Original Article

Lazarus type response to immunotherapy in three patients with poor performance status and locally advanced NSCLC: a case series and literature review

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Background: Immune checkpoint inhibitors (ICIs) have become the standard treatment for patients with advanced non-small cell lung cancer (NSCLC). However, the safety and efficacy of ICIs in severe advanced NSCLC patients with poor performance status (PS) are still unclear.

Methods: In the current study, we report a retrospective case series of three critically ill NSCLC patients with poor PS treated with immunotherapy in our hospital, and discussed these cases with reference to the existing literature and guidelines.

Results: Before treatment, the Eastern Cooperative Oncology Group (ECOG) PS scores of all three patients were 4, while programmed cell death protein ligand-1 (PD-L1) was strongly expressed (over 50%). After initiating anti-programmed cell death 1 (PD-1)/PD-L1 agents, the PS score of the three patients improved rapidly to 0–1 in a short time. A Lazarus type response was observed in all patients. There were no grade 3–4 immune-related adverse events (irAEs) in any of the patients, and only one patient developed rash (grade 2 irAE) and hypothyroidism (grade 2 irAE). The best response across all three patients was partial response (PR). As of the latest follow-up date on June 10, 2020, two patients are still alive, with the other having died on January 14, 2020, whose progression-free survival (PFS) and overall survival (OS) were 11 and 16 months, respectively.

Conclusions: Immunotherapy is still an effective and low-toxicity option for severe advanced NSCLC patients with poor PS. Lazarus type response may occur, especially in patients whose PD-L1 is strongly expressed (≥50%). However, a greater amount of real-world data or randomized clinical trials are needed in this setting.

Keywords: Non-small cell lung cancer (NSCLC); poor performance status (poor PS); immunotherapy; programmed cell death 1 inhibitor (PD-1 inhibitor); programmed cell death protein ligand-1 (PD-L1)

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Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide. Most patients with this lung cancer present with advanced, unresectable disease on diagnosis (1,2), and nearly 34% of patients have a poor performance status (PS) (PS: 2–4) (3). Due to the lack of effective treatments, most PS ≥3 patients die within 2–4 months from the date of diagnosis (4). However, studies have reported that targeted

Table 1 Patients and tumor characteristics

Number of case series	Case 1	Case 2	Case 3
Age, years	63	70	74
Sex	Male	Male	Female
Pathology	SCC	ADC	SCC
Stage	IIIc	IVb	IIIb
ECOG PS (baseline)	4	4	4
PD-L1 expression	80%	50%	80%
TMB (muts/Mb)	4.6	13.71	–
Drug	Pembrolizumab	Nivolumab	Nivolumab
Time to symptom relief (days)	1	1	3
Best response	PR	PR	PR
Maximum tumor shrinkage	–60%	–36%	–68%

ECOG PS, Eastern Cooperative Oncology Group Performance Status; ADC, adenoma carcinoma; SCC, squamous cell carcinoma; PD-L1, programmed death-ligand 1; TMB, tumor mutation burden; PR, partial response.

therapy is efficacious in patients with poor PS, and even a Lazarus response has been observed in those patients with oncogenic drivers (5,6). In modern medical parlance, the Lazarus-type response refers to an event in which a person miraculous recuperate from near death. Just as in the new testament of the Bible, Jesus raised Lazarus of Bethany from the dead (7).

Immunotherapy with immune checkpoint inhibitors (ICIs), including those targeting programmed cell death 1 (PD-1), or programmed cell death protein ligand-1 (PD-L1) has revolutionized the treatment of advanced non-small cell lung cancer (NSCLC) in patients without oncogenic drivers (8). Four phase III randomized trials have shown that ICIs such as nivolumab, atezolizumab and pembrolizumab significantly improve overall survival (OS) and progression-free survival (PFS) when compared with standard chemotherapy (9-11). PD-L1 expression in tumor cells and tumor mutation burden (TMB) has been the main predictive biomarker for ICIs efficacy in NSCLC (11,12). Pembrolizumab monotherapy regimens reported an incidence of grade III–IV treatment-related adverse events (TRAEs) of 15–30%, while nivolumab monotherapy revealed a grade III–IV TRAEs incidence of 10% (13,14). The most frequent potential immune related adverse events (irAEs) of anti-PD-1 therapies involved rash, pruritus, colitis, diarrhea, hyperthyroidism, hypothyroidism, lymphopenia, hepatitis, *et al.* These drug-related adverse events are well tolerated and manageable in most patients with Eastern Cooperative Oncology Group (ECOG) PS 0–1 (15).

Patients with PS ≥2 are usually excluded or underrepresented in clinical studies, and thus there is little data available on the safety and efficacy of immunotherapy in this population (16,17). In the four published prospective trials that have included PS ≥2 patients, the incidence of grade 3–4 irAEs was similar, while OS was worse compared with the overall population (18-21). For NSCLC patients who are critically ill or have PS 3–4, there are currently no dedicated ongoing trials, and few real-world case reports exist on the role of ICIs in patients with PS 3–4. Roesel *et al.* reported two cases of patients with lung sarcomatoid carcinoma and high PD-L1 expression, one of which presented with progressive dyspnea accompanied by hypoxemic respiratory insufficiency. Immunotherapy with nivolumab was initiated, which resulted in fast and extensive tumour regression and relief of tumour symptoms (22). The safety and efficacy of ICIs when administered to patients who are critically ill or have very poor PS (3,4) remain controversial and largely unexplored. In this study, we describe a group of three severe (locally) advanced NSCLC patients with PD-L1 expression over 50% successfully treated with anti-PD-1 immune checkpoint monoclonal antibodies, and showed rapid symptom relief and lesion response (*Table 1*).

We present the following article in accordance with the AME Case Series Checklist (available at http://dx.doi.org/10.21037/apm-20-2279).

Methods

Study design

We reviewed clinical data retrospectively from three patients with poor PS and (locally) advanced NSCLC who received immunotherapy in Daping hospital (Chongqing, China). Data collected from the patient's electronic medical record included: age, sex, ECOG PS, oxygenation index (OI), tumor histology, and drugs for PD-1/PD-L1 blockade. Data regarding PD-L1 expression, and tumor mutation burden were analyzed. Treatment decision was made according to the National Comprehensive Cancer Network (NCCN) Guideline and local guidelines for NSCLC. The patients described herein provided written informed consent. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethical board of the Daping Hospital, Army Medical University [No.: 2020(163)].

Statistical analysis

Descriptive statistics were used to summarize patients and disease characteristics. The primary outcome was time-to-response, efficiency, rate of ECOG PS recovery, and safety. Response to treatment was determined by using Response Evaluation Criteria in Solid Tumor (RECIST), version 1.1. PFS was defined as the interval from the date of first pembrolizumab administration to the date of radiological/clinical progression or death due to any cause, whichever occurred first, or to the date of last follow-up visit for patients alive without disease progression. OS was defined as the interval from the date of first pembrolizumab administration to the date of death or to the date of last follow-up for alive patients.

Results

Case 1

Patient 1 was a 63-year-old male smoker, who presented with severe dyspnea, reversal fever, and hemoptysis. Bronchoscopy revealed that the squamous cell carcinoma had invaded the tracheal carina (*Figure 1A*,*B*). The chest computed tomography (CT) scan showed lesions in the left lung with partial atelectasis (*Figure 1C*), and thus the clinical stage was determined to be IIIc (cT4N3M0, American Joint Committee on Cancer, 8th edition). Due to severe pulmonary infection (white blood cell 26.52×10^9/L neutrophil 92.6%) and respiratory failure with an OI of 180, the patient received oxygen therapy, antibiotics (imipenem, 1 g, q8h, ivgtt), and hemostatic drugs. After 1 week, the patient developed severe hemoptysis (100–150 mL/day) and respiratory distress (OI 120), although the fever was controlled. Chest X-ray revealed atelectasis of the left lung (*Figure 1D*). Tissues were examined for the expression of PD-L1 and TMB and were collected at the time of the diagnosis. However, the patient was weakened with a PS of 4 before the start of treatment. Due to strong PD-L1 expression levels (80%, 22C3 antibody) (*Figure 1E*), the patient received treatment with pembrolizumab (200 mg) every 3 weeks beginning March 12, 2019. One day after the initiation of pembrolizumab, dyspnea was relieved. The OI was improved to 310 two days later. The left lung atelectasis was partially relieved, and a PS score of 4 improved to 1 within the span of less than 1 week (*Figure 1F*). After two cycles of pembrolizumab, a rapid tumor partial response was obtained. The left lung atelectasis was completely relieved without the need of intervention therapy (*Figure 1G*). Bronchoscopy revealed that there were no neoplasms in the mainstem bronchus (*Figure 1H*). Meanwhile, the CT scan showed over 60% reduction in the size of left hilar mass (*Figure 1I*). Treatment-related side-effects were not observed during the treatment. After 18 cycles of pembrolizumab and when the lesion was stable, radiotherapy was successfully finished. The patient has continued with treatment of pembrolizumab, and his improvements on clinical and radiographic examination have continued as of the latest follow-up (*Figure 1J*).

Case 2

A 70-year-old man was diagnosed with stage IV lung adenocarcinoma of the right lower lobe associated with left frontal lobe, right pleural, and multiple bone metastasis (*Figure 2A*,*B*,*C*). After one cycle of cytotoxic drug regimens (carboplatin plus pemetrexed), pleural effusion was increased and encapsulated, which made it difficult to drain (*Figure 2D*,*E*). More seriously, the patient developed arrhythmias (atrial fibrillation and tachycardia) related to chemotherapy. Clinical symptoms such as pain, dyspnea, and cough deteriorated with time. The patient was forced to sleep on the right side, and the OI was only 150. Prior to the second line of therapy, the PS score of the patient was 4. Owing to the high tissue TMB (13.71 muts/Mb) and strong PD-L1 expression (50%, 28–8 antibody) of the

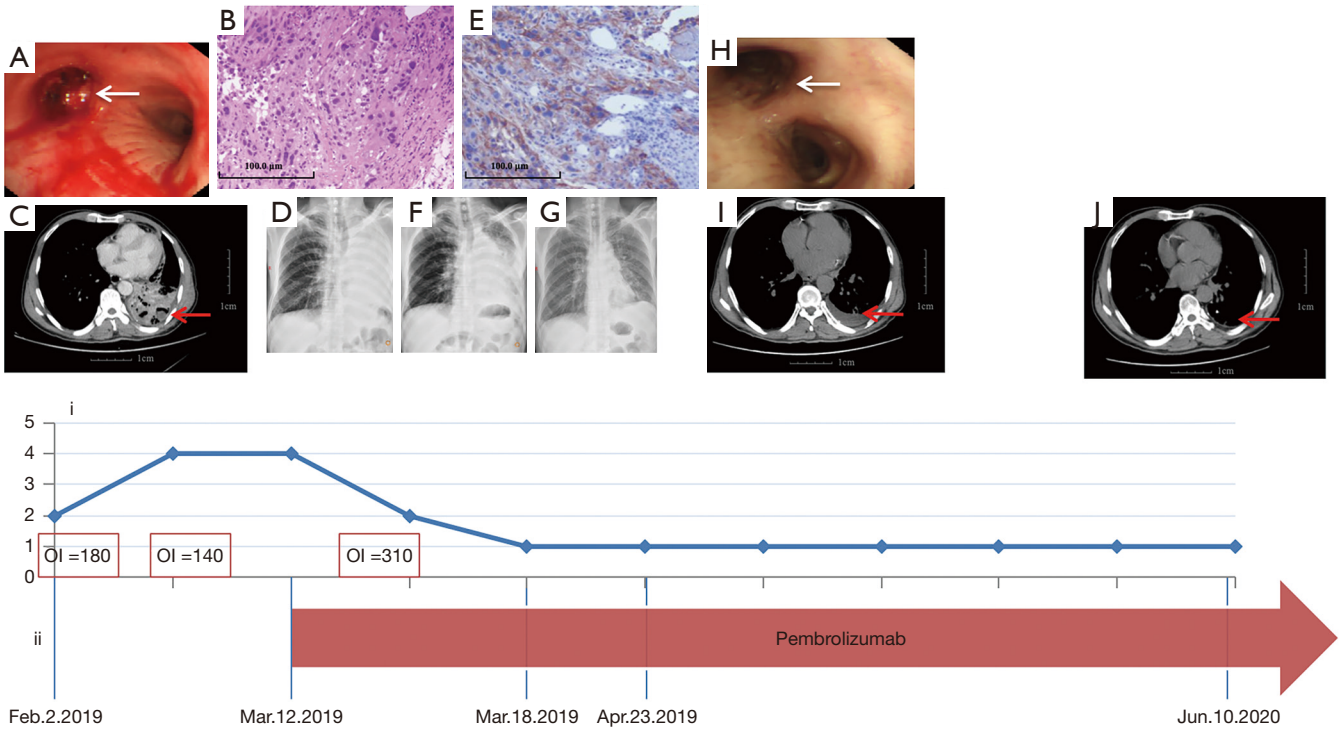

Figure 1 Graphic summary of patient 1. (A) A neoplasm (white arrow) obstructing the left mainstem bronchus was found by bronchoscopy (baseline). (B) Hematoxylin-eosin (HE) staining of tissue sample from patient 1 revealed squamous cell carcinoma of the lung. (C) CT scans revealed lesions (red arrow) in the left lung with partial atelectasis. (D) Chest X-ray revealed atelectasis of the left lung before starting pembrolizumab. (E) Programmed death-ligand 1 (PD-L1) was found positive (80%) using immunohistochemistry (IHC, 22C3, Dako; ×200). (F) After initiating pembrolizumab treatment, the left lung atelectasis was partially relieved within the span of less than 1 week. (G) Three weeks later, the left lung atelectasis was completely relieved. (H) No neoplasm (white arrow) was found by bronchoscopy after four cycles of pembrolizumab. (I) A computed tomography (CT) scan showed about 60% reduction in the size of the left hilar mass (red arrow) after two cycles of pembrolizumab. (J) The latest findings of CT scans showed partial response of the primary tumor (red arrow). i, performance status (PS) evolution over time; ii, timeline of therapies OI improved rapidly after initiating pembrolizumab. OI, oxygenation index.

tumor (*Figure 2F*), the patient was started on a regimen of nivolumab (140 mg) every 2 weeks beginning August 30, 2018. On that day of intravenous infusion of nivolumab, the patient could sleep his the left side and dyspnea was relieved. On day 3 after administration of nivolumab, his PS score rapidly improved to 1, and the OI was increased to 310. Reexamination with X-ray showed that pleural effusion had reduced (*Figure 2G,H*). After two cycles of nivolumab, although the lesions were stable on CT scan, clinical symptoms of the patient were obviously relieved. After 3 months (6 cycles of ICIs), a marked response was observed with an apparent reduction of the primary tumor, brain metastasis, and pleural effusion (*Figure 2I,J*). ICI-related rash (grade 2 irAE) and hypothyroidism (grade 2 irAE) occurred. Betamethasone ointment and thyroxine tablets were used to handle with irAEs. Maintenance ICIs have continued as of the time of writing, (June 14, 2020), and the lesions are still slowly shrinking (*Figure 2K*).

Case 3

The patient was a 75-year-old female who complained of severe dyspnea with an OI of 146. As for her breathing state, oxygen saturation (SpO_2) was around 90% under the conditions of an oxygen flow rate of 10 L/min with a reservoir bag mask. A Chest CT scan showed a huge mass on the right upper lobe which had invaded the mediastinum (*Figure 3A*). Bronchoscopy showed a neoplasm completely obstructing the right mainstem bronchus. Finally, the patient was diagnosed with lung squamous cell carcinoma

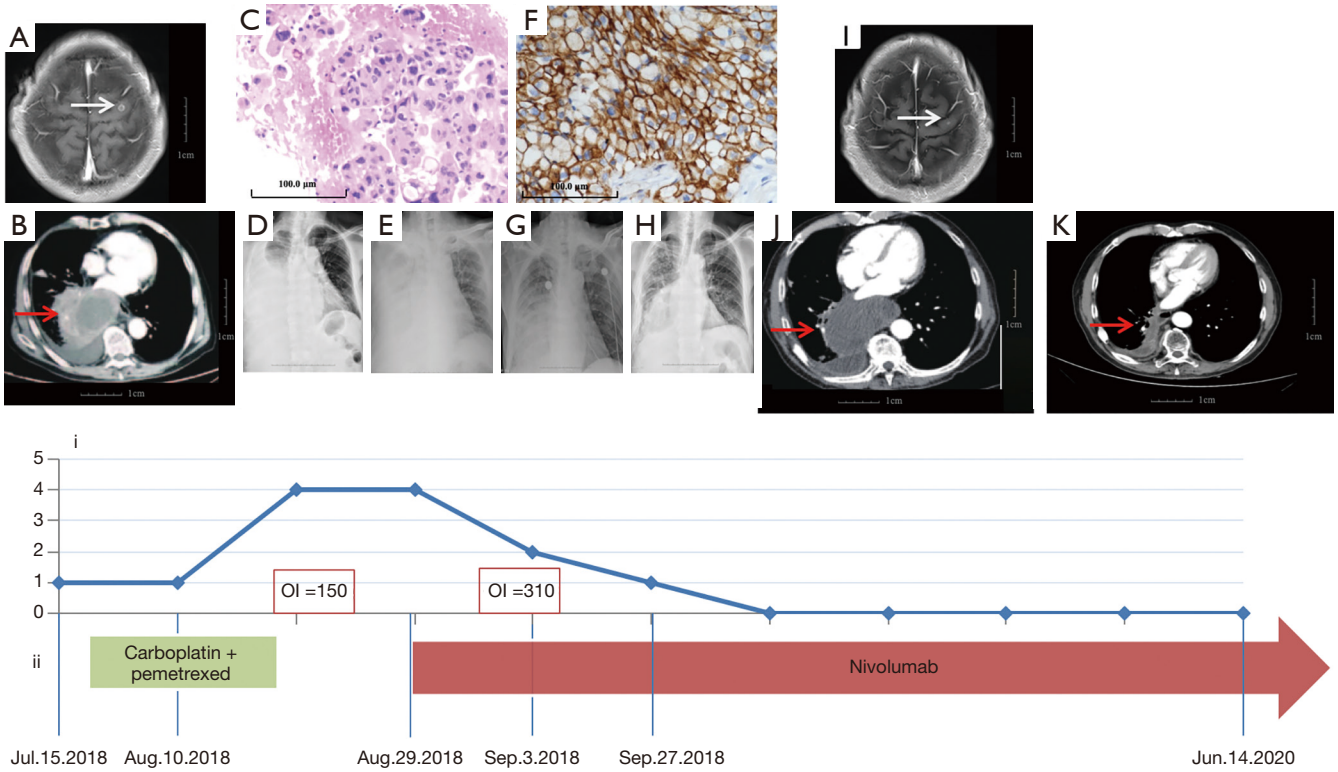

Figure 2 Graphic summary of patient 2. (A) Magnetic resonance imaging (MRI) of the brain revealed a left frontal lobe (white arrow) metastasis. (B) CT scans showed an extensive mass (red arrow) in the right lung. (C) HE staining of tissue sample from patient 2 revealed adenocarcinoma of the lung. (D,E) Chest X-ray revealed that pleural effusion was increased and encapsulated after chemotherapy. (F) PD-L1 was found positive (50%) using immunohistochemistry (IHC, 28-8, Dako; ×200). (G,H) Pleural effusion was reduced after initiating nivolumab. (I,J) The size of the lesions in the right lung (red arrow) and brain (white arrow) were reduced after six cycles of nivolumab. (K) The latest findings of computed tomography (CT) scans showed partial response of the primary tumor (red arrow). i, performance status (PS) evolution over time; ii, timeline of therapies. OI improved rapidly after initiating pembrolizumab. OI, oxygenation index.

(cT3N2M0, stage IIIb) (*Figure 3B*), and PD-L1 expression was 80% using the 28-8 antibody (*Figure 3C*). Prior to the initiation of treatment, the PS score of the patient was 4. The patient started to receive nivolumab (140 mg) every 2 weeks beginning September 14, 2018. After 3 days of treatment, dyspnea was relieved and OI was improved to 320. Although her PS score gradually improved to 1, the tumor size was only reduced by about 7% on CT imaging after three courses of ICIs (*Figure 3D*). The patient then began to receive six courses of nivolumab combined with chemotherapy (paclitaxel plus platinum), and finished lung radiotherapy. Reexamination with a CT scan showed partial response of the lung lesions (*Figure 3E*). The patient was able to continue maintenance therapy of nivolumab without any other adverse events. However, disease progression occurred on August 14, 2019. After this time, the patient only received symptomatic treatment due to financial constraints, and the patient died on January 14, 2020. The OS of the patient was 16 months.

Discussion

The NCCN Guideline recommends only the best supportive care for patients with advanced NSCLC and poor PS (≥2) (23). Palliative care is considered an ineffective antitumor method, and thus patients treated with this approach have a very poor prognosis (4). Although targeted therapy based on molecular types has been reported to have successfully treated critically ill NSCLC patients, effective treatment strategies for patients without oncogenic drivers still need to be explored (24,25). Immunotherapy, including use of PD-1/PD-L1 inhibitors, has significantly

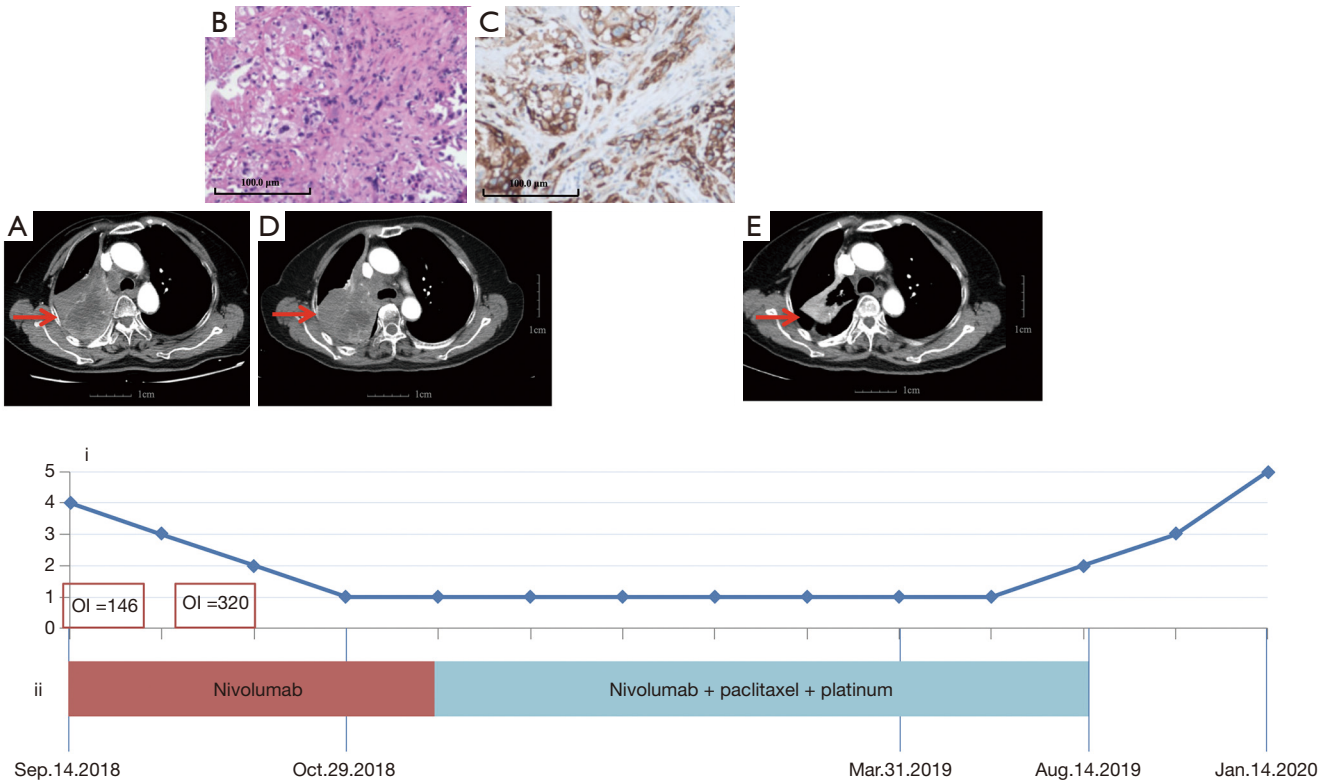

Figure 3 Graphic summary of patient 3. (A) A computed tomography (CT) scan showed a large mass (red arrow) in the right lung (baseline). (B) HE staining of tissue sample from patient 3 revealed squamous cell carcinoma of the lung. (C) PD-L1 was found positive (80%) using immunohistochemistry (IHC, 28-8, Dako; ×200). (D) The tumor size (red arrow) was only slightly reduced after two cycles of nivolumab. (E) CT scans showed partial response of the lung lesions (red arrow) after administering six cycles of nivolumab + chemotherapy. i, performance status (PS) evolution over time; ii, timeline of therapies. OI improved rapidly after initiating pembrolizumab. OI, oxygenation index.

improved the survival of advanced NSCLC patients without oncogenic drivers. The potential efficacy and favorable toxicity profile of ICIs make them an attractive option for NSCLC patients who are critically ill or who have poor PS. Although the U.S. Food and Drug Administration (FDA) authorization for using ICIs does not restrict the use of these drugs to PS 0–1 patients, the evidence for making treatment decisions about using ICIs in PS ≥2 patients are scarce and are derived mostly from heterogeneous meta-analyses or real-world studies (26,27). Therefore, there is still a need to apply rigorous clinical practice, with the aim of providing reliable data on the safety and effectiveness of immunotherapy in this special group.

We here report the cases of three (locally) advanced NSCLC patients presenting with critically ill or poor general condition (PS 4), who demonstrated rapid clinical improvement and a remarkable objective response from PD-1 blockade. The type of response has been dubbed the "Lazarus type" response, as it is similar to the miraculous resurrection of Lazarus in the New Testament of the Bible (5). The PS score of the three patients improved rapidly to 0–1 in a short time, which provided opportunities for other treatments, such as chemotherapy or radiotherapy. For all patients, next-generation sequencing (NGS) of the biopsied tissue lacked a targetable driver mutation, and intense PD-L1 expression was examined by immunohistochemistry of pretherapeutic biopsies. The first two cases achieved partial response (PR) and received prolonged benefits from single-agent immunotherapy, while the third case 3 obtained PR from combined use of chemotherapy after improvement of PS. At the time of writing, the first two patients are still alive, while the other patient died on January 14, 2020. This patient's PFS and OS were 11 months and 16 months, respectively. The safety of ICIs was acceptable for all three patients, and there were no grade 3–4 irAEs. Only one patient experienced rash

(grade 2 irAE) and hypothyroidism (grade 2 irAE) during immunotherapy.

Previous studies have confirmed that immunotherapy is safe and effective in NSCLC patients with a PS of 2 (18). The PePS2 trial revealed pembrolizumab to be safe in patients with a PS of 2. Similarly, the CheckMate 171 (19) and CheckMate 153 (20) trials with nivolumab showed no difference in the incidence of irAEs between the PS 2 and PS 0–1 populations (7% *vs.* 12% and 9% *vs.* 6%, respectively). However, the OS of PS 2 patients were shown to be worse compared with the overall population (5.2 *vs.* 9.9 months and 3.9 *vs.* 9.1 months, respectively). A retrospective analysis of the use of ICIs in patients with various cancers (including colorectal, small bowel, gastric, biliary tract, pancreatic, and endometrial cancers) with a PS of 2–3 (patients with a PS of 3 accounted for 26% of the cohort) showed an overall manageable safety profile (28). For NSCLC patients with a PS of 3–4, immunotherapy was still found to be safe, although only a few cases have been reported (29,30). In short, ICIs are generally well tolerated, and the side effects are manageable in most cases (15). In clinical practice, few patients with poor PS receive ICIs as first-line therapy. Almost invariably, the poor PS is an independent factor for poor outcomes (31,32). Of note, patients with poor PS due to the disease burden itself were found to have a worse outcome compared to those with a poor PS due to comorbidities (33). For one, patients with a PS ≥2 show heterogeneity, which included old age, cachexia, organ dysfunction, systemic inflammation, comorbidity, etc., all of which may lead to shorter survival time (33). Moreover, the efficacy of ICIs may be weakened due to antibiotics and the dependency on supportive corticosteroids (34,35). Furthermore, a poor condition may diminish immune cell activity and thus reduce ICI efficacy (36).

Although there are no dedicated ongoing trials for PS 3–4 patients, Lazarus type responses to ICIs have still been observed in those patients with strong PD-L1 expression (≥50%), as was the case in the three patients in our report (29). Even in critically ill patients with mechanical ventilation, rapid and long-lasting responses have also been observed (30). Therefore, when it comes to the special population of patients with poor PS, the use of anti-PD-1/PD-L1 agents may be justified by virtue of their favorable toxicity profile and long-term efficacy. Thus, the identification of biomarkers is urgently needed to guide the treatment of ICIs.

Currently, the PD-L1 expression levels of tumors may offer a selection criterion for NSCLC patients to predict their immunotherapy response. The population with intense PD-L1 expression (≥50%) accounts for 29.8% of NSCLC cases (37). The Keynote 024 trial (38) has confirmed that pembrolizumab monotherapy is superior to system chemotherapy in the treatment of newly diagnosed advanced NSCLC with PD-L1 expression over 50%. The median PFS (mPFS) of the pembrolizumab treatment group was significantly longer than that of chemotherapy group (10.3 *vs.* 6.0 months), and a significant improvement in median OS (mOS) was also achieved in the ICI group (30.0 *vs.* 14.2 months). Meanwhile, the CheckMate 026 trial (39) revealed that nivolumab was better compared with cytotoxic chemotherapy for patients with a high TMB (>243 missense mutation/sample) (mPFS 9.7 *vs.* 5.8 months). It is worth noting that the objective response rate (ORR) of patients with PD-L1 ≥50% in the high-TMB subgroup was as high as 75%.

As expected, in the presence of a high PD-L1 expression and/or high tumor mutation burden, the PFS of ICI treatment was also longer in NSCLC patients with poor PS. A single-arm phase II trial of ECOG PS 2 NSCLC patients using pembrolizumab monotherapy, the PePS 2 trial, confirmed that the higher PD-L1 expression was, the more clinical benefits there were (18). The ORR for PD-L1 <1% (n=27), PD-L1 1–49% (n=15), and PD-L1 ≥50% (n=15) was 19%, 33% and 47%, respectively, while the mPFS was 3.3 months, 6.8 months, and 8.5 months, respectively. In addition, the CheckMate 817 trial, which included a cohort of special populations with advanced NSCLC (ECOG PS 2 or ECOG PS 0–1 with asymptomatic untreated brain metastases, renal or hepatic dysfunction, or human immunodeficiency virus infection), showed that nivolumab plus ipilimumab could prolong the mPFS of the PS 2 subgroup with high TMB (≥10 muts/Mb) compared to those with low-TMB (<10 muts/Mb) (8.3 *vs.* 2.8 months) (21).

Therefore, PD-L1 expression combined with TMB may be synergistic predictive biomarker for response to anti-PD-1/PD-L1 immunotherapy. In our report, all three patients presented strong PD-L1 expressions over 50%, and one of them had high TMB. It is suggested that ICI treatment should be considered for patients with severe lung cancer or/and poor PS score when strong PD-L1 expression or/and high-TMB are found in this special group. In clinical practice, immunotherapy is one of the most expensive anticancer treatments; especially if there is no sufficient experimental evidence in advanced NSCLC patients with poor PS, this approach of gamble oncology may incur severe financial hardship on patients, families,

and society (40). Thus, relevant biomarkers are urgently needed to identify those patients with severe lung cancer who may derive potential benefits from immunotherapy.

However, some patients with rapid PS deterioration may miss the chance to receive ICIs. For first-line treatment, the median response time of monotherapy in the general population was found to be 2 months (41). Meanwhile, in patients with poor PS, the average response time for ICI treatment was found to be 3.1 months (28). In our report, the three patients treated with immunotherapy all demonstrated a rapid improvement of the symptoms and PS score, and two of them showed radiographic response in a short time. It is speculated that the onset time of immunotherapy may be positively correlated with the expression level of PD-L1 and TMB. However, more relevant studies are needed to support this view.

Conclusions

We described three critically ill or PS 4 (locally) advanced NSCLC patients with PD-L1 ≥50% who were successfully treated with anti-PD-1/PD-L1–based therapy. A Lazarus type response was observed in all patients. Both clinical symptoms and physical conditions showed rapid improvement. Although it is limited by its retrospective nature and small sample size, our report gives support to the safety and activity of ICI administration. The case series highlights that metastatic NSCLC patients who are critically ill or who have a poor PS score, immunotherapy, as opposed to best supportive care, is an effective and low-toxicity option. Those patients with high PD-L1 expression (≥50%) and/or high TMB may be best treated with salvage immunotherapy. More prospective studies are needed to identify reliable predictive biomarkers of efficacy and toxicity in advanced NSCLC patients with critical illness and/or a poor PS score.

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Footnote

Reporting Checklist: The authors have completed the AME Case Series Checklist. Available at http://dx.doi.org/10.21037/apm-20-2279

Data Sharing Statement: Available at http://dx.doi.org/10.21037/apm-20-2279

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-2279). The authors have no conflicts of interest to declare.

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. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved ethics board of Daping Hospital, Army Medical University [No.: (2020)163]. Informed consent was obtained from the patient described in this case report.

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