Hyperprogressive disease after immune checkpoint inhibitor therapy in a patient with non-small cell lung cancer who harbors a *TGFBR2* mutation: A case report

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Abstract. We previously demonstrated that a transforming growth factor β type II receptor (*TGFBR2*) mutation can predict resistance to immune checkpoint inhibitors (ICIs) in patients with advanced non-small cell lung cancer (NSCLC), based on publicly available immunotherapeutic cohorts. However, the efficacy of ICI-based regimens in patients with advanced NSCLC harboring *TGFBR2* mutations in the real-world setting is rarely reported. The present study describes the case of a patient with advanced NSCLC who harbors a *TGFBR2* mutation. The patient was treated with ICI monotherapy and experienced hyperprogressive disease (HPD). The clinical information was retrospectively collected. The progression-free survival (PFS) was only 1.3 months. In conclusion, HPD occurred in a patient with advanced NSCLC with a *TGFBR2* mutation who received an ICI monotherapy regimen. The findings suggested that caution may be required regarding the clinical delivery of ICI monotherapy to patients with NSCLC and *TGFBR2* mutations; ICIs combined with chemotherapy may be an alternative treatment option.

Introduction

Recently, the development of immune checkpoint inhibitors (ICIs) has improved the overall survival of the non-small cell lung cancer (NSCLC) (1-3). However, only a small subset of patients can respond to ICIs and the objective response rate (ORR) is only 20 to 30% for single-agent (4,5). Previous efforts have been made to identify the clinical or genetic biomarkers of response to ICIs, such as programmed cell death ligand 1 (PD-L1) expression (6), and tumor mutational burden (TMB) (7,8). However, it is of equal significance to identify patients who are resistant or even hyper-progress after ICIs, which helps develop novel strategies to overcome drug resistance.

Hyperprogressive disease (HPD) has been observed during immunotherapy in a small subset of patients (9,10). HPD is defined as a progressive disease on the first computed tomography (CT) scan during immunotherapy and the tumor growth rate (TGR) exceeds 50% compared with baseline, corresponding to an absolute increase in the TGR exceeding 50% per month (9). In previous studies, *murine double minute 2/4* (*MDM2/4)* amplification, *Janus kinase (JAK) 1/2* loss-of-function mutation and *EGFR* mutation have been reported to be associated with HPD (10,11). The incidence of HPD ranged from 8.0 to 30.4% in NSCLC after treatment with ICIs monotherapy (9,12,13).

Transforming growth factor β type II receptor (TGFBR2) is a transmembrane protein with a protein kinase domain, which is responsible for recruiting and phosphorylating TGFB1, and binding TGF-β, thus forming a heterodimeric complex (14,15). We previously demonstrated that *TGFBR2* mutation was a negative predictor of ICIs in patients with NSCLC using public immunotherapeutic cohorts (16). However, the efficacy of ICIs monotherapy in NSCLC patients harboring *TGFBR2* mutation in the real-world setting has not been reported. Besides, chemoimmunotherapy has been widely used as maintenance or as first line therapy in advanced NSCLC patients without *EGFR* or *ALK* alterations (17). Therefore, in the present study, we described one NSCLC case harboring *TGFBR2* mutations treated with immunotherapy, providing insights into the therapeutic outcome for these patients in a real-world setting.

Case report

The patient was a 39-year-old female who was diagnosed in our hospital with lymphoepithelioma-like carcinoma of lung cancer, a rare pathological type of NSCLC in April 2015

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by computed tomography (CT) and pathology results. The clinical stage was cT4N3M1 when diagnosed. The baseline characteristics, mutation status in driver genes, treatments, and responses were summarized in Table I. The expression of PD-L1 was tested by immunohistochemistry (IHC), and the result was negative.

The whole exome sequencing analysis of specimen acquired by puncture needle showed that the patient had *TGFBR2* p.S268* mutation, and no other target-druggable mutations. The TMB was 42 Muts/Mb. The patient then received gemcitabine and cisplatin as the first-line treatment. The best response was partial response (PR). However, on June 15th, 2016, the CT image showed increased tumor lesions in both size and number in bilateral lung with the largest tumor lesion of 16 mm x 14 mm, as well as liver metastasis with the largest tumor lesion of 36 mm x 29 mm (Fig. 1A). After progression during gemcitabine and cisplatin treatment, the patient was admitted into a clinical trial of nivolumab and started to receive 3 mg/kg nivolumab since June 21st, 2016. However, after three cycles of nivolumab, the tumor lesions in bilateral lung increased in size and number and the largest tumor lesion was 43 mm x 28 mm. The tumor lesion from the liver increased to 71 mm x 67 mm. The response was considered as progression disease (PD) based on response evaluation criteria in solid tumors (RECIST) version 1.1 and the progress free survival (PFS) was only 1.3 months. Then the patient received docetaxel as the third-line treatment. The lesion in the right lung decreased to 30 mm x 19 mm on September 12th, 2016. According to the definition of hyperprogression from a previous study (13), the patient experienced hyperprogression from ICIs, with the time-to-treatment failure less than two months, >50% increase in tumor burden compared with pre-immunotherapy imaging, and a >2-fold increase in progression pace (Fig. 1B).

Table I. The characteristics and clinical outcomes of the case.

Patient	Age, years	Sex	Smoking	Pathology	Stage	Metastases	ECOG	TGFBR2 mutation	EGFR/ ALK/ ROS1 mutation	TMB	PD-L1	ICIs based regimens	Line of treatment	Best of response	PFS, months
1	39	Female	No	LELC	IVB	Liver	1	p.S268*	None	42	0%	Nivolumab	2	PD	1.3

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; ROS1, repressor of silencing 1; TGFBR2, transforming growth factor β receptor 2; TMB, tumor mutation burden; ICIs, immune checkpoint inhibitors; PD, progressive disease; PFS, progression-free survival; LELC, lymphoepithelioma-like carcinoma.

Discussion

Herein, we described an advanced NSCLC patient who harbored *TFGBR2* mutation and experienced HPD after ICI monotherapy treatment. The previous study suggested that NSCLC patients with *TGFBR2* mutations may not benefit from ICI monotherapy, this case further indicated that they may even experience a rapid deteriorated outcome. More aggressive therapeutic regimens such as immunotherapy combined with chemotherapy may be an alternative.

TGF-β signaling pathways serve as a tumor suppressor in normal cells and early carcinomas, but in advanced tumors, TGF-β signaling turns to promote cancer progression, invasion, and tumor metastasis (18). In tumor microenvironment, TGF-β regulated cancer immunity through many kinds of immune cells. For example, TGF-β promoted the production of interleukin-10 (IL-10), which was secreted from tumor-associated macrophages (TAMs) and regulatory T cells (Tregs), and played an inverse role in anti-tumor immunity. Moreover, TGF-β inhibited the secretion of anti-tumor cytokine, interferon-gamma, and cytotoxic granzyme B from the natural killer (NK) cells and CD8+ T cells (18). Thus, TGF-β plays a crucial role in immune regulation.

The *TGFBR2* gene encodes the TGF-β receptor 2, a member of the TGF-β signaling, and forms a hetero-tetrameric

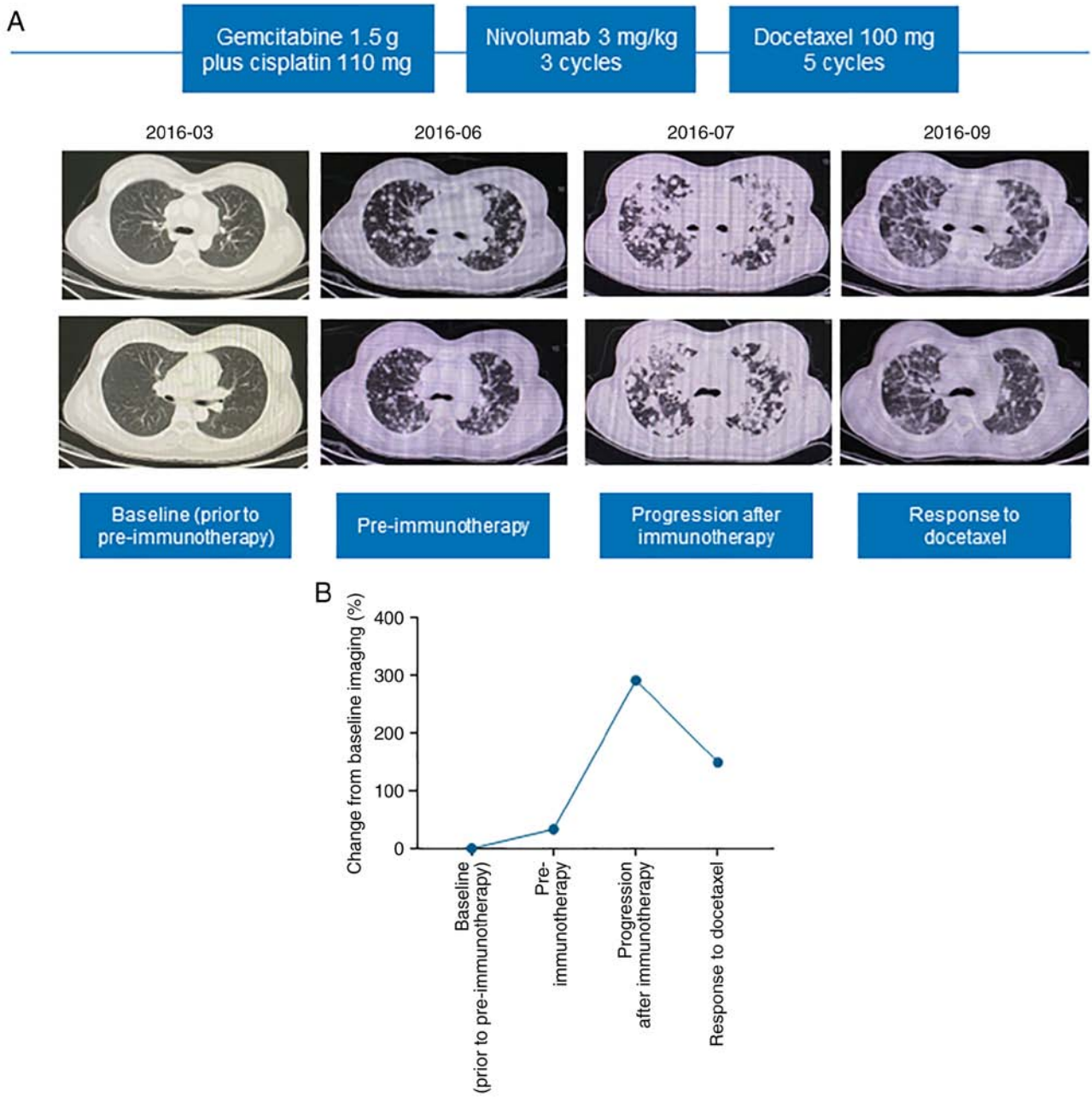

Figure 1. The change of radiological features. (A) Radiological features depicting the therapeutic course. (B) The percentage change of tumor size during the treatment course.

complex with TGFBR1. Genetic deletion of *TGFBR2* in CD4+ T cells suppressed tumor growth (19). Our previous study demonstrated that *TGFBR2* mutation served as a negative predictor of ICIs in patients with NSCLC in public datasets. In this study, one *TGFBR2* mutant NSCLC case was described in detail (20). The therapeutic efficacy was further observed in real-world settings in this study. The case further proved that patients with mutated *TGFBR2* might not respond to ICIs and even hyperprogress from ICIs. So the utility of immune monotherapy needs to be cautious in patients harboring *TGFBR2* mutation.

Chemotherapeutics can synergize with ICI and promote patients' immune system by enhancing immunogenic tumor cells death, increasing cancer cells neoantigens production, and augmenting the levels of tumor microenvironment pro-inflammatory cytokines (17). Thus, we propose that chemoimmunotherapy may overcome the immunosuppression environment caused by mutations in *TGBFR2* and be a hopeful treatment option for NSCLC patients with *TGFBR2* mutations.

Notably, the patient was diagnosed with NSCLC on April 30th, 2015, when the immune checkpoint inhibitor combined with chemotherapy has not been approved as the first-line regimen for the patients with NSCLC. Nowadays, both the immune checkpoint inhibitor combined with chemotherapy and immune checkpoint inhibitor monotherapy have been recommended by the national comprehensive cancer network (NCCN) (20) as the first-line treatment regimen for the patients with NSCLC. However, the biomarker for the immune checkpoint inhibitor mono- or combined therapy was not explicit.

Our result suggested that the clinical delivery of ICI monotherapy needs to be cautious in NSCLC patients with *TGFBR2* mutation and ICIs combined with chemotherapy might be an alternative. However, further studies with a larger sample size are warranted.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

XW conceived and designed the present study. XW and XM wrote the original draft. TL, CL and XM performed the analysis and interpretation of data. All authors read and approved the final manuscript. XW and TL confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The protocols involving patients were approved by the Ethics Committee of the Chongqing First Affiliated Hospital of Army Medical University (Third Military Medical University). The patients enrolled in this research provided written informed consent.

Patient consent for publication

The patient provided written informed consent for the publication of this case report and all accompanying images.

Competing interests

The authors declare that they have no competing interests.

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