Effective symptom and disease control with a PD-1 inhibitor in lung adenocarcinoma

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Presentation

A 72-year-old male who was a chronic heavy smoker (about 20 cigarettes/day for 15 years) presented with haemoptysis and weight loss in September 2015. PET-CT revealed a hypermetabolic mass in the left upper lobe of the lung abutting the left lateral border of the intrathoracic descending aorta, along with intrapulmonary, mediastinal and hilar lymph node as well as bone and brain metastases. Biopsy performed during bronchoscopy confirmed adenocarcinoma of lung primary with immunohistochemical analyses showing TTF-1 positivity. Tests for *EGFR*, *ALK* and *ROS-1* were negative.

Management and response

The initial management plan was to administer four cycles of first-line pemetrexed/carboplatin chemotherapy followed by whole-brain irradiation during the maintenance phase of pemetrexed monotherapy. However, the planned doublet chemotherapy was suspended for a mild chest infection, and the patient proceeded with whole-brain radiotherapy.

The patient received pemetrexed/carboplatin chemotherapy upon completion of radiotherapy in November 2015. He reported brain-related symptoms of generalized weakness and lethargy after the first cycle, with brain CT showing an increase in white matter oedema. The patient's condition worsened and he became wheelchair bound, making him unfit for further chemotherapy.

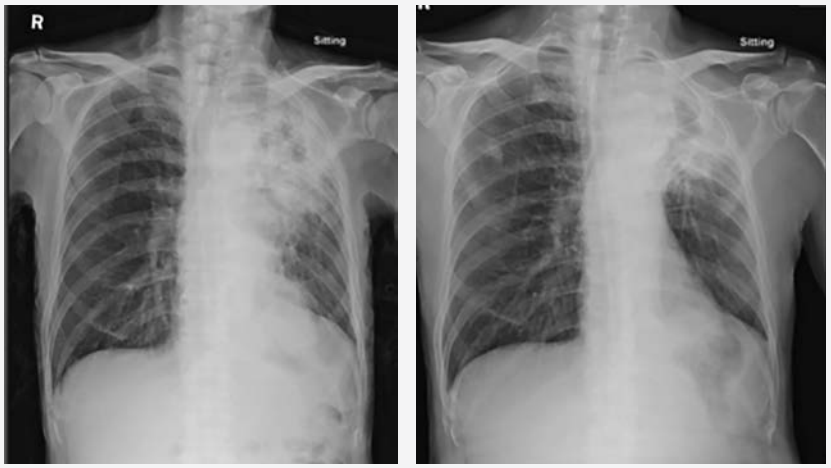
As active treatment was considered necessary, the patient was started on nivolumab monotherapy instead. His condition was further complicated with hypercalcaemia, confusion and chest infection while awaiting the availability of nivolumab. His glycaemic control was poor due to the use of dexamethasone to control brain-related symptoms.

Nivolumab (3 mg/kg every 2 weeks) was first initiated on an inpatient basis in early January 2016. (Figure 1A) A second cycle was administered in late January, with no infusion reactions noted.

During a follow-up visit for cycle 6 prescription at the end of March 2016, the patient reported no more confusion and was able to communicate well verbally. PET-CT in May 2016 revealed radiological progression of bone metastases alone but static disease otherwise. However, this should not be regarded as treatment failure, because the only PET-CT images available for comparison were taken a few months prior to initiation of nivolumab. Nivolumab monotherapy was therefore continued since there is improvement in general condition clinically and good tolerability to treatment.

Biochemical analyses revealed a marked decline in serum carcinoembryonic antigen (CEA) levels following an initial surge that was likely due to a delayed response to immunotherapy. CEA levels rose from 22.2 ng/mL in February 2016 to 80.9 ng/mL in April 2016, but decreased to 4.2 ng/mL in June 2016. (Figure 2) As of August 2016, the patient has received 16 cycles of nivolumab monotherapy. Chest X-ray showed good shrinkage in the primary tumour. (Figure 1B) The patient is currently residing in a nursing home, and is able to walk with aid and communicate freely. No treatment-related symptoms have been noted.

Figure 1. Chest X-ray showing shrinkage of the left upper lung tumour



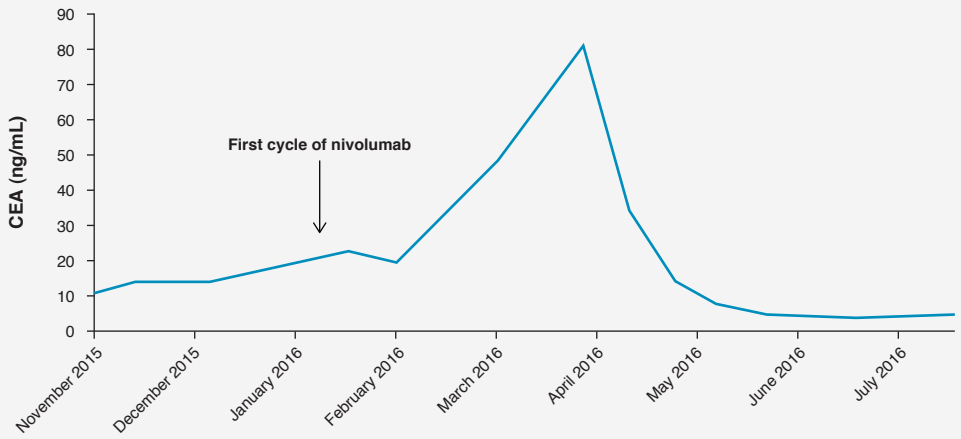
(A) January 2016, before nivolumab treatment

(B) August 2016, after 16 cycles of nivolumab monotherapy

Discussion

Nivolumab is a PD-1 immune checkpoint inhibitor that blocks T-cell

Figure 2. Serum CEA levels before and after nivolumab monotherapy



CEA = carcinoembryonic antigen

inhibitory signalling pathways by preventing the engagement of PD-1 with its ligands (PD-L1/2), thereby restoring the patient's own antitumour immunity.[1]

In March 2015, the US FDA approved the use of nivolumab in patients with advanced or metastatic squamous NSCLC who progressed on or after platinum-based chemotherapy.[1] The indication was expanded to include patients with metastatic nonsquamous NSCLC in October 2015 based on findings of the CheckMate 057 trial, which showed an improvement in overall survival (OS) vs docetaxel.[2,3]

In the trial, 582 patients with metastatic nonsquamous NSCLC refractory to platinum doublet chemotherapy were randomized to receive nivolumab or docetaxel monotherapy. At the prespecified interim analysis, median OS was 12.2 months among nivolumab recipients vs 9.4 months among patients in the docetaxel group (hazard ratio [HR], 0.73; p=0.0015). The objective response rate was also significantly improved among nivolumab recipients (19.2 percent vs 12.4 percent for docetaxel). Improvements were also noted in median duration of response (17 vs 6 months). However, median progression-free survival (PFS) was not significantly different between the groups (2.3 vs 4.2 months; HR 0.92; p=0.39). The researchers suggested that PFS may not be an optimal endpoint for defining clinical benefit of immunotherapies, and that the lack of difference in PFS may be due to heterogeneity of the patient population with respect to PD-L1 expression and *EGFR/ALK* status. At present, the role of nivolumab in patients who are *EGFR*- and *ALK*-positive remains unclear.[3]

> ***"One potential advantage of nivolumab over other immunotherapies is that treatment initiation does not require testing of PD-L1 expression levels"***

Our patient with *EGFR*-, *ALK*- and *ROS*-1–negative NSCLC showed good tumour shrinkage as well as clinically significant symptom relief following second-line nivolumab monotherapy. The treatment was also well-tolerated.

Nivolumab was selected as the second-line treatment for this patient because of our previous positive experience with this therapy and the limited choice in patients with poor performance status. One potential advantage of nivolumab over other immunotherapies is that treatment initiation does not require testing of PD-L1 expression levels, as per the US FDA recommendations.

In conclusion, the case illustrates the potential benefit of nivolumab monotherapy in elderly patients with metastatic NSCLC.

References
1. *The Oncologist* 2016;21:1-9. **2.** NCCN clinical practice guidelines in oncology: non-small cell lung cancer version 4.2016. **3.** *N Engl J Med* 2015;373:1627-1639.