Clinical Case Report

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Efficacy of short-term nivolumab treatment in a Chinese patient with relapsed advanced-stage lung squamous cell carcinoma

A case report

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Abstract

Introduction: Currently, the options are limited for the treatment of patients who have failed 2 lines of chemotherapy for advanced lung squamous cell carcinoma (SCC). Recently, nivolumab, a fully human IgG4 programmed death 1 immune checkpoint inhibitor antibody, was approved to treat patients with advanced stage, relapsed/refractory lung SCC. Although nivolumab has demonstrated antitumor activity with survival benefit in Caucasian patients, its efficacy in Asian patients is unknown.

Case Report: In this report, we describe a Chinese patient with relapsed advanced stage lung SCC who had an excellent response to nivolumab after only 2 doses without any adverse effects. Immunohistochemical analysis indicated the tumor was stained positive for programmed death-ligand 1.

Conclusion: To our knowledge, this is the first report of satisfactory efficacy of short-term nivolumab treatment in a Chinese patient with relapsed advanced-stage lung SCC. Further clinical trials in Asian countries are needed to test whether nivolumab immunotherapy is a safe and effective treatment for Asian patients with lung SCC.

Abbreviations: ALK = anaplastic lymphoma kinase, CI = confidence interval, CR = complete response, CT = computed tomography, EGFR = epidermal growth factor receptor, FDA = Food and Drug Administration, IHC = immunochemistry, IMRT = intensity-modulated radiotherapy, MRI = magnetic resonance imaging, NSCLC = nonsmall cell lung cancer, OS = overall survival, PD-1 = programmed death-1, PD-L1 = programmed death-ligand 1, PD-L2 = programmed death-ligand 2, PET-CT = positron emission tomography-computed tomography, PR = partial response, SCC = squamous cell carcinoma, SD = stable disease, TKI = tyrosine-kinase inhibitors.

Keywords: lung squamous cell carcinoma, nivolumab, PD-L1, relapsed, short-term

1. Introduction

In the past decade, targeted therapeutic agents including bevacizumab, epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitors (TKI), and anaplastic lymphoma kinase (ALK) inhibitors have improved the treatment for advanced-stage lung adenocarcinoma.[1–3] However, the treatment options for advanced stage lung squamous cell carcinoma (SCC) remain limited.[4] Furthermore, for the relapsed or refractory lung SCC, because of the absence of efficacious treatments, best supportive care is usually the only option. Therefore, novel therapeutic approaches are urgently needed.

Programmed death-1 (PD-1) is an inhibitory receptor that is expressed on T cells. Programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2) are the ligands for PD-1. PD-1/PD-L1 binding leads to the activation of immune checkpoint pathway and the inhibition of T-cell-mediated immune responses.[5] Nivolumab is a human IgG4 anti-PD-1 antibody that disrupts PD-1/PD-L1 binding and blocks immune checkpoint pathways, restoring antitumor immunity. Clinical trials have demonstrated that blocking PD-1 signaling using nivolumab could potentially inhibit tumor growth and improve the survival rate of cancer patients.[6] Thus, the US Food and Drug Administration (FDA) has approved the use of nivolumab in some advanced-stage malignancies including melanoma, kidney cancer, and non-small cell lung cancer. Although anti-PD-1 immunotherapy has demonstrated antitumor activity with survival benefits in Caucasian patients,[6] its safety and efficacy in Asian patients are unknown. Here, we reported a Chinese patient with relapsed lung SCC who had a remarkable response to a 4-week therapy of nivolumab after progressing through cytotoxic chemotherapy.

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GP and HH contributed equally to this work.

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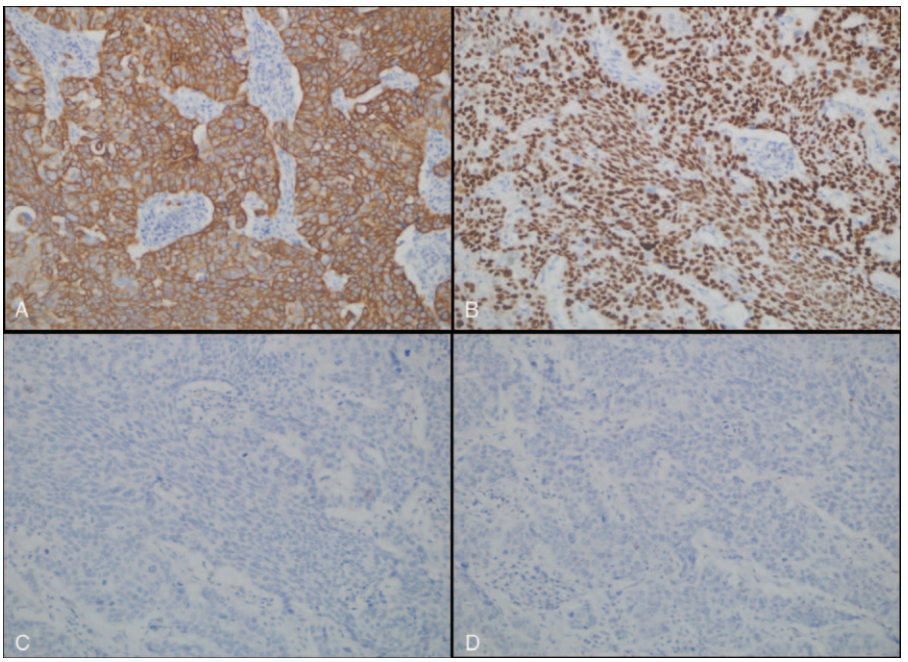

Figure 1. Immunohistochemistry staining for the tumor. Tumor cells had diffuse cytoplasmic reactivity for CK5/6 (A) and p63 (B), but had negative staining for Napsin A (C) and TTF-1 (D). Original magnification ×200.

2. Case report

A 62-year-old, Chinese male, who was previously in good health but had a 30-year history of smoking and alcohol-drinking, accidently discovered an enlarged right supraclavicular lymph node in December 2010. A biopsy of the supraclavicular lymph node revealed metastatic SCC. Immunohistochemistry (IHC) staining showed positive for CK5/6 and p63 and negative for NapsinA and TTF-1 (Fig. 1A–D). In addition, IHC staining also showed that over 50% tumor cells had membranous staining of PD-L1 (Fig. 2). Dako (Monoclonal Mouse Anti-PD-L1, Clone 22C3 antibody) is thought to be a standard antibody for IHC; however, it is not available in China. Therefore, we used Mouse anti-PD-L1/CD274 Monoclonal antibody (catalog number: 66248-1-Ig, Proteintech Group Inc, Chicago, IL) for PD-L1 immunostaining. A full-body positron emission tomography–-computed tomography (PET-CT) revealed a hypermetabolic right lung hilar mass and hypermetabolic right supraclavicular and mediastinal lymphadenopathy (Fig. 3A). A brain magnetic resonance imaging (MRI) was negative for metastatic lesions. He was diagnosed with a stage III B disease (UICC 7th edition) and received chemotherapy with gemcitabine and cisplatin. A computed tomography (CT) scan of the neck and chest after 2 cycles of chemotherapy revealed a stable disease (SD) on both the primary and metastatic lesions. He continued with 2 more cycles of chemotherapy with gemcitabine and cisplatin, which was followed by radiotherapy administered at a dose of 64.5 Gy in 32 fractions using the intensity-modulated radiotherapy (IMRT) technique on both the primary and metastatic lesions. At the end of radiotherapy, the supraclavicular metastases had a clinically complete response as determined by physical examination, and a partial response (PR) on a CT scan. Subsequently, the patient received 2 more cycles of chemotherapy with gemcitabine and cisplatin, which was completed in July 2011.

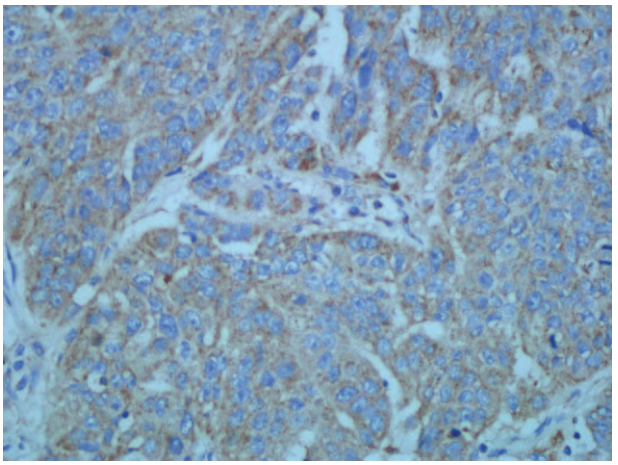

Figure 2. Immunohistochemistry staining for PD-L1 in a pretreated formalin-fixed paraffin-embedded tissue specimen before treatment. Over 50% tumor cells were positive for membranous PD-L1 expression. Original magnification ×400. PD-L1 = programmed death-ligand 1.

A PET-CT 1 month after the completion of the above-mentioned therapy revealed a complete response (CR) (Fig. 3B). He was then followed up every 3 months. In September 2014, a follow-up CT scan revealed recurrent disease in the right upper lobe of lung and the left adrenal gland. He received 2 cycles of salvage chemotherapy with docetaxel and cisplatin, but a follow-up CT scan showed disease progression (Fig. 4A and B). The patient refused further chemotherapy. In April 2015, the patient received palliative radiotherapy to relieve bone pain. A CT scan revealed that the lesions in the lung and adrenal gland had further increased in size since the last scan. We recommended immunotherapy with nivolumab. Due to economic reasons, the patient received only 2 doses of nivolumab (2 mg/kg, once every 2 weeks) which were given on May 11, 2015 and May 25, 2015. During and after the treatment of nivolumab, he did not

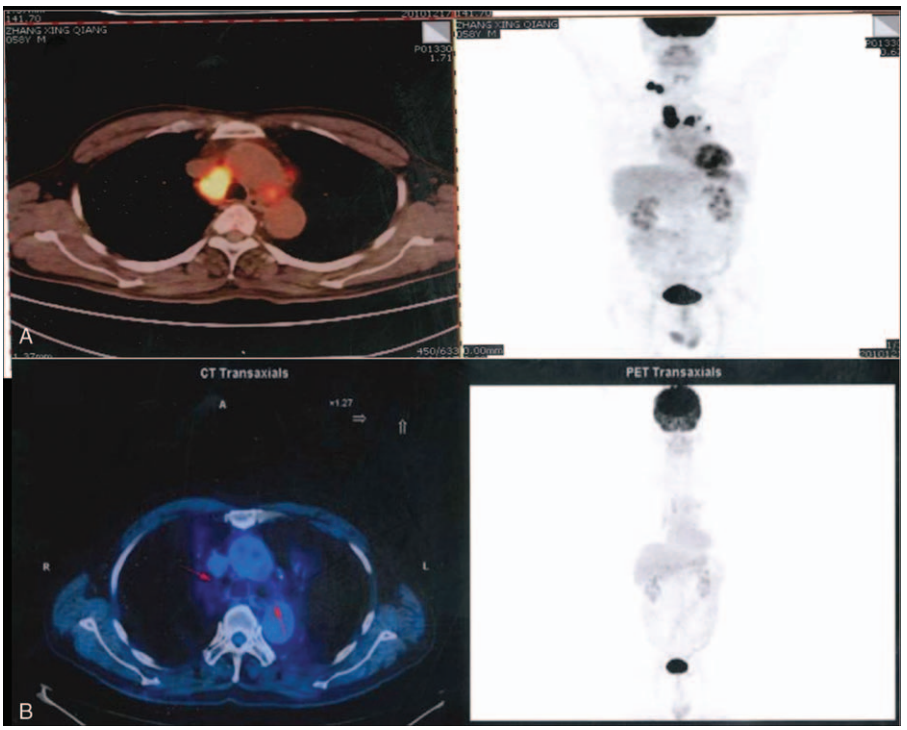

Figure 3. Images of PET-CT scans. A, Prior to the combination treatment. B, After the combination treatment, the patient was disease free. PET-CT = positron emission tomography-computed tomography.

experience any significant adverse effects. Three months later, a CT scan revealed that the lesions in the lung and left adrenal gland had decreased in size more than 30%, meeting the response evaluation criteria for a PR (Fig. 4C and D). The patient died from brain metastases in December 2015, 2 months after the whole brain irradiation (30 Gy in 10 fractions).

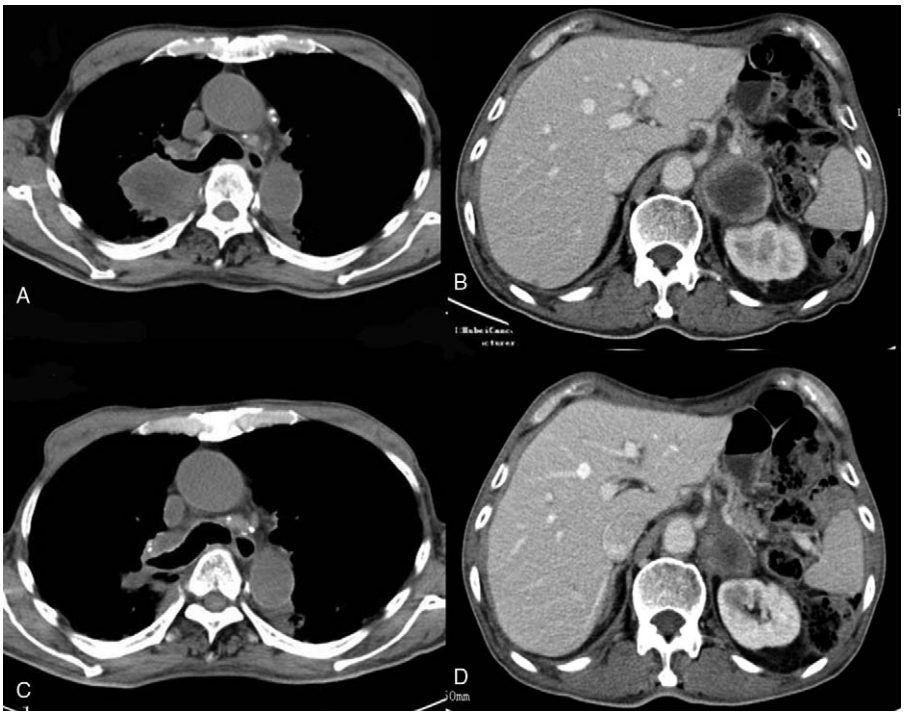

Figure 4. Axial CT scans. The recurrent primary lesion in the right upper lobe of the lung (A) and a metastatic lesion in the left adrenal gland (B). Ninety-six days after a short-term treatment of nivolumab, both the right upper lobe lung lesion (C) and the left adrenal gland lesion (D) decreased in size remarkably. CT = computed tomography.

Ethical statement: Ethical approval of this case report was granted by our institutional ethic committee (Hubei Cancer Hospital). Since this is a retrospective case report, patient consent was waived by our institutional ethic committee.

3. Discussion

Squamous-cell carcinoma of the lung represents 25% and 30% of nonsmall cell lung cancer (NSCLC). The first-line treatment for lung SCC is platinum-based doublet chemotherapy. Most new agents, such as pemetrexed and bevacizumab, are not indicated for use in lung SCC treatment due to the lack of efficacy or their toxicity. The complexity of genetic alterations in lung SCC limits the application of molecular-targeted therapies.[7–9] Little progress has been made since the approval of the use of docetaxel for lung SCC in 1999. Currently, single-agent docetaxel chemotherapy is standard second-line treatment for the relapsed or refractory lung SCC, resulting in median overall survival (OS) of approximately 7 months.[10,11] Therefore, the discovery of novel therapeutic approaches is an urgent task.

Immune checkpoint blockades may promote tumor regression by reversing tumor-induced immunosuppression and restoring antitumor immune response.[12,13] PD-1, an immune checkpoint receptor that negatively regulates T-cell activation, is up-regulated in tumor-infiltrating lymphocytes. The expression of its ligand PD-L1 has been associated with poor prognosis in NSCLC.[14–16] Nivolumab is a fully humanized IgG4 anti PD-1 recombinant monoclonal antibody that inhibits the binding of PD-1 to PD-L1 and PD-L2, thereby blocking PD-1-mediated signaling and restoring antitumor immunity.[15,17] After a series of phase 2 clinical trials, nivolumab has shown encouraging antitumor activity among previously treated patients with advanced-stage lung SCC with response rates of 15% to 17%, a median overall survival of 8.2 to 9.2 months, a 1-year survival rate of 41%, and a 3-year survival rate of 19%.[14,15] In an open-label, randomized phase 3 trial, patients received either nivolumab (3 mg/kg every 2 weeks, intravenously) or docetaxel (75 mg/m^2 every 3 weeks, intravenously). Median overall survival was 9.2 months in 135 patients in the nivolumab group and 6.0 months in 137 patients in the docetaxel group. One year overall survival was 42% in the nivolumab group and 24% in the docetaxel group. Nine (7%) of 131 patients in the nivolumab group and 71 (55%) of 129 in the docetaxel group had grade 3 or 4 treatment-related adverse events.[17] In 2015, the FDA approved the use of nivolumab in lung SCC patients as the second-line therapy for advanced-stage lung SCC.[18]

According to the guideline, nivolumab should be used continuously as monotherapy (3 mg/kg every 2 weeks) until disease progression.[19] However, in our case report, a dramatic response was observed with short-term use of nivolumab (only 2 doses, a dose of 2 mg/kg, every 2 weeks). This is the first report of such a dramatic response in a Chinese patient with relapsed lung SCC with such a short-term treatment of nivolumab. The dosage and time administration for an Asian patient may not be the same as for a Caucasian, which needs to be further investigated.

It is unclear why the patient had such a good response to short-term nivolumab treatment in this case. Whether there are any biomarkers that may predict the therapeutic effect of nivolumab is unknown. Numerous types of tumor cells are able to express PD-L1, including urothelial, ovarian, breast, cervical, colorectal, pancreatic and gastric cancer, melanoma, glioblastoma, and NSCLC, suggesting that PD-1/PD-L1 pathway may be involved in immune evasion by many different human cancers.[20] Therefore, PD-L1 has been postulated as a potential biomarker for patients who may respond to nivolumab. Several clinical studies had shown that the levels of PD-1 on tumor infiltrating T cells were significantly less predictive of responses to nivolumab therapy than PD-L1 expression on solid tumors. The patients with PD-L1-positive tumors have shown higher objective responses in comparison to patients with PD-L1-negative tumors.[6,21,22] Usually, an indication of an IHC staining as positive was defined as membranous PD-L1 expression in $\geq$5% or $\geq$10% tumor cells.[23,24] In our institution, the positive staining of IHC on PD-L1 was defined as the membranous expression of PD-L1 in over 50% tumor cells. In this particular case, over 50% tumor cells had membranous staining of PD-L1. This may explain why our patient had such a dramatic response with only 2 suboptimal doses of treatment with nivolumab. However, unlike genetic mutations used to identify patients potentially responsive to targeted therapies, PD-L1 is an inducible marker that can be up-regulated and down-regulated. It can be expressed by tumor cells and/or tumor-infiltrating lymphocytes. Furthermore, the sensitivity and specificity of PD-L1 detection can vary by the assay type and the quality of the tissue sample. Some clinical trials had revealed that PD-L1 expression was neither prognostic nor predictive of efficacy in the population of patients with advanced-stage lung SCC.[17] Thus, the potential predictive role of PD-L1 expression on tumor cells still requires further studies.

Pneumonitis is a clinically important adverse event associated with the treatment of NSCLC, including nivolumab treatment.[25,26] In our case, no adverse events were observed during and after the treatment of nivolumab. The possible reasons could be the dose was suboptimal (2 mg/kg instead of 3 mg/kg), the treatment course was short, and the follow-up was short. Given that this is only a single case report and that there was no long-term follow-up, the safety of nivolumab in Chinese patients should be investigated in future clinical trials.

4. Conclusion

This is the first report of satisfactory efficacy in a Chinese patient with relapsed advanced-stage lung SCC of a short-term nivolumab treatment. Further clinical trials in Asian countries are needed to test whether nivolumab immunotherapy is a safe and effective treatment for Asian patients with lung SCC. At the same time, choice of effective dosage and time administration as well as choice of effective population also needs to be investigated further.

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