

“Lazarus response” of nivolumab in a frail patient with non-small-cell lung cancer

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Keywords

Lazarus response, nivolumab, non-small-cell lung cancer, non-squamous non-small-cell lung cancer, poor performance status.

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Abstract

Lung cancer has aggressive behaviour which often progresses rapidly with disseminated disease and leads to poor performance status (PS) in patients. Because cytotoxic chemotherapy is not recommended under these conditions, there are currently no alternative therapeutic options other than providing supportive care. Immune checkpoint inhibitors have been developed, but their efficacy and tolerability have not been fully investigated in patients with poor PS.

A 72-year-old male patient with lung adenocarcinoma harbouring no EGFR-sensitizing mutation or ALK translocation was receiving second-line chemotherapy with S-1 monotherapy when he complained of worsening dyspnea. Chest computed tomography (CT) demonstrated disease progression at the primary site that was accompanied by bilateral pulmonary lymphangitic carcinomatosis, which was the cause for respiratory failure. Oxygen administration at 10 L/min was required due to the rapid progression of the tumour that resulted in poor PS. A retrospective study was conducted to assess the upregulation of programmed death ligand 1 (PD-L1) using anti-PD-L1 22C3 mouse monoclonal primary antibody and found that the PD-L1 expression was 50–60% (i.e. tumour proportion score $\geq 50\%$). Since cytotoxic chemotherapy could not be considered due to a poor PS of 4, nivolumab was cautiously administered. After the introduction of nivolumab, ground glass opacities, and consolidations on chest CT temporarily deteriorated on day 4 without any other clinical signs and symptoms. The reevaluation on day 10 demonstrated significant improvements on chest X-ray. Then the patient was subsequently diagnosed with pseudoprogression. Thereafter, both the respiratory status and the PS improved gradually. The PS recovered to baseline conditions with oxygen administration at 1 L/min after four cycles of treatment. The patient currently remains at a PS of 1 and is progression-free for eight months after the introduction of nivolumab.

Introduction

Lung cancer has aggressive behaviour which often progresses rapidly with disseminated disease and leads to poor performance status (PS) in patients. Because cytotoxic chemotherapy is not recommended under such conditions, there are currently no alternative therapeutic options other than providing supportive care. The efficacy and tolerability of immune checkpoint inhibitors (ICIs) in poor PS

patients have not been fully investigated but could be an alternative therapeutic option for certain cases.

Case Report

A 72-year-old male patient with lung adenocarcinoma harbouring no EGFR-sensitizing mutation or ALK translocation, who had liver metastases (clinical stage was cT3N3M1c

(HEP), stage IVB), was treated with a combination of carboplatin and pemetrexed for six cycles, followed by pemetrexed maintenance therapy for seven cycles. The primary site progressed and he started receiving second-line chemotherapy with S-1 monotherapy [1] for three months, when he complained of worsening dyspnea. Chest computed tomography (CT) demonstrated disease progression at the primary site (Fig. 1A) that was accompanied by bilateral pulmonary lymphangitic carcinomatosis (Fig. 1B), which was the cause for respiratory failure. The tumour quickly progressed and caused his condition to rapidly deteriorate to a PS of 4 at which point oxygen was administered at 10 L/min. A study to assess the upregulation of programmed death ligand 1 (PD-L1) in the tissue obtained at initial diagnosis was conducted retrospectively using anti-PD-L1 22C3 mouse monoclonal primary antibody. The PD-L1 expression was found to be 50–60% (i.e. the tumour proportion score (TPS) was $\geq 50\%$). Since cytotoxic chemotherapy could not be considered due to a PS of 4, nivolumab was cautiously administered. After the initial administration, ground glass opacities (GGOs) and consolidations on chest CT temporarily deteriorated on day 4 (Fig. 1C,D) without any other clinical signs and symptoms suggestive of disease progression. The reevaluation on day 10 demonstrated significant improvements on chest X-ray. Then the patient was subsequently diagnosed with pseudoprogression. Thereafter, both the respiratory status and the PS improved gradually. The PS recovered to baseline conditions (PS 1) with oxygen administration at 1 L/min after four cycles of treatment, two months after nivolumab introduction. Shrinkage of the primary site (Fig. 2A) and improvements in GGOs and consolidations

(Fig. 2A,B) were observed after six cycles of treatment, three months after nivolumab introduction.

The remarkable response to nivolumab in a poor PS patient resembles the “Lazarus response” observed in patients harbouring EGFR-sensitizing mutations with PS 3–4 who were treated with gefitinib.

The patient currently remains at a PS of 1 and is progression-free for 8 months after the administration of nivolumab.

Discussion

The development and introduction of ICIs into clinics have widened treatment options for patients with non-small-cell lung cancer (NSCLC). Several phase 3 clinical trials have demonstrated marked efficacy of ICIs in the treatment of NSCLC not only in second-line [2] but also in first-line treatments if the TPS is $\geq 50\%$ [3]. Although the proportion of patients who respond to ICIs is not satisfactory, durable response has been demonstrated in patients who have attained stable disease (SD) or greater. The superiority of nivolumab over docetaxel as second-line treatment has been established in both non-squamous NSCLC (CheckMate057) [2] and squamous cell carcinoma (CheckMate017) [4].

Although there are currently no effective biomarkers to predict the effectiveness of ICIs, the expression of PD-L1 has been reported to correlate with progression-free survival (PFS) and overall survival (OS) [5]. The median OS of non-squamous NSCLC patients treated with nivolumab was significantly greater than docetaxel in a subgroup with

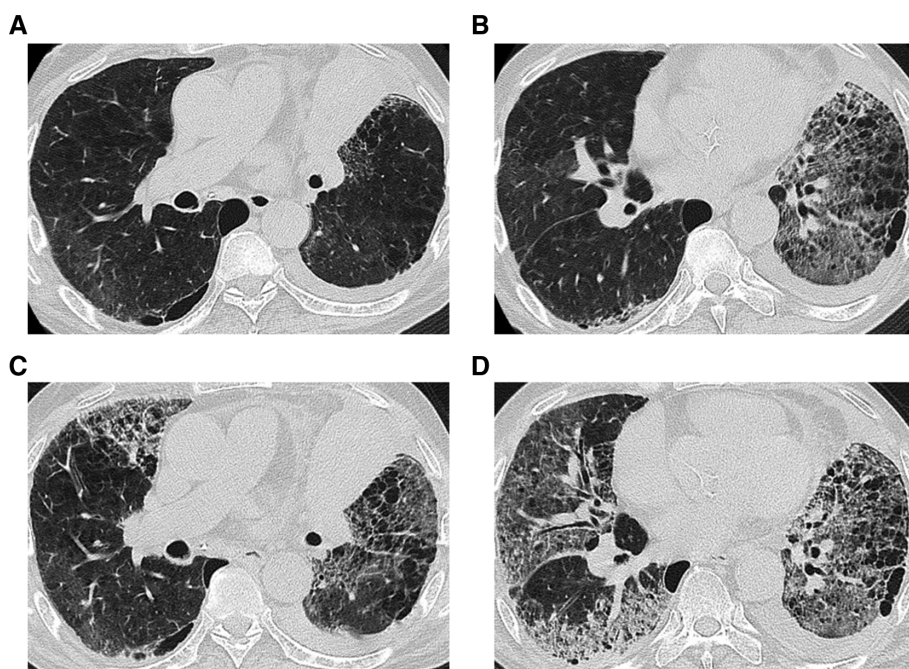
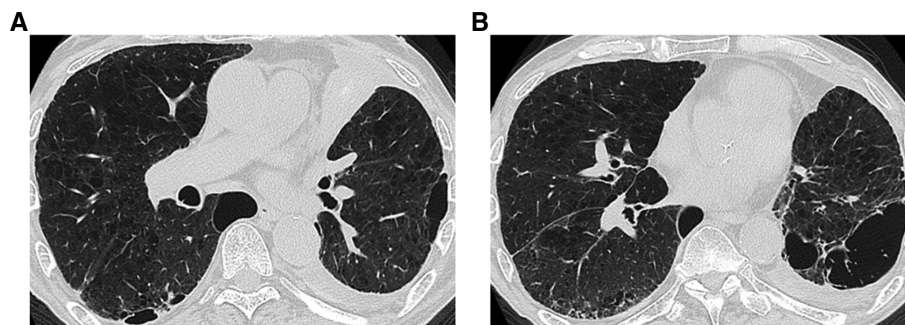


Figure 1. Chest computed tomography (CT) prior to the administration of nivolumab showed a consolidated mass at the primary site in the lingula (S5b) of the left upper lobe (A) accompanied by predominating left-side diffuse ground glass opacities (GGOs), interlobular septal thickening, prominent bronchovascular bundles, and pleural effusion (A, B), which suggested pulmonary lymphangitic carcinomatosis. Chest CT four days after the administration of nivolumab showed widespread deterioration of GGOs with some consolidation (C, D) and an increase in the size of the primary site (C).

Figure 2. Chest computed tomography (CT) three months after the administration of nivolumab showed significant response; shrinkage of the primary site (A) was observed, and both ground glass opacities and consolidations had almost disappeared (A, B), which demonstrated improvements in pulmonary lymphangitic carcinomatosis.



PD-L1 expression of 1% or greater. The hazard ratio (HR) for the OS was 0.59 (95% confidence interval (CI); 0.43–0.81); however, the HR was 0.90 (95% CI; 0.66–1.24) for a subgroup with PD-L1 expression of less than 1% [2,5]. Furthermore, the time to first disease-related deterioration in the average symptom burden index (ASBI)—Lung Cancer Symptom Scale based on 6 symptoms (anorexia, fatigue, cough, dyspnea, hemoptysis, and pain) was significantly longer in nivolumab group compared to docetaxel group, the HR was 0.65 (95% CI; 0.49–0.85) [6].

For non-squamous NSCLC, the Kaplan-Meier curve (OS analysis) of nivolumab temporarily drops below docetaxel during the first six months [2], which suggests that there may be a sub-population who may not benefit from nivolumab treatment. Therefore, a method to detect non-responders to nivolumab at an early time point is crucial.

The median duration of response in non-squamous NSCLC patients treated with nivolumab was 17.2 months (95% CI; 8.4-not estimated (NE)) compared with 5.6 months (95% CI; 4.4–6.9) for those treated with docetaxel [7]. This suggests that the effect of nivolumab tends to last longer once the patient achieves SD or greater [2,7]. The subgroup analysis of CheckMate057 by best overall response [5] revealed that the median survival time (MST) for patients administered with nivolumab who resulted in complete response (CR) or partial response (PR) was not reached (NR, 95% CI; 25.5 months-NR), and the MST for those who achieved SD was 19.9 months (95% CI; 14.7–24.4). In contrast, the MST for patients administered with docetaxel was 19.2 months (95% CI; 14.5–23.3) and 11.9 months (95% CI; 10.6–13.9) for those who achieved CR or PR and SD, respectively. These results suggest that durable response could be expected in patients who achieve SD or greater.

Considering the above mentioned superiority of nivolumab over docetaxel, it would be better to choose ICIs as second-line treatment. Administering ICIs at an early point in time could be more effective in terms of the cancer-immunity cycle, since ICIs are considered to possess stronger power when the host immunity is preserved.

However, appropriate evaluations at appropriate time points are critical since the progressive disease (PD) rate of patients administered with nivolumab is relatively high [2]. The time to response for nivolumab and docetaxel was 2.1 months (95% CI; 1.2–8.6) and 2.6 months (95% CI; 1.4–6.3), respectively, in CheckMate057 [2]. Therefore, evaluations by CT to exclude PD cases should be conducted within two months after the introduction of nivolumab treatment and should continue at regular intervals. Furthermore, frequent assessment by chest X-ray or CT is indispensable in cases in which the PS remains stable at the time of PD, in order to discriminate pseudoprogression from PD.

Disclosure Statements

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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