Review Article

The landscape of immune therapy in vulnerable patients with advanced non-small cell lung cancer: a narrative review

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Background and Objective: The clinical development of immune checkpoint inhibitors (ICIs) has led to substantial advances in the treatment of lung cancer. In particular, the contribution of ICIs to the long-term survival of certain patients with non-small cell lung cancer (NSCLC) has been reported. With the accumulated experience in the use of ICIs, numerous studies have documented the efficacy and safety of ICIs in patients with diverse backgrounds, including those with problematic indications for drug therapy. In the current review, we summarize the most recent literature-based findings on ICI administration in vulnerable patients with NSCLC and provide an overview of the current status and prospects of ICIs.

Methods: Herein, we defined vulnerable as the group of patients with NSCLC and performance status (PS) ≥2 (poor PS), advanced age (≥75 years), or cancer cachexia. We conducted a narrative review of the literature on the efficacy and safety of ICIs in vulnerable patients with advanced NSCLC.

Key Content and Findings: Among the vulnerable patient group, poor PS was a strong, poor prognostic factor, even in patients undergoing ICI therapy. ICI therapy in older patients can be effective, although adverse events (AEs) should be carefully monitored. The efficacy of ICI therapy in patients with cancer cachexia is poor, with further therapeutic development warranted.

Conclusions: Although prior studies have evaluated lung cancer pharmacotherapy in various vulnerable populations, clinical studies on the application of ICIs in patients with vulnerable NSCLC are lacking in both number and quality. Further development of these therapeutic agents, with the emergence of additional evidence regarding their appropriate use in this population, is expected.

Keywords: Age; poor performance status (poor PS); cancer cachexia; non-small cell lung cancer (NSCLC); immune checkpoint inhibitor (ICI)

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Introduction

Background

Following the approval of immune checkpoint inhibitors (ICIs) to treat malignant melanoma, ICIs targeting programmed death-ligand 1 (PD-L1), programmed death-1 (PD-1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) have been approved and widely used to treat various types of cancer (1-7).

Rationale and knowledge gap

Since their introduction, ICIs have been deemed a promising new treatment for patients with advanced-stage non-small cell lung cancer (NSCLC), given their ability to facilitate long-term patient survival. Currently, ICIs

Table 1 The search strategy summary

Items	Specification
Date of search	August 31, 2023
Databases and other sources searched	PubMed and clinicaltrials.gov
Search terms used	Poor performance status, cancer cachexia, non-small cell lung cancer, immune checkpoint inhibitor, and elderly patients
Timeframe	Mainly literature published from 2011 onward
Inclusion and exclusion criteria	Inclusion criteria: (I) English-language article; (II) Original publications, including the clinical trial, literature review, and review paper
	Exclusion criteria: (I) non-English language article
Selection process	Study selection and full-text articles were assessed by first author (K.M.) and the consensus was obtained by other authors

are approved both as monotherapy and in combination with cytotoxic anticancer agents (chemoimmunotherapy) to address NSCLC (6,8-12). In addition, with the rapid implementation of ICI-based treatments, these therapeutics are being administered to patients with NSCLC from diverse health backgrounds. However, some of these patient backgrounds remain poorly evaluated in clinical trials, and evidence regarding ICI efficacy in these groups is lacking.

Objective

In the current narrative review, we present a literature review of the current evidence regarding the administration of ICIs in patients with NSCLC and problematic indications for drug therapy, such as poor performance status (PS), advanced age (≥75 years), and the presence of cancer cachexia. We present this article in accordance with the Narrative Review reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-581/rc).

Methods

To identify relevant articles, we searched PubMed and clinicaltrials.gov for articles published in English through August 31, 2023, using the following terms: poor performance status, cancer cachexia, non-small cell lung cancer, immune checkpoint inhibitor, and elderly patients. We mainly included literature published after 2011 and referred to original articles and reviews (*Table 1*). We defined "vulnerable" patients as those in whom the indication for pharmacotherapy was problematic; vulnerable patients with NSCLC and PS ≥2 (poor PS), elderly patients with NSCLC, and patients with NSCLC and cancer cachexia were included in the current review.

Vulnerable patients with cancer and the effectiveness and safety of drug therapy

Vulnerable patients with cancer include those with a range of conditions, including medical, socio-cultural-, and socio-economically-related vulnerabilities (13). However, owing to their vulnerability, these cancer populations are frequently excluded from clinical trials. Thus, although clinical trial results are informative for a limited population, they are inadequately evaluated for the majority of patients with cancer. Importantly, the application of clinical trial results to patients with cancer who are ineligible for clinical trials may fail to provide as much benefit as observed in the trial participants (14,15). Therefore, the potential for limited clinical benefit and increased toxicity in vulnerable patients is of concern. In this narrative review, we focus on poor PS, advanced age, and cancer cachexia among the diverse patient vulnerabilities, given that these have been found to occur at relatively high frequency in patients with NSCLC.

Poor performance

Treatment outcome of poor PS

Typically, patients with NSCLC and poor PS are ineligible for participation in clinical trials. However, in real-world settings, patients with PS of 2 or 3 account for nearly 30% of patients with lung cancer, whether in early or advanced stages,

representing a sizable population for which limited empirical data are available (16). PS of 2 has been reported as a poor prognostic factor in patients with advanced NSCLC (17). Regarding immunotherapy, several retrospective studies found that a PS of 2 could be a poor prognostic factor for ICI monotherapy (17-21). Furthermore, in a meta-analysis evaluating the efficacy and safety of ICIs in patients with NSCLC and PS ≥2, the population with PS ≥2 exhibited markedly lower response rate, disease control rate, progression-free survival (PFS), and overall survival (OS) than the population with PS ≤1 (22). Conversely, safety was comparable between the two groups.

ICI monotherapy in patients with poor PS

CheckMate 171, a large phase 2 trial, has evaluated the efficacy and safety of nivolumab in patients with previously treated advanced NSCLC (23). Of the 811 patients in the overall population, 103 had a PS of 2. The median OS in the overall population was 10.0 months, whereas that of patients with PS of 2 was relatively poor at 5.2 months. Among patients with a PS of 2, 47.6% experienced treatment-related adverse events (AEs), with a 6.8% incidence of grade 3–4 treatment-related AEs, indicating good tolerability. Accordingly, it can be suggested that although nivolumab is well-tolerated by patients with PS of 2, treatment outcomes remain poor.

The PePS2 trial was a phase II trial conducted in the United Kingdom to evaluate the efficacy and safety of pembrolizumab in patients with advanced NSCLC and PS of 2 (24). The trial was open to enrollment regardless of PD-L1 expression, with 60 patients included in the analysis. Durable clinical benefit (DCB), one of the primary endpoints of the study, was defined as complete response, partial response, or stable disease continuing until the second computed tomography (CT) scan scheduled at least 18 weeks later. The frequency of DCB was 38% in first-time treated patients (n=24) and 36% in second-time treated patients (n=36). Furthermore, DCB frequency was 22% in patients with a PD-L1 tumor proportional score (TPS) <1% (n=27), 47% in patients with PD-L1 TPS 1–49% (n=15), and 53% in patients with PD-L1 TPS ≥50% (n=15), thereby suggesting an association between higher PD-L1 TPS and increased DCB frequency. Accordingly, PD-L1 TPS could predict response in patients with NSCLC and PS of 2. Considering safety, treatment deferral was undertaken in 18% of patients, while 10% discontinued treatment. There were no grade 5 treatment-related AEs or early deaths due to hyperprogression. Accordingly, pembrolizumab can be safely administered to patients with NSCLC and PS of 2.

The OLCSG1801 trial evaluated the efficacy and safety of pembrolizumab monotherapy in patients with advanced NSCLC and poor PS plus high PD-L1 expression (25). Fourteen patients were enrolled, with a response rate of 57.1%, median PFS of 5.8 months, and median OS of 9.9 months. One patient died of liver failure, and two patients with PS of 3 exhibited disease progression and died within two months. The findings of the trial revealed that pembrolizumab was effective and tolerable for treating patients with NSCLC with PS of 2 plus high PD-L1 expression (25). The IPSOS trial was a phase III trial evaluating the safety and efficacy of atezolizumab versus single-agent chemotherapy (vinorelbine or gemcitabine) in patients with NSCLC ineligible for treatment with a platinum-containing regimen (26). Overall, 453 patients were included, of whom more than 80% had PS ≥2. Atezolizumab monotherapy substantially prolonged OS when compared with single-agent chemotherapy [hazard ratio (HR) 0.78; 95% confidence interval (CI): 0.63–0.97], with similar trends observed in populations presenting PS of 2 (HR 0.86; 95% CI: 0.67–1.10) and 3 (HR 0.74; 95% CI: 0.35–1.57). The IPSOS trial revealed that first-line treatment with atezolizumab monotherapy is associated with improved OS and a favorable safety profile compared to single-agent chemotherapy.

In a prospective observational study, we previously evaluated the efficacy and safety of pembrolizumab monotherapy in 16 PD-L1-positive patients with advanced NSCLC with PS of 2, revealing a median PFS of 4.4 months and median OS of 11.6 months (27). There was no clear association between PS and treatment discontinuation rate. Collectively, these findings suggest that ICI monotherapy is moderately effective and safe even in patients with PS of 2. Alternatively, there is no clear evidence to recommend ICI monotherapy in patients with PS ≥3; in particular, a retrospective observational study of fifteen patients with NSCLC and PS of 3 or 4 showed a median PFS of 1.1 months and a median OS of 1.9 months (19).

Furthermore, patients with poor PS constitute a heterogeneous population. Facchinetti *et al.* (21) evaluated the efficacy of pembrolizumab monotherapy in 153 patients with advanced NSCLC with high PD-L1 expression and PS of 2. The overall population had a median PFS of 2.4 months and a median OS of 3.0 months. Notably, 41 patients with PS reduced owing to complications achieved substantially

Table 2 Review of ICI efficacy in patients with NSCLC with poor PS

Study	Study design	N (PS of 2)	Drug (treatment line)	PD-L1 status	Response rate (%)	Median PFS (months)	Median OS (months)
Felip *et al.* (23)	Phase 2	103	Nivolumab (second-line)	–	2.0	–	5.2
Middleton *et al.* (24)	Phase 2	60	Pembrolizumab (first-line/second-line)	–	27.0	4.4	9.8
Hosokawa *et al.* (25)	Phase 2	14*	Pembrolizumab (first-line)	≥50%	57.1	5.8	9.9
Lee *et al.* (26)	Phase 3	228	Atezolizumab (first-line)	–	–	4.1	9.7
Ready *et al.* (28)	Phase 3B	139	Nivolumab plus ipilimumab (first-line)	–	19.0	3.6	9.0
Lena *et al.* (29)	Phase 3	40	Nivolumab plus ipilimumab (first-line)	–	–	–	2.9

*, two patients had a PS of 3. ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; PS, performance status; PD-L1, programmed death-ligand 1; PFS, progression-free survival; OS, overall survival.

better PFS and OS than 112 patients with PS reduced by disease burden (median PFS 5.6 *vs.* 1.8 months; median OS 11.8 *vs.* 2.8 months, respectively) (21). These results suggest that the efficacy of ICIs may differ depending on the reason underlying the reduction in PS.

Nivolumab-plus-ipilimumab in patients with poor PS

The CheckMate 817 trial evaluated the efficacy and safety of nivolumab plus ipilimumab in patients with NSCLC and PS of 2 (28). A total of 139 patients were included in the analysis, revealing a response rate of 19%, median PFS of 3.6 months, and median OS of 9.0 months (28). In contrast, the eNErgy trial was a phase III trial that compared nivolumab plus ipilimumab with carboplatin in the first-line treatment of patients with advanced NSCLC, aged ≥70 years, with a PS of 2 (29). The trial was stopped after a preplanned interim analysis showed a risk of futility in patients with PS of 2 (HR 1.8; 95% CI: 0.99–3.3). Specifically, among patients with NSCLC and PS of 2, 40 had a median OS of 2.9 months in the nivolumab plus ipilimumab arm, while 39 achieved a median OS of 6.1 months in the carboplatin combination arm. Accordingly, no definitive conclusions could be drawn regarding the benefit of nivolumab plus ipilimumab therapy for patients with advanced NSCLC and PS of 2. Detailed information regarding clinical trials on ICI therapy in patients with NSCLC and poor PS is presented in *Table 2*.

ICI plus chemotherapy in patients with poor PS

Waterhouse *et al.* retrospectively evaluated patients with NSCLC who received chemoimmunotherapy as first-line therapy and found that PS ≥2 was a poor prognostic factor (14). In patients with PS ≥2, the median OS for non-small cell squamous cell carcinoma was 8.0 months, and that for non-small cell non-squamous cell carcinoma was 6.3 months. According to the ESMO Clinical Practice Guideline for managing non-oncogene-addicted metastatic NSCLC, chemoimmunotherapy has not been evaluated in clinical trials and cannot be recommended for patients with PS of 2 (30).

Elderly patients

Impact of advanced age

Several older patients are deemed unfit and cannot receive the same standard of care as healthy young individuals (31). Compared with younger patients with cancer, older patients need to consider a decreased ability to perform daily activities, a history of multiple comorbidities, reduced organ function, cognitive decline, and physical changes (32). Aging is known to increase the risk of developing lung cancer. Moreover, the proportion of older patients with lung cancer is growing, reflecting the global aging population. Given that eligibility for clinical trials on first-line ICIs in patients with NSCLC was based on the eligibility for platinum-based chemotherapy, only ~10% of the total population were patients aged ≥75 years. Therefore, further validation of ICI effectiveness among patients aged ≥75 years is urgently warranted (33).

Given that older patients comprise a heterogeneous population with diverse characteristics, various functional assessments have been applied to screen patient populations unfit to undergo conventional chemotherapy and attempt to link them to clinical outcomes. The

Geriatric-8 (G8) and Vulnerable Elders Survey-13 have been widely employed as screening tools for geriatric assessment (34). The G8 comprises eight questions, can be completed in a few minutes, and is suitable for functional assessment screening in older individuals. The ELDERS study evaluated the role of G8 scale screening and geriatric functional assessment in predicting the safety outcome in ICI-treated patients (35). The study evaluated 70 patients, aged ≥70 years, with NSCLC or malignant melanoma using the G8 screening tool. Among patients aged ≥70 years, G8 positivity (<15 points) was a predictor of hospitalization (P=0.031), with 32% of hospitalizations attributed to treatment-related AEs. Conversely, 58% of hospitalizations among G8-negative (≥15 points) patients aged ≥70 years were treatment-related. G8 positivity was also associated with an increased risk of mortality (P=0.01). Accordingly, G8 screening could identify patients with a high risk of hospital admission and mortality (35).

ICI monotherapy in elderly patients

A pooled analysis based on the KEYNOTE-024, KEYNOTE-042, and KEYNOTE-010 clinical trials was conducted to evaluate the safety and efficacy of pembrolizumab monotherapy in older patients aged ≥75 years (36). Pembrolizumab monotherapy improved OS when compared with cytotoxic chemotherapy in PD-L1-positive patients with NSCLC aged ≥75 years (HR 0.76; 95% CI: 0.56–1.02). Pembrolizumab monotherapy was also acceptably safe, although treatment-related AEs of grade ≥3 were more common in patients aged ≥75 years than in those aged <75 years (16.9% *vs.* 24.2%). In addition, several retrospective studies have demonstrated the efficacy and safety of ICI monotherapy in patients with NSCLC aged ≥75 years (20,37-39). In our prospective observational study of 31 patients with NSCLC aged ≥75 years, pembrolizumab monotherapy elicited a good therapeutic response, with a median PFS of 5.3 months, a median OS of 11.6 months, and an acceptable safety profile (27). Collectively, these results indicate the efficacy and safety of ICI monotherapy in older patients with NSCLC.

Nivolumab plus Ipilimumab in elderly patients

In a pooled analysis of clinical trials (CheckMate 227 part 1, CheckMate 817 cohort A, and CheckMate 568 part 1) of nivolumab plus ipilimumab as first-line therapy in patients with advanced NSCLC, safety in 174 patients aged ≥75 years was similar to that observed in the overall population; however, a higher rate of AE-related discontinuation was observed (29.3% *vs.* 20.6%) (40). Accordingly, nivolumab plus ipilimumab may be an effective treatment option for older fit patients with NSCLC. However, given that several older patients with NSCLC are unfit in real-world clinical settings, the efficacy and safety of nivolumab plus ipilimumab therapy should be verified using clinical data.

ICI plus chemotherapy in elderly patients

Real-world data on the effects of chemoimmunotherapy in the older population has been documented. Fujimoto *et al.* (41) conducted a retrospective study of 299 patients with non-small cell non-squamous lung cancer who received platinum plus pemetrexed plus pembrolizumab. Among these, 43 patients aged ≥75 years had a considerably higher overall discontinuation rate owing to AEs than that in 256 patients aged <75 years (40% *vs.* 21%, P=0.012) (41). Furthermore, we performed a retrospective study of 203 patients with NSCLC who received platinum plus pemetrexed plus pembrolizumab (n=122) or a carboplatin-plus-paclitaxel regimen plus pembrolizumab (n=81). Patients aged ≥75 years and patients aged <75 years were evaluated according to treatment regimen (42). Considering patients who received pemetrexed-based therapy, PFS and OS were markedly shorter in those aged ≥75 years than in those aged <75 years, with no notable difference observed according to patient age in those administered taxane-based therapy. The incidence of non-hematologic and hematologic AEs upon pemetrexed-based treatment was 36.0% *vs.* 26.8% (P=0.46) and 32.0% *vs.* 26.8% (P=0.62) in patients aged ≥75 years and those aged <75 years, respectively. The rates of non-hematologic and hematologic AEs for taxane-based therapy were 27.8% *vs.* 28.6% (P=1.0) and 55.6% *vs.* 30.2% (P=0.09). Grade 3–5 pneumonitis occurred at a significantly higher rate in patients aged ≥75 years treated with pemetrexed-based therapy than in those aged <75 years (16.0% *vs.* 2.1%; P=0.02). The results of our observational study suggest that there may be differences in the efficacy and safety of treatment regimens in older patients when compared with profiles in younger patients (42).

A retrospective study has evaluated the efficacy and safety of platinum plus pemetrexed plus pembrolizumab treatment in 99 older patients with non-small cell non-squamous lung cancer aged ≥75 under real-world clinical conditions (43). Pemetrexed therapy was discontinued earlier than

pembrolizumab (32% discontinued owing to toxicity); the duration of treatment with pembrolizumab and pemetrexed was 4.9 and 2.8 months, respectively (43). The duration of pemetrexed treatment is a risk factor associated with acute kidney injury. Moreover, cases of early pemetrexed discontinuation and difficulties in continuing long-term treatment have been reported in practice owing to concerns regarding kidney injury (44). Accordingly, these findings suggest that the application of platinum plus pemetrexed plus pembrolizumab in patients with NSCLC aged ≥75 years needs to be considered cautiously in terms of safety.

In a meta-analysis of chemoimmunotherapy, patients with NSCLC aged ≥65 years were reported to experience efficacy similar to that in patients aged <65 years (45). However, although clinical trials have reported the results of subset analyses of chemoimmunotherapy in patients aged ≥75 years, evaluating the statistical utility presents a considerable challenge. Some clinical trials have reported benefits of chemoimmunotherapy in older patients (e.g., IMpower130, IMpower131), whereas others found limited benefits (e.g., KEYNOTE-189, CheckMate9LA), and the trend is inconsistent (46). Therefore, caution should be exercised in evaluating the efficacy and safety of chemoimmunotherapy in older patients.

Which ICI-based treatment is better for elderly patients?

The NEJ057 study retrospectively analyzed 1,245 patients with advanced NSCLC aged ≥75 years who started first-line systemic chemotherapy (47). The median PFS was 7.7 months (95% CI: 6.5–8.7) in the chemoimmunotherapy group, 7.7 months (95% CI: 6.6–8.8) in the ICI monotherapy group, 5.4 months (95% CI: 4.8–5.7) in the platinum combination therapy group, and 3.4 months in the single-agent chemotherapy group. The median OS was 20.0 months (95% CI: 17.1–23.6) in the chemoimmunotherapy group, 19.8 months (95% CI: 16.5–23.8) in the ICI monotherapy group, 12.8 months in the platinum combination therapy group (95% CI: 10.7–15.6), and 9.5 months (95% CI: 7.4–13.4) in the single-agent chemotherapy group. The chemoimmunotherapy group exhibited a significantly higher incidence of grade ≥3 immune-related AEs than the ICI monotherapy group (24.3% *vs.* 17.9%; P=0.03). The efficacy of the chemoimmunotherapy group was comparable to that of the ICI monotherapy group. Considering the findings of the study in terms of safety, ICI monotherapy was preferable to chemoimmunotherapy in patients with advanced NSCLC aged ≥75 years (47). We summarize ICI efficacy in older patients with NSCLC in *Table 3*.

Following the approval of ICIs, their use rapidly increased in all age groups, accompanied by a concurrent improvement in OS. The OS of patients with NSCLC aged <55 years increased from 11.5 to 16.0 months during the study period, whereas that of patients with NSCLC aged ≥75 years increased from 9.1 to 10.2 months, with a modest improvement in survival when compared with that observed in younger patients (48). These results highlight that the establishment of clinical biomarkers to guide the use of ICI treatment among older patients and to identify cases where it would be effective and safe constitutes an important future challenge.

Cancer cachexia

Definition and impact of cancer cachexia

The definition and diagnostic criteria for cancer cachexia have been reported in an international consensus (49). Cancer cachexia is defined as "a multifactorial syndrome characterized by a persistent loss of skeletal muscle mass (with or without fat loss) that cannot be completely reversed by conventional nutritional therapy and progresses to functional disability". Cancer-related cachexia is diagnosed as follows: (I) weight loss of 5% or more in the previous six months; (II) weight loss of 2% or more if body mass index (BMI) was less than 20 kg/m^2 in the previous six months; or (III) weight loss of >2% in cases of concomitant sarcopenia in the previous six months (49). Cancer cachexia is classified into three stages: precachexia, cachexia, and refractory cachexia. Given the challenges associated with the treatment of refractory cachexia, intervention from the precachexia stage is recommended. Cancer cachexia frequently occurs in 50–80% of patients with advanced cancer (50). Cancer cachexia is the most commonly documented in gastrointestinal, head and neck, and lung cancers. Although populations of patients with lung cancer enrolled in clinical trials also include a certain number of patients with cancer cachexia, the frequency of the latter remains unknown in most trials. A recent study revealed that 45.6% of patients with advanced NSCLC had cancer cachexia at baseline (51). Smoking history, emphysema, clinical stage, metastatic site, histology, epidermal growth factor receptor mutation, serum calcium level, and serum albumin level are known to be substantially associated with cancer cachexia, and weight loss associated with cancer progression was found to be a poor prognostic factor (52,53). Moreover, variations in BMI

Table 3 Review of ICI efficacy in elderly patients (aged ≥75 years) with NSCLC

Study	Study design	Drug (treatment line)	N (patients)	PD-L1 status	Treatment discontinuation (%)	Median PFS (months)	Median OS (months)
Nosaki *et al.* (36)	Pooled analysis (KEYNOTE-010, KEYNOTE-024, KEYNOTE-042)	Pembrolizumab (first-line)	149	≥1%	10.7	–	15.7
Paz-Ares *et al.* (40)	Pooled analysis (CheckMate 227 part 1, CheckMate 817 cohort A, CheckMate 568 part 1)	Nivolumab plus ipilimumab (first-line)	174	–	29.3	–	–
Fujimoto *et al.* (41)	Retrospective	Platinum + pemetrexed + pembrolizumab (first-line)	43	–	40.0	8.5	Not reached
Morimoto *et al.* (42)	Retrospective	Platinum + pemetrexed + pembrolizumab/carboplatin + nab-paclitaxel + pembrolizumab (first-line)	25/18	–	48.0/16.7	6.2/5.7	11.0/17.0
Velcheti *et al.* (43)	Retrospective	Carboplatin + pemetrexed + pembrolizumab (first-line)	99	–	–	6.9	15.5
Uematsu *et al.* (47)	Retrospective	ICI/chemoimmunotherapy/ platinum combination therapy/ single-agent chemotherapy (first-line)	425/354/ 311/155	–	–	7.7/7.7/ 5.4/3.4	19.8/20.0/ 12.8/9.5

ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; PFS, progression-free survival; OS, overall survival.

have been shown to affect response rate, PFS, and OS in patients with NSCLC who received pembrolizumab and chemotherapy (54). Thus, weight loss, which is essential for the diagnosis of cancer cachexia, could negatively impact not only chemotherapy but also immunotherapy.

ICI monotherapy in patients with cancer cachexia

Cancer cachexia and sarcopenia are known to negatively impact therapeutic efficacy in patients with advanced NSCLC. In patients with cachexia, tumor-induced interleukin (IL)-6 was shown to reduce gluconeogenesis in the liver, leading to elevated circulating glucocorticoid levels, suppressing anti-tumor immunity, and reducing therapeutic efficacy (55-57). Miyawaki *et al.* (58) enrolled 108 patients with advanced NSCLC treated with ICIs at their institution and compared treatment efficacy in patients with and without cancer cachexia. Patients with cancer cachexia had substantially lower ICI response rates and PFS than patients without cancer cachexia. Notably, no clear difference was observed in response rate or PFS to pembrolizumab monotherapy, as determined by PD-L1 expression rate, in patients with NSCLC and cancer cachexia (58). Jo *et al.* (59) reported that patients with NSCLC and cancer cachexia exhibited a substantially lower response rate to pembrolizumab monotherapy than those without cancer cachexia. Following pembrolizumab monotherapy, patients with NSCLC and cancer cachexia had markedly shorter PFS and OS than those without cancer cachexia (59). The cancer cachexia group exhibited substantially higher levels of proinflammatory cytokines, including tumor necrosis factor-α, IL-1α, IL-8, and IL-10, which are thought to be involved in the pathogenesis of cancer cachexia, than the non-cancer cachexia group; however, these elevated levels were not associated with therapeutic response. In turn, we retrospectively evaluated the presence of sarcopenia in 38 patients with advanced NSCLC receiving anti-PD-1 antibodies by measuring the cross-sectional area of the psoas major muscle on CT images, revealing that the PFS associated with anti-PD-1 antibody therapy was substantially better in the group without sarcopenia than that in the group with sarcopenia (60).

Table 4 Review of ICI efficacy in NSCLC patients with cancer cachexia

Study	Study design	Drug (treatment line)	N (cachexia)	PD-L1 status	Response rate (%)	Median PFS (months)	Median OS (months)
Miyawaki *et al.* (58)	Retrospective	PD-1 or PD-L1 inhibitor (first-line/second-line)	52	–	15.0	2.3	12.9
Jo *et al.* (59)	Retrospective	Pembrolizumab (first-line/second-line)	47	≥1%	30.0	4.2	10.0
Morimoto *et al.* (61)	Retrospective	Chemoimmunotherapy (first-line)	50	–	62.0	6.7	Not reached
Miyawaki *et al.* (62)	Retrospective	Chemoimmunotherapy (first-line)	37	–	30.0	5.2	10.8

ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; PFS, progression-free survival; OS, overall survival; PD-1, programmed cell death-1.

Nivolumab plus ipilimumab in patients with cancer cachexia

The impact of cancer cachexia on the efficacy and safety of nivolumab plus ipilimumab therapy in patients with NSCLC remains unknown, thereby warranting the need for clinical investigations.

ICI plus chemotherapy in patients with cancer cachexia

In a retrospective study of 235 patients with advanced NSCLC treated with chemoimmunotherapy, patients with cancer cachexia exhibited substantially shorter PFS than those without cachexia. Regarding safety, no significant difference in the AE-induced discontinuation rate was observed between the cachexia and non-cachexia groups (32% *vs.* 27.2%, P=0.66) (61). Consistently, Miyawaki *et al.* (62) reported that weight loss before treatment initiation was associated with shorter PFS and OS following chemoimmunotherapy. However, the majority of reports on treatment, including ICI therapy in patients with advanced NSCLC and cancer cachexia, are retrospective studies, with findings from prospective clinical trials yet to be reported. In addition, although several reports have evaluated the efficacy of ICI therapy in patients with NSCLC and cancer cachexia, data on safety are scarce and require further validation (63-66). We summarize the main studies on the efficacy of ICI in NSCLC patients with cancer cachexia in *Table 4*.

Future perspective for cancer cachexia

Although the OS of patients with NSCLC has improved, potential interventions in patients with cancer cachexia, known to have a poor prognosis, need to be explored. Recently, anamorelin was approved as the first drug with anticancer cachexia activity. Anamorelin has been shown to substantially increase lean body mass and improve anorexia (67-69). However, anamorelin did not show any effect with regard to improving motor function (67-69). The impact of anamorelin on the efficacy and safety of immunotherapy is unclear. Currently, randomized controlled clinical trials are underway in Japan and Western countries to evaluate the benefit of non-pharmacologic treatments such as exercise and nutritional therapy in addition to anamorelin therapy (70,71). Currently, the NEXTAC-3 trial in Japan is evaluating the effect of anamorelin alone and combined with exercise and nutritional therapy on the efficacy of immunotherapy for patients with NSCLC and cachexia (72). In addition to anamorelin, neutralizing antibodies against growth differentiation factor-15 (GDF-15), a member of the transforming growth factor beta family, are also of interest as anti-cachexia drugs. In particular, GDF-15 has been reported to affect the brain's feeding center, causing anorexia and reducing lean body mass (73). The safety of the GDF-15 neutralizing antibody CTL-002 in combination with nivolumab was verified in a phase 1 trial, and a phase 2 trial is currently ongoing (74).

Conclusions

The current review presents existing evidence regarding the use of ICIs in vulnerable patient groups with problematic indications for chemotherapy. Poor PS is a robust, negative prognostic factor for ICI therapy. In general, patients with

advanced NSCLC and poor PS have an OS of less than six months to one year, highlighting the need for novel treatment strategies to improve treatment outcomes. Treatment of patients with cancer cachexia should include not only cancer therapies such as ICI therapy but also interventions such as pharmacologic and non-pharmacologic treatment of cancer cachexia to improve outcomes. ICI monotherapy may be effective and recommended, whereas chemoimmunotherapy appears to be more toxic based on some retrospective studies. Further clinical trials in vulnerable patients with NSCLC are needed. In the future, it is expected that clinical biomarkers will be identified and established to predict beneficial therapeutic effects and safety in this heterogeneous population.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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