about weight change and CT images at a clinical practice; it does not require invasive tests. Therefore, we believe that our clinical immuno-predictive model is more convenient than the existing prognostic models.

Several studies have previously suggested that cancer cachexia has a negative impact on the therapeutic efficacy and prognosis of monotherapy with PD-1/PD-L1 inhibitors in patients with advanced NSCLC or PD-1/PD-L1 inhibitor.
plus chemotherapy. Previous basic and clinical studies identified multiple mechanisms by which cancer cachexia negatively regulates tumor immunity. Several studies have demonstrated that cancer cachexia stimulates the upregulation of various proinflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor-α, which in turn suppress cytotoxic T cells as components of tumor immunity.

Tumor burden is suggested to have an adverse effect on the efficacy and prognosis of PD-1/PD-L1 inhibitors plus chemotherapy or pembrolizumab monotherapy in patients with advanced NSCLC. Basic research has demonstrated that an increased tumor burden is correlated with increased CD8\(^+\) T cell exhaustion, which may reduce the therapeutic efficacy of PD-1 inhibitors. Additionally, other studies...
have indicated that CD8\(^+\) tumor infiltrating lymphocytes (TILs), an essential component of response to PD-1/PD-L1 inhibitor monotherapy, are impaired with higher tumor burden.\textsuperscript{26–29} Consistent with the present study, previous clinical trials have shown that the benefit of PD-1/PD-L1 inhibitor monotherapy decreases with higher tumor burden in patients with advanced NSCLC and other solid tumors, confirming previous basic hypotheses.\textsuperscript{12,13,30,31}

Although tumor burden and cancer cachexia are both critical factors in predicting the therapeutic efficacy and prognosis of PD-1/PD-L1 inhibitors, few studies have focused on the concurrent assessment of both tumor burden

\begin{figure}
(a) Kaplan–Meier estimates of progression-free survival among patients in low-risk, medium-risk, and high-risk groups in patients treated with PD-1/PD-L1 inhibitors plus chemotherapy. (b) Kaplan–Meier estimates of overall survival among patients in low-, medium-, and high-risk groups in patients treated with PD-1/PD-L1 inhibitors plus chemotherapy.
\end{figure}
and cancer cachexia, and their effects on the therapeutic efficacy of PD-1/PD-L1 inhibitors. We demonstrated no clinically meaningful correlation between tumor burden and cancer cachexia, and each factor was independently associated with PFS and OS in the multivariate analysis.

Prognostic and predictive models may play an essential role in selecting the optimal treatment for patients with NSCLC. Furthermore, identifying patients for whom tumor immunotherapy may not be effective would clarify potential patients requiring the development of new therapies, thereby contributing to the development of efficient new therapies. Especially for patients with high risk by clinical immuno-predictive score, both PD-1/PD-L1 inhibitors plus chemotherapy and pembrolizumab monotherapy might
provide poor therapeutic efficacy, suggesting a need for the further development of new therapies.

Our study had some limitations. First, the present study was a retrospective study; thus, unknown confounding factors were not considered. Second, the sample size of the present study was relatively small, comprising a single Japanese cancer center and considered only exploratory. Third, we did not have an independent validation cohort, which may have resulted in the overfitting of our models. Fourth, the pretreatment weight change was based on interviews with patients or family members; therefore, further verification is needed to determine the accuracy of the data obtained. In addition to weight loss, muscle mass may be critical in assessing cachexia; however, it was not assessed in this study. Finally, the tumor microenvironment and tumor immune status (except for PD-L1-TPS), such as the tumor mutation burden, could not be examined in this study.

The clinical immune prediction model including tumor burden and cancer cachexia proposed in this study may be useful for predicting therapeutic efficacy and survival outcomes of first-line immunotherapy in patients with advanced NSCLC. In future, our prospective validation cohort will have to be verified to confirm the accuracy of the clinical immuno-predictive scoring system. We believe that artificial intelligence (AI)-based assessment of tumor burden and muscle mass will provide a more accurate and reproducible measurement. By verifying the results of the present study using AI-based image analysis and Big Data, we may be able to achieve genuinely individualized treatment for each patient in the future.

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