Immune Checkpoint Inhibitors in Non-Small-Cell Lung Cancer

Subjects: Oncology
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Immune checkpoint inhibitors (ICIs) are standard treatments for patients with lung cancer. PD-1/PD-L1 or CTLA4 antibodies are chosen as the first-line therapy, contributing to the long-term survival and tolerability. Unlike molecular targeting agents, such as gefitinib, lung cancer patients with a poor performance status (PS) display unsatisfactory clinical improvements after ICI treatment.

Keywords: 18F-FDG PET ; PD-1 blockade ; immunotherapy ; lung cancer ; long-term survival ; metabolic response

1. Introduction

Immune checkpoint inhibitors (ICIs), such as programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) antibodies, are widely administered to patients with several types of cancers. In particular, it is surprising that long-term survival of more than 5 years was observed in patients with advanced malignant melanoma and metastatic/recurrent non-small-cell lung cancer (NSCLC) after the initiation of PD-1 blockade monotherapy [1][2]. Thus, we believe that a PD-1 blockade may also bring clinical benefits to cancer patients with a poor performance status (PS). Unfortunately, several previous reports demonstrated that PD-1 blockade monotherapy was not effective in such patients [3][4][5]. As a first-line setting, chemotherapeutic regimens, including a PD-1 blockade, are universally established as standard treatment for patients with advanced NSCLC without any driver mutations. Unlike molecular targeting agents, such as gefitinib, advanced or recurrent NSCLC patients with poor PSs displayed unsatisfactory clinical improvements after ICI treatment. Several previous reports also showed that the PS is one of the most important prognostic factors for predicting poor outcomes after ICI treatment [3][4][5]. However, first-line pembrolizumab or atezolizumab seemed to be effective for NSCLC patients with a PS of 2 if PD-L1 expression was greater than 50%.

2. PS as a Prognostic Factor after a PD-1 Blockade

Recently, several studies demonstrated that the Eastern Cooperative Oncology Group (ECOG) PS was an independent factor for predicting worse outcomes after PD-1 blockade monotherapy in patients with advanced or recurrent NSCLC [4][5][6][7]. Fujimoto et al. retrospectively analyzed the prognostic significance in 613 patients that were treated with nivolumab in a second-line or over setting [4]. Of the 613 patients, an ECOG PS of 0 or 1 was observed in 472 patients, an ECOG PS of 2 in 94 patients, and an ECOG PS of 3 or 4 in 47 patients. The objective response rate (ORR) of patients with an ECOG PS of 0 or 1, ECOG PS of 2, and ECOG PS of 3 or 4 were 24, 11, and 4%, respectively. A statistically significant difference in the progression-free survival (PFS) was observed between the patients with an ECOG PS of 0 or 1 and an ECOG PS of 2 ($p < 0.001$), and between those with an ECOG PS of 2 and an ECOG PS of 3 or 4 ($p = 0.022$). Their multivariate analysis identified never-smokers, poor ECOG PS, and epidermal growth factor receptor (*EGFR*) mutations or anaplastic lymphoma kinase (*ALK*) rearrangements as independent predictors of worse PFS. Katsura et al. also investigated the difference in efficacy between an ECOG PS of 0–1 (good PS, $n = 43$) and an ECOG PS of 2–4 (poor PS, $n = 20$) in previously treated NSCLC patients receiving nivolumab [6]. The median overall survival (OS) was 412 days for an ECOG PS of 0 or 1, 32 days for an ECOG PS of 2–4, and 31 days in best supportive care (ECOG PS of 0 or 1 vs. ECOG PS of 2–4, $p < 0.001$; ECOG PS of 2–4 vs. best supportive care, $p = 0.137$). Moreover, a statistically significant difference in the ORR was recognized between an ECOG PS of 0 or 1 and an ECOG PS of 2–4 (23% vs. 0%, $p < 0.001$). Imai et al. evaluated the efficacy of first-line pembrolizumab monotherapy in elderly patients with NSCLC with PD-L1 ≥ 50% [3]. Thirty-seven (78.7%) of 47 patients had an ECOG PS of 0 or 1, 7 (15.0%) had an ECOG PS of 2, and 3 (6.3%) had an ECOG PS of 3 or 4. An ECOG PS of 2 or 3 was identified as an independent factor for predicting poor outcomes using multivariate analysis. Other studies also demonstrated that an ECOG PS of 2–4 was identified as an independent factor for predicting worse outcomes in NSCLC patients that were treated with nivolumab or pembrolizumab [5][7]. In

previous retrospective studies, the ECOG PS was the most important prognostic factor for predicting worse outcomes after PD-1 blockade treatment in patients with NSCLC. However, the relationship between a worse ECOG PS and the failed efficacy of PD-1 blockade remains unclear. **Table 1** shows several studies that examined the prognostic factors in NSCLC patients who received PD-1 blockade.

Table 1. Independent prognostic factors in NSCLC patients that were treated with a PD-1 blockade.

First Author [Ref.]	No. of Pts	Drug Type (Treatment Line)	PD-L1 (%)	Smoking Yes/No (Patient's Number)	ECOG PS 0–1/≥2 (Patient's Number)	Independent Prognostic Factors for Predicting Negative Outcome (Multivariate Analysis)
Imai H. [3]	47	Pembro (1st-line)	≥50%	43/4	37/10	PS (0–1/2–3), smoking (yes/no), response (non-PD/PD)
Fujimoto D. [4]	613	Nivo (2nd-line~)	Any	482/131	472/141	PS (0–1/2–4), smoking (yes/no), driver mutations (yes/no)
Ichiki Y. [7]	44	Nivo or Pembro (1st- or 2nd-line~)	Any	8/36	32/12	PS (0–1/2–4), histology (Ad/Sq), PET (SUV) (SD), WBC (SD), Neutro (SD), NLR (SD), LDH (SD), Alb (SD)
Ahn B. C. [5]	155	Nivo or Pembro (1st- or 2nd-line~)	Any	104/51	121/34	PS (0–1/2–3), PD-L1 (<50%/≥50%), driver mutations (yes/no), liver metastasis(yes/no)
Kano H. [8]	527	Nivo or Pembro (1st- or 2nd-line~)	Any	445/94	448/79	Staging, smoking (yes/no), PS (0–1/2–4), treatment line (1st/2nd)

Abbreviations: Ref., reference; NSCLC, non-small cell lung cancer; Nivo, nivolumab; Pembro, pembrolizumab; PD-L1, programmed death ligand-1; no. of pts, number of patients; PS, performance status; PD, progressive disease; driver mutations, EGFR mutations or ALK translocation; PET, positron emission tomography; SUV, standardized uptake value; SD, standard deviation; WBC, white blood cell; Neutro, neutrophil; NLR, neutrophil-to-lymphocyte ratio; LDH, lactate dehydrogenase; Alb, albumin; Ad, adenocarcinoma; Sq, squamous cell carcinoma.

3. Efficacy of a PD-1 Blockade in NSCLC Patients with a PS of 2

Recently, Kano et al. reported the clinical features of a PD-1 blockade in patients with NSCLC with a poor PS [8]. They retrospectively analyzed and compared the prognostic significance after PD-1 blockade initiation in 448 patients with an ECOG PS of 0–1 to 79 patients with an ECOG PS of 2–4. The median PFS was 4.1 months for an ECOG PS of 0–1 and 2.0 months for an ECOG PS of 2–4, with a significant difference ($p < 0.001$). The patients with an ECOG PS of 0–1 exhibited a better OS (median, 17.4 months) than those with an ECOG PS of 2–4 (median, 4.0 months) ($p < 0.001$). In the analysis according to the ECOG PS level, the median PFS was 6.9 months for a PS of 1, 3.5 months for an ECOG PS of 2, 2.3 months for an ECOG PS of 2, and 1.1 months for an ECOG PS of 3–4. Their multivariate analysis also demonstrated that the ECOG PS was an independent predictor of worse outcomes. It is noteworthy that there was no statistically significant difference in the PFS (8.1 months vs. 7.3 months; $p = 0.321$) and OS (reached vs. not reached; $p = 0.148$) between the patients with an ECOG PS of 0–1 and an ECOG PS of 2 harboring PD-L1 ≥ 50%. However, the

median PFS (3.5 months vs. 2.0 months; $p < 0.001$) and OS (16.7 months vs. 4.7 months; $p < 0.001$) in patients with any PD-L1 expression displayed a significant difference between patients with an ECOG PS of 0–1 and those with an ECOG PS of 2. The results of this study suggest that a PD-1 blockade is effective in a limited population of NSCLC patients with PD-L1 ≥ 50%. Next, we focus on the efficacy of a PD-1 blockade in NSCLC patients with an ECOG PS of 2 in a previous literature review (**Table 2**).

Table 2. Review of ICI blockade efficacy in patients with a PS of 2.

First Author [Ref.]	Study Design	Drug Type	Histology	Treatment Setting	PD-L1 Status	No. of Pts (PS = 2)	ORR (%)	mPFS (Months)	mOS (Months)
Felip E. [9]	Phase 2	Nivo	SQC	2nd-line~	NA	103	2	NA	5.2
Spigel D. R. [10]	Phase 3	Nivo	All-comers	2nd-line~	NA	128	20	NA	4.0
Barlesi F. [11]	Phase 3	Nivo/Ipi	All-comers	1st-line	NA	139	20	3.6	NA
Middleton G. [12]	Phase 2	Pembro	All-comers	1st or 2nd	Yes	60	27	4.4	9.8
					<1%	27	11	3.7	8.1
					1–49%	15	33	8.3	12.6
					≥50%	15	47	12.6	14.6
Fujimoto D. [4]	Retro	Nivo	All-comers	2nd-line~	NA	94	11	1.2	NA
Alessi J. V. [13]	Retro	Pembro	All-comers	1st-line	≥50%	39	25.6	4.0	7.4
Kano H. [8]	Retro	Pembro	All-comers	1st-line	≥50%	11	NA	7.3	NR
		Nivo/Pembro		2nd-line~	NA	53	NA	2.0	4.7

Abbreviations: Nivo, nivolumab; Pembro, pembrolizumab; SQC, squamous cell lung cancer; NA, not applicable; NR, not reached; PD-L1, programmed death-1; no. of pts, number of patients; PS, performance status; ORR, objective response rate; mPFS, median progression-free survival; mOS, median overall survival; ref., reference.

In three studies that focused on PD-L1 ≥ 50% in a first-line setting, the median PFS was 4.0 to 12.3 months and the median OS was greater than 7.4 months [8][12][13]. Aside from the high PD-L1 expression, the median PFS yielded 1.2 to 8.3 months, indicating the difference in efficacy of the PD-1 blockade according to the expression of PD-L1 in patients with an ECOG PS of 2 (**Table 2**). Regarding tumor shrinkage, the ORR of patients with PD-L1 ≥ 50% seemed to be favorable compared with those with any PD-L1 expression. PePS2 was a prospective phase 2 study that investigated the efficacy and safety of pembrolizumab according to PD-L1 expression in NSCLC patients with a PS of 2 [12]. Sixty patients were eligible for the analysis, and the ORR was 21% in first-line patients ($n = 24$) and 31% in subsequent-line patients ($n = 36$); the ORR was 11% in patients with PD-L1 < 1% ($n = 27$), 33% in those with PD-L1 of 1–49% ($n = 15$), and 47% in those

with PD-L1 ≥ 50% (*n* = 15). The median PFS and OS were 3.7 and 8.1 months, respectively, in patients with PD-L1 less than 1%, 8.3 and 12.6 months, respectively, in those with PD-L1 of 1–49%, and 12.6 and 14.6 months, respectively, in those with PD-L1 of 50% or greater. Adverse events were recognized in 28% of patients without early death or grade 5 treatment-associated toxicity. The authors concluded that pembrolizumab can be safely administered with comparable efficacy to patients with an ECOG PS of 0–1 with no increase in the occurrence of immune-related toxicities [12]. Patients with an ECOG PS of 2 represent 20–30% of the proportion that is diagnosed with advanced NSCLC and are sometimes candidates for carboplatin doublets, although their prognosis is dismal [14]. The therapeutic efficacy of PD-1 blockade monotherapy in second or further lines for NSCLC patients with an ECOG PS ≥ 2, an ORR of 3 to 11%, a median PFS of less than 2 months, and a median OS of 3.5–6.0 months is disappointing [15]. Considering the results of previous reports, pembrolizumab in a first-line setting serves as a suitable regimen for advanced NSCLC patients with an ECOG PS of 2 if their PD-L1 expression is ≥50%.

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