Dramatic Response to Teriprilumab and Anlotinib Combination Therapy in a patient with EGFR-Mutant Lung Adenocarcinoma Who Experienced Small-Cell Transformation—Mediated Erlotinib Resistance After Failure of Chemotherapy

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Introduction

EGFR tyrosine kinase inhibitors (TKIs) are approved with durable response as the first-line treatment for patients with NSCLC harboring EGFR-sensitive mutation.1 Almost all patients eventually developed acquired resistance to EGFR TKIs, and phenotypic transformation has occurred in almost 10% of cases.2 After transformation to SCLC, platinum plus etoposide was regarded as the accepted standard, but most patients died quickly owing to limited treatment strategies after failed chemotherapy.3

Here, we report the first clinical evidence of efficacy using a combination of teriprilumab plus anlotinib in a patient with lung adenocarcinoma who had small-cell transformation—mediated erlotinib resistance after failure of chemotherapy.

Case presentation

A 56-year-old female nonsmoker presented to Hunan Cancer Hospital with cough for almost 1 month. Radiological evaluation revealed the primary tumor located in the right lung with widespread bone metastasis. Tissue biopsy and next-generation sequencing (NGS) revealed a diagnosis of lung adenocarcinoma with EGFR exon 19 deletion (Fig. 1A−C). This patient was administered with erlotinib (150 mg daily) as first-line treatment for a duration of 33 months. Because of the increasing tumor size, the patient was evaluated to have progressive disease. Another biopsy was performed, and immunohistochemistry revealed SCLC transformation with positive thyroid transcription factor 1, Syn, and glycoprotein hormones alpha—positive (CGA). NGS further revealed that the patient was still carrying EGFR exon 19 deletion. Concurrent chemotherapy (etoposide plus carboplatin) with radiotherapy (95% planning target volumes, 60 Gy in 30 fractions of 2 Gy for 47 d) was initiated, and erlotinib was chosen as maintenance treatment for 10 months (Fig. 1). With increasing complaint of dysphagia to fluids for 1 month, she was deemed to have progressive disease with newly occurring metastasis in large mediastinal lymph nodes (Fig. 2, left). This caused

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external pressure and stenosis, resulting in failure to perform esophagoscopy. Ultrasound-guided fine-needle aspiration biopsy was then performed. Immunohistochemistry revealed persistent SCLC with positive thyroid transcription factor 1, Syn, and glycoprotein hormones alpha; NGS likewise confirmed that the patient was still carrying EGFR exon 19 deletion. Teriprilumab and anlotinib were then administrated, and a dramatic partial response was achieved as reflected by the decrease in symptoms and improvement of lesions in the mediastinal lymph nodes. Until data cutoff on January 20, 2020, a durable partial response was achieved by at least 9 months with manageable adverse events.

**Figure 1.** Diagram illustrating the various treatments the patient received for metastatic EGFR-mutant NSCLC including the duration of each treatment in months (A), phenotypic transformation (B), and mutations identified by next-generation sequencing performed on tissue and blood samples at specific time-points (C).

**Discussion**

Our case provides a reference that programmed cell death-1 (PD-1) antibody combined with multitarget TKI for tumor angiogenesis and proliferative signaling can be chosen as potential treatment strategies for lung adenocarcinoma developing SCLC transformation after failure of chemotherapy.

Teriprilumab, a humanized IgG-4 monoclonal antibody against the PD-1 receptor, blocks the interaction of PD-1 with its ligands and promotes T-cell activation in clinical studies. It has been approved in advanced melanoma with robust anticancer activity in China. Anlotinib, a novel multitarget TKI for tumor angiogenesis and proliferative signaling (including vascular
Figure 2. Radiological evaluation of the patient before (A) and after (B) teriprilumab and anlotinib combination therapy. Red arrows show the mass.
endothelial growth factor receptor 1 to 3, EGFR, fibroblast growth factor receptor 1 to 4, platelet-derived growth factor receptor α and β, and stem cell factor receptor), has also been approved as standard treatment after failure of initial treatment in NSCLC. Although previous studies reported that monotherapy of checkpoint inhibitors did not yield responses in patients who exhibited transformation to SCLC, our data provided the first evidence in the efficacy of PD-1 inhibitor plus anlotinib in patients with phenotypic transformation. This may be associated with the function of vascular endothelial growth factor (VEGF) as an immunomodulator and illustrate the evidence for anti-VEGF in reprogramming the tumor milieu from an immunosuppressive to an immune-permissive microenvironment in human cancers, thus elucidating the role of anti-VEGF as an optimal combination partner for immune checkpoint inhibitors.

The EGFR-mutant patients with NSCLC who are resistant to EGFR TKI mediated by SCLC transformation covered a large cohort. Beyond etoposide-based chemotherapy, there is a pressing need to find novel effective drugs urgently. Although it was just a case of one patient, our data do provide useful information that checkpoint inhibitors plus antiangiogenic drugs should be considered as a valuable treatment strategy in oncogenic mutant patients with adenocarcinoma who transformed to SCLC. With the remarkable response seen with our patient, a larger cohort clinical trial is needed for further investigation.

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