Respiratory Medicine Case Reports 29 (2020) 100979

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: http://www.elsevier.com/locate/rmcr

Case report

A case of non-small cell lung cancer with long-term response after re-challenge with nivolumab

Keima Ito [a], Tetsuya Oguri [a,b,*], Norihisa Takeda [a], Kensuke Fukumitsu [a], Satoshi Fukuda [a], Yoshihiro Kanemitsu [a], Tomoko Tajiri [a], Hirotsugu Ohkubo [a], Masaya Takemura [a,b], Ken Maeno [a], Yutaka Ito [a], Akio Niimi [a]

[a] Department of Respiratory Medicine, Allergy and Clinical Immunology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan
[b] Department of Education and Research Center for Community Medicine, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

ARTICLE INFO

Keywords:
Lung cancer
Nivolumab
Immune checkpoint inhibitors
PD-L1

ABSTRACT

A 76-year-old man was admitted to our hospital with cough and dyspnea. He was diagnosed with advanced lung cancer. Nivolumab was given as second-line treatment, cytotoxic chemotherapy was given as third-line treatment, and nivolumab re-challenge was given as fourth-line treatment. Thereafter, 41 chemotherapy courses were administered over 2 years. Currently, he is being followed with no recurrence at least 10 months after treatment. Thus, the case of a patient with advanced lung cancer who was previously unsuccessfully treated with nivolumab and then demonstrated a long-term clinical response to a re-challenge with nivolumab after cytotoxic chemotherapy and radiation therapy is presented.

1. Introduction

The development of immune checkpoint inhibitors (ICIs) has dramatically changed lung cancer treatment, demonstrating an overall survival benefit [1]. Furthermore, ICI or ICI plus chemotherapy treatment showed superiority compared to chemotherapy as first-line therapy [2,3]. A few reports of ICI re-challenge have been published in patients with melanoma and involved ipilimumab monotherapy or combination therapy with ipilimumab and nivolumab [4,5]. These reports showed that ICI re-challenge achieved good results for some patients. Some patients achieve a long-term response with ICIs; however, not all patients obtain a response from immunotherapy. Patients with disease progression after ICIs also generally receive conventional cytotoxic chemotherapy. However, limited data are available about the efficacy and safety of ICI re-challenge in cases of non-small cell lung cancer (NSCLC).

The case of a patient with advanced NSCLC who was previously treated with nivolumab and demonstrated long-term clinical response to re-challenge with nivolumab after receiving cytotoxic chemotherapy and radiation therapy is presented.

2. Case report

A 76-year-old man was admitted to our hospital with cough and dyspnea. A mass shadow was found in the right upper lobe on computed tomography (CT), and transbronchial lung biopsy by an endobronchial fiberscope showed advanced squamous cell carcinoma, cT3N3M1b (OSS, BRA, PUL, PLE) stage IVB (Fig. 1a), without epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) translocation, and the tumor was positive for programmed cell death ligand-1 (PD-L1) expression [tumor proportion score (TPS) 30%]. The patient had previously smoked 50 packs of cigarettes per year and had no specific medical history. His Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 0.

Four courses of carboplatin (AUC 6, day 1, every 3 weeks) plus tegafur-gimeracil-oteracil (S-1) (100 mg/day, days 1–14) and five courses of consolidation therapy with S-1 were given as the first-line treatment. He achieved a partial response (PR), but an increase in the brain metastasis was observed, and the patient underwent stereotactic irradiation for the brain metastasis (10 Gy × 3 fr, total 30 Gy). Nivolumab (3 mg/kg, day 1, every 2 weeks) was then administered as second-line treatment. However, after administration of three courses, increases in the lymph nodes and brain metastasis and elevation of the tumor marker carcinoembryonic antigen (CEA), from 4.9 to 7.8 ng/ml,

* Corresponding author. 1, Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya, Aichi, Japan.
E-mail address: t-oguri@med.nagoya-cu.ac.jp (T. Oguri).

https://doi.org/10.1016/j.rmcr.2019.100979
Received 2 November 2019; Received in revised form 7 December 2019; Accepted 7 December 2019
Available online 10 December 2019

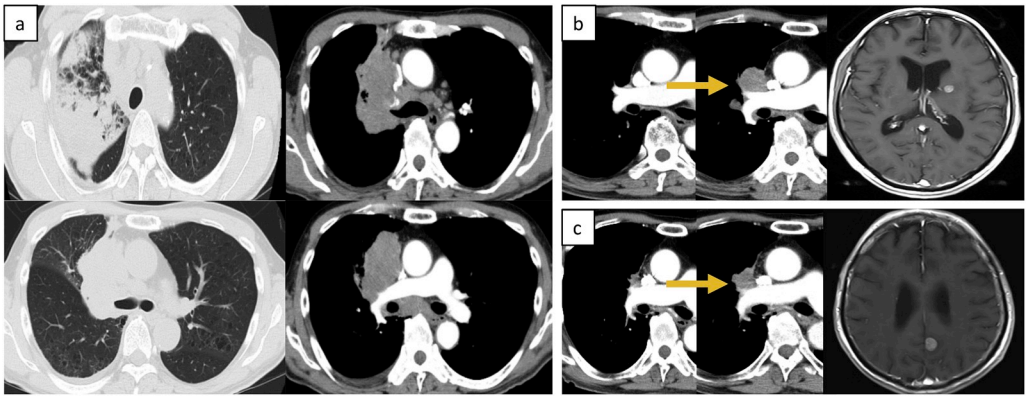

Fig. 1. a: Chest contrast computed tomography (CT) on admission shows enlarged mediastinal and hilar lymph nodes and consolidation in the right upper lobe, b: Chest contrast CT and head contrast MRI after administration of 3 courses of nivolumab show an increase in the right mediastinal lymph nodes and brain metastasis, c: Chest contrast CT and head contrast MRI after administration of 6 courses of nab-paclitaxel show an increase in the right mediastinal lymph nodes and brain metastasis.

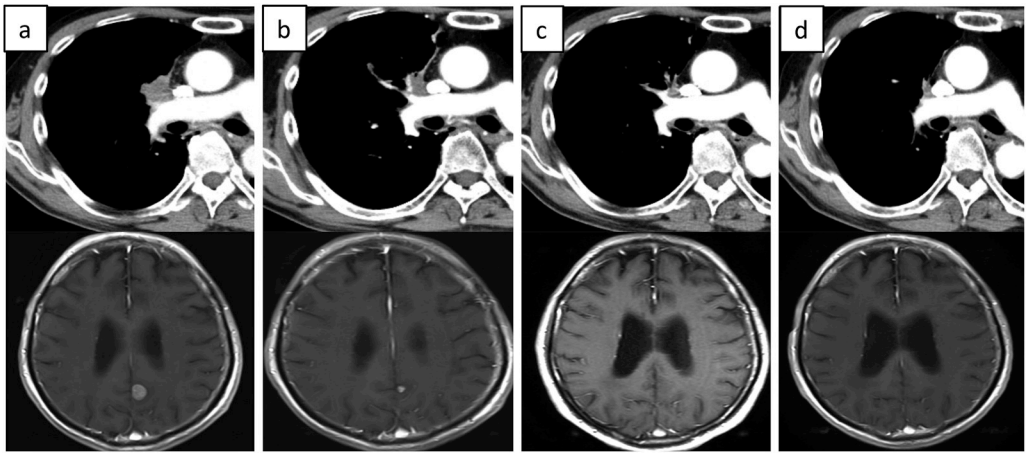

Fig. 2. a: Chest contrast computed tomography (CT) and head contrast MRI before nivolumab re-challenge show increased right mediastinal lymph nodes and brain metastasis in the right occipital lobe, b: Chest contrast CT and head contrast MRI 4 months after nivolumab re-challenge show a reduction of right mediastinal lymph nodes and brain metastasis in the right occipital lobe, c: Chest contrast CT and head contrast MRI 2 years after nivolumab re-challenge show maintenance of the reductions of the lesions. d: Chest contrast CT and head contrast MRI 10 months after the end of treatment show maintenance of the reductions of the lesions.

were observed, and he was judged to have progressive disease (PD) (Fig. 1b). After repeat stereotactic irradiation for the brain metastasis (10 Gy × 3 fr, total 30 Gy), he was given six courses of nab-paclitaxel (100 mg/m^2, days 1, 8, and 15, every 3 weeks) as the third-line treatment, and he achieved PR. However, 3 months later, an increase in the lymph nodes and brain metastasis occurred and was considered PD (Fig. 1c). After further stereotactic irradiation for the brain metastasis (10 Gy × 3 fr, total 30 Gy), the patient was treated with re-challenge with nivolumab (2 mg/kg, day 1, every 2 weeks) as the fourth-line therapy. Four months after the nivolumab re-challenge, CT showed PR in the lymph nodes and brain metastasis. Thereafter, 41 chemotherapy courses were administered over 2 years. Currently, the patient's nivolumab has been discontinued, and he is being followed with no recurrence at least 10 months after treatment (Fig. 2a–d).

3. Discussion

A case in which the initial administration of nivolumab was ineffective, but re-challenge was effective and a long-term clinical response was obtained, was described. Furthermore, this is the first report of long-term survival following ICI re-challenge. In this case, there was no difference in PS and the patient's dose of corticosteroids at the time of first ICI treatment and ICI retreatment.

Today, ICIs are key drugs in the treatment of advanced NSCLC. Some cases are long-term responders, but specific predictors of treatment response have not been established. Recently, the efficacy of ICI re-challenge has been reported. Since ICI re-challenge could provide clinical benefit in selected patients, it is important to determine in which patients the re-challenge might be effective. From the previous reports, there are three possible predictors of the effectiveness of ICI re-challenge.

First, PD-L1 expression could be one of the biomarkers for predicting the efficacy of ICI re-challenge. In a previous large clinical trial, patients with high (TPS $\geq$ 50%) PD-L1 expression showed a good response [2]. In a previous report, all three patients with very high (TPS $\geq$ 80%) PD-L1 expression showed efficacy of retreatment with pembrolizumab [6]. Patients with very high (TPS $\geq$ 80%) PD-L1 expression may benefit from ICI re-challenge. Second, development of immune-related adverse events (irAEs) is also mentioned as a predictor of the effect of ICI retreatment. Randomized studies of ipilimumab in melanoma have shown that patients with irAEs have high response rates and excellent clinical outcomes with observation alone [7,8]. In patients with NSCLC, the presence of irAEs during the first ICI treatment might be a predictor of the efficacy of ICI re-challenge [9]. Third, the response to the initial treatment with an ICI could be one of the parameters reflecting the efficacy of ICI re-challenge. In reports of ICI re-challenge, most first ICI responders showed a good response to re-challenge [9,10]. In contrast, in another report involving NSCLC, the duration of PFS after the first ICI showed no relationship to the efficacy of ICI re-treatment [6].

However, none of the above predictors was applicable in the current case. Although the initial treatment was ineffective, re-challenge with nivolumab was effective, leading to a long-term clinical response. To attempt to explain this, we considered the possibility of the effect of the chemotherapy and radiotherapy between ICI treatments. The 'abscopal effect' is a theory about cancer antigen presentation by radiation [11]. A recent report of NSCLC demonstrated that patients who had previously received radiotherapy for the treatment of NSCLC before receiving pembrolizumab had significantly longer progression-free survival and overall survival, compared with patients who did not receive previous radiotherapy [12]. However, more large-scale studies to evaluate the

relationship between radiotherapy and immunotherapy are needed. In the present case, cytotoxic chemotherapy with nab-paclitaxel was administered between the first ICI treatment and ICI retreatment. Although a change in antigenicity of the tumor secondary to administration of cytotoxic chemotherapy might induce a therapeutic response to ICIs, the mechanism is unclear. The present case suggests that, even if the initial treatment is ineffective, cytotoxic chemotherapy and radiation therapy might induce a therapeutic response to a second ICI challenge.

Thus, a case of a patient with advanced NSCLC who was previously unsuccessfully treated with nivolumab and then demonstrated a long-term clinical response to re-challenge with nivolumab after cytotoxic chemotherapy and radiation therapy was described. However, it is desirable to determine the biomarkers and clinical background characteristics of patients that would facilitate prediction of the efficacy of ICI re-challenge.

Funding sources

The authors have no funding sources to declare. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare no conflict of interest.

References

[1] M. Reck, D. Rodriguez-Abreu, A.G. Robinson, R. Hui, T. Csoszi, J.R. Brahmer, et al., Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater, J. Clin. Oncol. 37 (2019) 537–546.

[2] M. Reck, D. Rodriguez-Abreu, A.G. Robinson, R. Hui, T. Csoszi, J.R. Brahmer, et al., Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer, N. Engl. J. Med. 375 (2016) 1823–1833.

[3] L. Gandhi, D. Rodriguez-Abreu, S. Gadgeel, E. Esteban, E. Felip, M.C. Garassino, et al., Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer, N. Engl. J. Med. 378 (2018) 2078–2092.

[4] M.H. Pollack, A. Betof, H. Dearden, K. Rapazzo, I. Valentine, A.N. Shoushtari, et al., Safety of resuming anti-PD-1 in patients with immune-related adverse events (irAEs) during combined anti-CTLA-4 and anti-PD1 in metastatic melanoma, Ann. Oncol. 29 (2018) 250–255.

[5] C. Lebbe, J.S. Weber, M. Maio, B. Neyns, K. Harmankaya, J.D. Wolchok, et al., Survival follow-up and ipilimumab retreatment of patients with advanced melanoma who received ipilimumab in prior phase II studies, Ann. Oncol. 25 (2014) 2277–2284.

[6] K. Fujita, N. Uchida, O. Kanai, M. Okamura, K. Nakatani, T. Mio, Retreatment with pembrolizumab in advanced non-small cell lung cancer patients previously treated with nivolumab: emerging reports of 12 cases, Cancer Chemother. Pharmacol. 81 (2018) 1105–1109.

[7] M.A. Postow, J. Chesney, A.C. Pavlick, C. Robert, K. Grossmann, F.S. Hodi, et al., Nivolumab and ipilimumab versus ipilimumab in untreated melanoma, N. Engl. J. Med. 372 (2015) 2006–2017.

[8] J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.J. Grob, C.L. Cowey, J.D. Wolchok, et al., Combined nivolumab and ipilimumab or monotherapy in untreated melanoma, N. Engl. J. Med. 373 (2015) 23–34.

[9] M. Niki, A. Nakaya, T. Kurata, H. Yoshioka, T. Kaneda, S. Nomura, et al., Immune checkpoint inhibitor re-challenge in patients with advanced non-small cell lung cancer, Oncotarget 9 (2018) 32298–32304.

[10] M. Nomura, A. Otsuka, T. Kondo, H. Nagai, Y. Nonomura, M. Muto, et al., Efficacy and safety of retreatment with nivolumab in metastatic melanoma patients previously treated with nivolumab, Cancer Chemother. Pharmacol. 80 (2017) 999–1004.

[11] C. Twyman-Saint Victor, A.J. Rech, A. Maity, R. Rengan, K.E. Pauken, A.J. Minn, et al., Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer, Nature 520 (2015) 373–377.

[12] N. Shaverdian, A.E. Lisberg, K. Bornazyan, D. Veruttipong, J.W. Goldman, P. Lee, et al., Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial, Lancet Oncol. 18 (2017) 895–903.