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Case Report Open Access

Durable Response to Immune Checkpoint Blockade Plus Albumin-Bound Paclitaxel in Two Osimertinib-Refractory Patients with EGFR-mutated Lung Adenocarcinoma

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Abstract

Osimertinib (AZD9291, Tagrisso) is an irreversible third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) compound. Limited effective therapeutic regimens are recommended for patients who progress with osimertinib. We retrospectively reviewed two patients with EGFR mutations who were resistant to osimertinib and received anti-programmed cell death-1 (anti-PD-1) agents combined with Abraxane with stage IV cancer. The two patients (one male and one female) were diagnosed with EGFR mutation-positive advanced lung adenocarcinoma and received first- or second-generation EGFR-TKIs. When these patients became resistant, both received osimertinib. Both patients had disease progression after osimertinib and received combination therapy of immune checkpoint blockade (nivolumab or pembrolizumab) and albumin-bound paclitaxel (Abraxane). These patients achieved partial remission (PR), and their progression-free survival (PFS) were respectively 8.0 months and 10.0 months. The combination of immunotherapy and Abraxane could be an effective option for the treatment of patients resistant to osimertinib.

Keywords: Osimertinib; Resistance; Immune checkpoint inhibitors; Combined modality therapy

Abbreviations: EGFR: Epidermal Growth Factor Receptor; TKI: Tyrosine Kinase Inhibitor; anti-PD-1: Anti-programmed Cell Death-1; Abraxane: Albumin-bound Paclitaxel; PR: Partial Remission; PFS: Progression-free Survival; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; L858R: Leucine-to-arginine Substitution at Amino Acid Position 858; PD: Progressive Disease; CTCAE: Common Terminology Criteria for Adverse Events

Cases and Methods Section

Case 1

A 55-year-old male with no previous history of smoking began complaining of a cough during a physical examination. The patient underwent a computed tomography (CT) scan, which identified a left lung mass with multiple small lesions in both lungs and suspected liver metastasis. The pathological findings were consistent with a diagnosis of adenocarcinoma with negative PD-L1 expression. The patient was treated with six cycles of chemotherapy with cisplatin and pemetrexed with stable disease after two, four and six cycles. Pemetrexed maintenance was discontinued after eight cycles. Next-generation sequencing analysis was performed on a lung lesion, which revealed a positive EGFR exon 19 deletion (ex19del). The patient was therefore started on 250 mg gefitinib, which was administered daily from day 1 to day 21 each month. After 25 months of treatment, the right lung lobe mass progressed again. Considering the oligo-progressive pattern, the patient was treated with thoracic radiotherapy. CT scans showed the emerging appearance of multiple small lesions in the right upper lobe and an increased left pleural effusion. The patient was treated with cisplatin combined with gefitinib. However, CT scans continued to reveal disease progression due to an increasing number of multiple small lesions in both lungs. Plasma samples for mutational reassessment were taken, resulting in positive results for EGFR ex19del and a missense variant of S752F on EGFR exon 19. The patient then commenced a new treatment with osimertinib. Restaging after six months of treatment showed disease progression in lung lesions. Genetic testing was conducted again, showing wild-type EGFR and ALK genes. Afterwards, pembrolizumab plus Abraxane therapy was performed, and CT scans demonstrated partial remission in multiple lung metastases without evidence of brain metastases. Therapy was continued for a total of approximately ten months until the disease progressed to include metastases to the brain. Increasing the tumor mutation burden was observed by the time of tumor progression (Figure 1a). The change trend curve for tumor markers is shown in Figure 1b.

Case 2

A 36-year-old woman with no previous history of smoking presented with increasing headaches. A magnetic resonance imaging (MRI) demonstrated multiple brain lesions on the bilateral frontal and parietal lobes. CT scans revealed multiple metastases at the right hilum associated with a mass in right lower lobes. Metastatic tumors in the ribs and vertebrae were diagnosed. After radiological documentation of lung, bone and brain lesions, a percutaneous aspiration lung biopsy allowed for the diagnosis of lung adenocarcinoma with 80% PD-L1 expression, which was positive for a leucine-to-arginine substitution at amino acid position 858 (L858R) in EGFR on exon 21, with a missense variant in KRAS on exon 2 (c, c.38G >A p.G13D) and a missense variant of TP53 on exon 4 (c, c.215C >G p.P72R). The patient started 250 mg gefitinib, which was administered daily from day 1 to day 21 each month, achieving partial response. After 14 months of treatment,

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the right mass progressed. Therefore, osimertinib was added to the treatment. Nevertheless, five months later, the response was assessed as progressive disease (PD). Afterwards, the patient was treated with three cycles of chemotherapy with carboplatin and pemetrexed, which was discontinued due to the dimensional increase of the right lung mass again. She tried afatinib combined with erlotinib. No evident remission was observed. During the treatment process, the patient received palliative brain radiotherapy and treatment of methotrexate and nimotuzumab intrathecal injections to relieve the neurologic symptoms. Thereafter, she received nivolumab combined with Abraxane and bevacizumab as a multiline treatment and obtained PR for 2 months after the initial of combination therapy. Even the Abraxane had to be applied intermittently for grade 3 myelosuppression according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. PFS was achieved for eight months. Interestingly, after multiple cycles of combination therapy, molecular characterization from liquid biopsy revealed an amplification of MET and exon 21-point mutation at the residue of L858R (Figure 2a). The change in the trend curve for tumor markers is shown in Figure 2b. OS was achieved for eleven months.

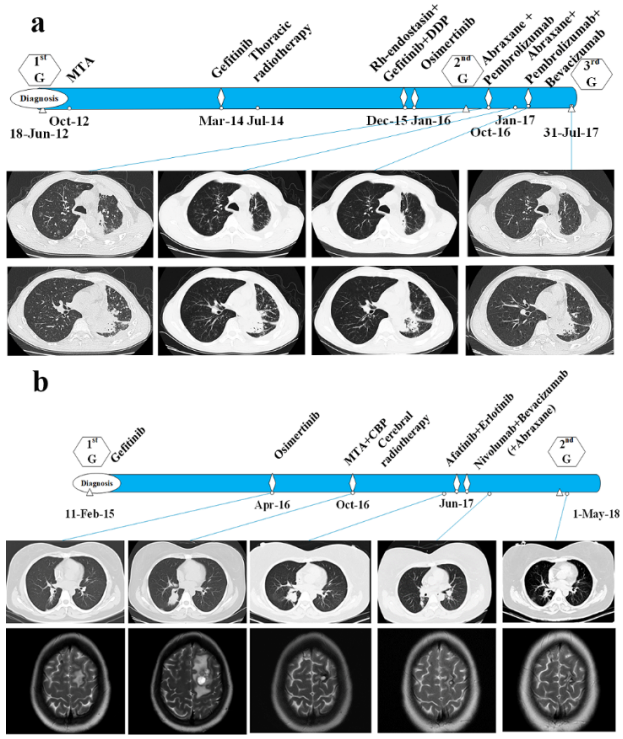

Figure 1: (a) Timeline of treatment and morphologic changes in lung tumors by chest CT in patient 1. Axial CT images are shown, corresponding to the timeline showing therapy and disease statuses. Both panels of CT images show lung lesions when the patient failed in the 4th line of osimertinib and was administered Abraxane and pembrolizumab. After the treatment therapy, the primary lesion was diminished. Multiple metastatic lesions in the right lung disappeared. Lymphangitis carcinomatosa in the left lung was relieved. Pleural effusion was absorbed. During the treatment period, gene detection was performed 3 times. For the first time, the patient was diagnosed with an EGFR exon 19 deletion in tumor tissue. After resistance to osimertinib, the second gene detection in serum was applied and proven as wildtype EGFR. Then, the patient accepted anti-PD-1 agents and Abraxane. Reexamination of NGS in serum was applied with a higher tumor mutation burden as follows: PTEN exon 3 c.183dup p.lys62f 17.61%, EGFR exon 19 del c.2237_2255delinsT p.Glu746_Ser752delinsval 8.34%, CDK 12q14.1 amp(CN=4.62%), ROS1 exon 13 p.K747Q c.1936A>C.p.Lys646Glin 17.3%, EGFR exon 18 missense mutation p.G724S c.2170G>A p.Gly724Ser 7.24%, PTPRD exon44 c.5534 +7_5534+8insACAGTTCAGGAATGGAATGGTAAGTT 21.26%, and BAP1 exon 12 frame shift mutation c.1183_1184del p.Ser395fs 17.06%, MDM2 amp (CN=8.27%) **(b)** Timeline of treatment and morphologic changes in lung and cerebral metastases by chest CT and head MRI scans of patient 2. Representative axial CT scans of lung (top panels) and cerebral (bottom panels) metastases show marked attenuation of radiologic following combined administration of nivolumab plus Abraxane in a patient with metastatic lung adenocarcinoma after resistance to AZD9291. During the treatment period, gene detection was performed 3 times. For the first time, the patient was diagnosed with an EGFR exon 21 mutation in the tumor tissue: EGFR exon 21 p.L858R, KRAS exon 2 missense variant (c, c.38G >A p.G13D), and TP53 exon 4 missense variant (c, c.215C >G p.P72R). After the combination therapy, reexamination by NGS in cerebrospinal fluid was applied with a higher tumor mutation burden detected as follows: EGFR exon 21 p.L858R 86.69%, EGFR amp. (n=14.96), KRAS amp. (n=7.99) and Met amp. (n=3.05).

Discussion

Our case series provides information regarding the efficacy of chemoimmunotherapy as a post-line treatment for lung adenocarcinoma with EGFR mutations and resistant to osimertinib. To date, there have been no reported retrospective studies or prospective clinical trials of the chemoimmunotherapy after resistance to osimertinib treatment in cases of lung adenocarcinoma with EGFR mutation.

These 2 cases presented herein have two unusual features: (1) both

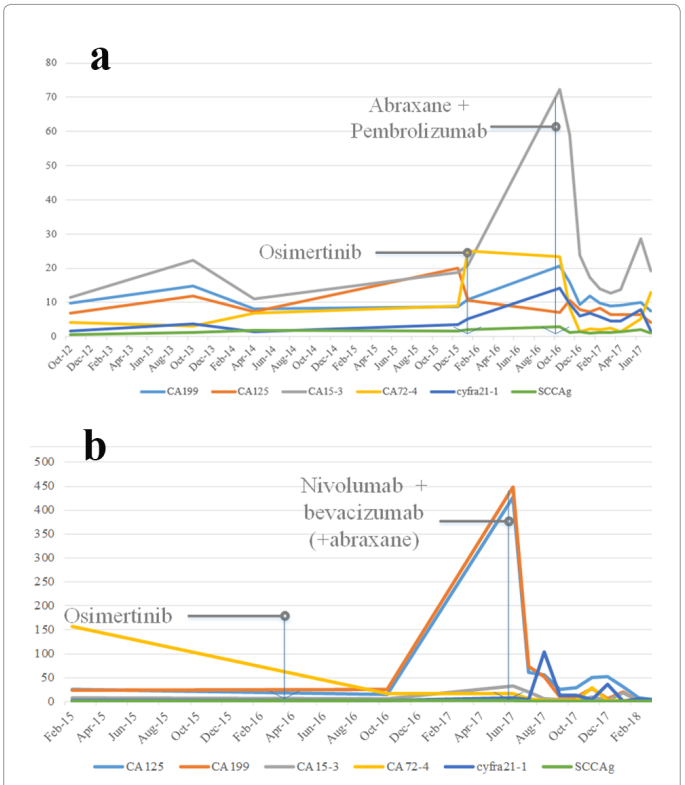

Figure 2: (a) Patterns of tumor markers (CA 19-9, CA 125, CA 15-3, CA 72-4, cyfra 21-1 and SCCAg) tendency of patient 1 from the diagnosed time to the progression of combination therapy of Abraxane and pembrolizumab. The figure shows a sharp decrease in CA 15-3, CA 72-4 and CA 199 after initiation of the combination therapy. **(b)** Patterns of tumor markers (CA 19-9, CA 125, CA 15-3, CA 72-4, cyfra 21-1 and SCCAg) tendency of patient 2 from the diagnosed time to the progression of combination therapy of Abraxane and nivolumab. The figure shows a sharp decrease in CA 12-5 and CA 199 after initiation of the combination therapy. CA 19-9 (carbohydrate antigen 19-9), CA 125 (carbohydrate antigen 125), CA 15-3 (carbohydrate antigen 15-3) and CA 72-4 (carbohydrate antigen 72-4) Units/ml on the Y-axis as indicated, cyfra 21-1 (cytokeratin 19 fragment) and SCCAg (squamous cell carcinoma antigen) ng/ml on the Y-axis as indicated.

patients harbored the EGFR mutation, including exon 19 deletion and the EGFR L858R mutation and resistance to osimertinb and (2) Both patients received anti-PD-1 agent plus Abraxane as post-line therapy. The first case of a patient having a lung adenocarcinoma with multiple small lesions in both lungs and suspected liver metastasis and negative PD-L1 expression. Regarding adverse effects and toxicity reactions, pyrexia and appetite reduction were the most frequently occurring adverse effects for the first case. The second patient in this case study developed seizures from multiple brain metastases, received whole-brain radiotherapy and had a good cerebral response to the combination therapy. Both patients imaging demonstrated an excellent response of primary and brain lesions to the combination of immunotherapy and abraxane treatment.

Aiming at achieving higher efficacy, Prior studies such as KEYNOTE-189 study, KEYNOTE-407 and IMpower 150 that have proved the significant survival benefit with manageable toxicitys of combination chemotherapy with immune checkpoint inhibitors for first-line therapy in patients with metastatic non-squamous NSCLC in patients without EGFR or ALK mutations, which has transformed therapeutic standard [1-3]. However Harboring EGFR mutation was proved to be associated with lower response rates to PD-1/PD-L1 inhibitors compared to EGFR wildtype patients [4,5]. PD-1/PD-L1 inhibitors did not improve the OS over docetaxel therapy in EGFR-mutated advanced NSCLC as a second-line therapy [6]. The most interesting finding in our report was both our cases with EGFR mutation are resistant to osimertinib. Based on the results of clinical trials using anti-PD-1 agents with chemotherapy, we hypothesize that immunotherapy may have its place in patients' resistance to third-generation EGFR-TKI treatments. These results may change the current view that immunotherapy was not applicable to patients who harbor EGFR-sensitive mutations. Immunotherapy is a potential strategy to be utilized as the post-line treatment for patients with EGFR mutation to increase antitumor efficacy immunotherapy-induced chemosensitization effect [1,7-10].

Our case series provides hint of the efficacy of post-line chemoimmunotherapy in lung adenocarcinoma patients resistance to osimertinib. Herein, as we report only 2 cases, Further studies including greater numbers of patients are required to confirm our findings and provide a rationale for future prospective studies.

Conclusion

The combination of anti-PD-1 agents and Abraxane may offer promising alternatives for advanced NSCLC patients harboring EGFR mutations with an acquired resistance to third-generation EGFR TKIs. Our case reports raise several considerations that need to be explored in subsequent studies.

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