Combination of Pembrolizumab With Platinum-containing Chemotherapy for Pulmonary Enteric Adenocarcinoma

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Abstract. Background/Aim: Pulmonary enteric adenocarcinoma (PEAC) is a rare type of non-small cell lung cancer (NSCLC), for which no established standard treatment exists. Combination therapy with the anti-programmed cell death protein 1 antibody pembrolizumab and platinum-containing chemotherapy is the standard treatment for NSCLC patients, but its effectiveness in PEAC is uncertain. Case Report: We present a 68-year-old man with chemotherapy-naïve advanced PEAC who responded to a combination of pembrolizumab and platinum-containing chemotherapy. Conclusion: The number of PEAC cases is small, and no clinical trials have been conducted to determine an optimal chemotherapy regimen. In this case, we showed that pembrolizumab combined with platinum-containing chemotherapy might effectively treat PEAC.

Although a few case reports and case studies on PEAC have been published, no standard treatment has been established. Chemotherapy regimens similar to those used for treating colorectal cancer, including a combination of 5-fluorouracil, oxaliplatin, or irinotecan as a base, have been reported to be largely ineffective (2–4). In contrast, chemotherapy regimens similar to those used in non-small cell lung cancer (NSCLC), such as taxanes, gemcitabine, or carboplatin, have been shown to be effective (2, 5).

Recently, combination therapy with immune checkpoint inhibitors (ICIs) and platinum-containing chemotherapy has been established as standard treatment for advanced-stage NSCLC (6). Here, we present the case of a patient with PEAC who received the anti-programmed cell death protein 1 antibody pembrolizumab combined with platinum-containing chemotherapy. The results suggest that this combination chemotherapy may be the key to treating this rare advanced-stage lung cancer.

Case Report

A 68-year-old man visited the orthopedic department of our hospital with the chief complaint of left hip pain. The patient was a past-smoker with a Brinkman index of 640. A chest to pelvis computed tomography scan showed a mass, 7 cm in diameter, in the lower lobe of the right lung, enlarged ipsilateral mediastinal lymph nodes, multiple hepatic masses, left adrenal nodules, and osteolytic lesions in the left femur, right ilium, and sacral vertebrae. A biopsy specimen taken from the lower lobe of the right lung showed tumor cells having a cylindrical morphology and forming glandular tubular structures. Immunostaining showed that among the markers of lung differentiation, novel aspartic proteinase of the pepsin family A (NapsinA) and thyroid transcription factor-1 (TTF-1) were negative, while cytokeratin (CK) 7 was positive. The typical colon...
markers such as caudal-type homeobox transcription factor 2 (CDX2) and CK20 were positive (Figure 1). We performed upper and lower gastrointestinal endoscopy, which showed no malignant findings. Therefore, the patient was diagnosed with PEAC cT3N2M1c stage IVB. The Oncomine Dx Target Test multi-Cdx system (Thermo Fisher Scientific Inc., Waltham, MA, USA) showed that the tumor was positive for \( \text{KRA S} \) G12D mutation, and the tumor proportion score (TPS) for programmed cell death ligand 1 (PD-L1) was less than 1%.

The patient received palliative radiation for the bone metastases, which were the cause of pain, and chemotherapy with pembrolizumab (200 mg, q 3 weeks), carboplatin (area under the curve=5 mg/ml/min, q 3 weeks), and pemetrexed (500 mg/m², q 3 weeks) was started in parallel. After four cycles, both the primary and metastatic lesions had shrunk, and the patient was switched to maintenance therapy with pembrolizumab and pemetrexed (Figure 2). After three cycles of maintenance therapy, the patient developed grade 3 interstitial lung disease, probably due to pembrolizumab or pemetrexed, and required steroid therapy. Steroid therapy was tapered off after the improvement in interstitial lung disease (Figure 3). Although chemotherapy was discontinued, the primary and metastatic lesions continued to shrink five months after discontinuation (Figure 2).

**Discussion**

PEAC occurs infrequently and accounts for 0.5% of all NSCLCs (7). The average age of patients is between 50 and 60 years, with an almost equal male to female ratio, and 45% of patients have a history of smoking (8-11). PEAC is a primary lung adenocarcinoma with more than 50% intestinal component (12-14). However, its immunohistochemical and molecular characteristics have not been studied in detail because of its rarity, which makes establishing a definitive diagnosis difficult. To confirm the diagnosis, it is necessary to ensure that at least one of the intestinal differentiation markers (CDX2, CK20, mucin 2) is expressed by the tumor and exclude metastatic colorectal cancer (1, 12). In this case, the tumor cells showed a cylindrical morphology and formed glandular tubular structures, and this histology accounted for the majority of the tumor. Immunostaining showed that the intestinal differentiation markers CDX2 and CK20 were positive, while the pulmonary differentiation markers NapsinA and TTF-1 were negative while CK7 was positive. Since upper and lower gastrointestinal endoscopy showed no malignant findings, PEAC was diagnosed.

Genetic analysis has shown that the frequency of \( \text{EGFR} \) mutations in PEAC is low (2-20%), while that of \( \text{HER2} \) and \( \text{KRA S} \) mutations is high (40% and 20-60%, respectively) (15-18). It has also been reported that mutations in DNA
mismatch repair genes, which cause microsatellite instability, are present in 20-80% of patients and that the tumor mutation burden is high; therefore, ICI is expected to be effective (15, 17).

In this case, the Oncomine Dx Target Test multi-Cdx system was used to search for the driver mutation, and KRAS G12D mutation was identified; however, there is no effective drug that targets this mutation. The combined use of ICI and platinum-containing chemotherapy is the first-line treatment for driver mutation-negative advanced-stage NSCLC. Therefore, we started treatment with the three-drug regimen containing pembrolizumab, carboplatin, and pemetrexed. After four cycles of combination chemotherapy, the patient was switched to maintenance therapy with pembrolizumab and pemetrexed. After three cycles of maintenance therapy, chemotherapy was discontinued because of adverse events. Since then, the patient has been undergoing follow-up without receiving treatment, and has not shown any disease progression for five months, indicating that pembrolizumab is expected to have a long-term effect.

There are several case reports on the treatment of PEAC with platinum-containing chemotherapy. However, to our knowledge, there are no reports of combination therapy with pembrolizumab and platinum-containing chemotherapy being effective. A study on the combined use of ICI and platinum-containing chemotherapy for advanced NSCLC showed that the objective response rates and progression-free survival tended to be inferior in patients with PD-L1 TPS less than 1% compared to those of patients with PD-L1 TPS greater than 1% (6). In this case, we observed the interesting phenomenon of a longer duration of response despite PD-L1 TPS being less than 1%. Therapeutic efficacy of pembrolizumab alone also needs to be explored. Accumulation of clinical experience is necessary to better

Figure 2. Computed tomography (CT) before the start of treatment showed a primary tumor, 7 cm in diameter, in the lower lobe of the right lung (A), as well as a metastatic liver mass (B) and a left adrenal nodule (C). CT after four cycles of triple chemotherapy the primary and metastatic lesions shrank (D, E, F). After three cycles of maintenance therapy, chemotherapy was discontinued due to adverse events, and CT at five months did not show progression of primary or metastatic disease (G, H, I).

Figure 3. Chest computed tomography (CT) shows interstitial lung disease after three cycles of maintenance therapy (A). Repeat chest CT shows improvement in interstitial lung disease after steroid administration (B).
treat this rare lung cancer. Our case indicates the potential benefit of the combined use of pembrolizumab and platinum-containing chemotherapy for the treatment of PEAC.

**Conclusion**

Due to its rarity, a standard treatment strategy for PEAC has not been established. In this case, we showed that the combined use of pembrolizumab and platinum-containing chemotherapy might effectively treat PEAC. However, large-scale prospective clinical trials are needed to confirm the safety and efficacy of this regimen.

**Conflicts of Interest**

The Authors have no conflicts of interest to declare in relation to this study.

**Authors’ Contributions**

ST designed the study. CS, KN, WS, AM, SH, CM, HT and ST collected the data. NM, YN, NH, ST, NK, MY, MK and TK analyzed the data and prepared the article. All Authors approved the final version of the article.

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