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Long-Lasting Response with Anti-PD-1 Antibody Following Progression on Anti-PD-L 1 Antibody in Advanced Non-Small Cell Lung Cancer (NSCLC): A Case Report and Review of the Literature

Introduction

Lung cancer is the leading cause of cancer incidence and mortality worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases, with around 1 million new diagnoses of advanced NSCLC (aNSCLC) each year worldwide [2,3]. The prognosis for aNSCLC remains poor, with a 1-year survival rate of only 29% following cytotoxic chemotherapy [4]. Before the advent of immune and target therapy, treatment options were limited to chemotherapy, which offered a median survival of about 12 months and had a challenging adverse event profile [5]. One-third of individuals with aNSCLC experience brain metastases [6]. At this time, the prognosis is even worse. More specifically, median overall survival (OS) estimated at 7.8 months, regardless of whether patients initially present with or later develop brain metastases [7].

Immune checkpoint inhibitors (ICIs) have transformed the treatment landscape for NSCLC. These therapies, particularly programmed death 1/programmed death 1 ligand (PD-1/PD-L1) inhibitors, have demonstrated more durable responses than traditional cytotoxic agents [8-11]. In the era of immunotherapy, these inhibitors are increasingly used, especially for aNSCLC patients without oncogenic driver mutations [12,13]. Pembrolizumab, an anti-PD-1 monoclonal antibody, has shown significant improvements in OS in the first-line setting, both as monotherapy for patients with a PD-L1 tumor proportion score (TPS) of ≥ 1% and in combination with platinum-based chemotherapy, regardless of PD-L1 expression [14-16].

Despite these advancements, the rapid clinical decline often observed during disease progression means that fewer than half of patients with aNSCLC receive second-line therapy [17,18]. For these patients, introducing ICIs for second-line treatment has further improved survival rates, whether used as a first-line or second-line option, especially for those with driver gene-negative aNSCLC [19,20].

Notwithstanding this progress, there is currently limited evidence supporting the use of ICIs as a second-line treatment after initial ICI therapy in aNSCLC. This case report presents an intriguing example of a 36-year-old patient with poor performance status who was diagnosed with metastatic lung adenocarcinoma in 2022. After disease progression on first-line therapy with combination of anti-PD-L1 inhibitor and platinum-based chemotherapy, the patient was treated with a second-line regimen re-challenging agents targeting PD-L1 on agents targeting PD-1. Remarkably, this approach yielded significant radiological and clinical improvements, leading to a notable enhancement in the patient's performance status and overall quality of life.

Case Report

A 36-year-old patient was diagnosed with Non-Small Cell Lung Cancer in August 2022. The diagnosis was confirmed through a biopsy performed by lymph node excision, which revealed lung adenocarcinoma with PD-L1 expression levels (PD-L1 IHC SP263) TPS 3% and CPS-4, No EGFR, ALK and BRAF mutations were detected. Initial imaging studies, including a chest and abdomen CT scan, indicated the presence of bone metastatic lesions, bilateral supraclavicular metastatic lymph nodes, mediastinal lymphadenopathy, a right lung node, bilateral lung tumor nodules, metastatic lesion in the liver. Brain MRI doesn't revealed any metastatic lesion. The patient has a history of smoking for 12 years 1 pack/day. In terms of family medical history, his grandfather had lung cancer.

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Before admission to our hospital, the patient received the first-line immunochemotherapy with Cisplatin, Etoposide, and Atezolizumab (3 cycles, from 08-10.2022 in another institution). After three cycles his performance status was worsen, and clinical and Radiological assessment showed disease progression (FIG.1). In October 2022, the patient began experiencing neurological symptoms (ataxia, Cognitive Impairment, seizures, fatigue, ECOG PS 2-3) and hospitalized in emergency department. A brain MRI detected intra- and extracranial multiple metastatic lesions (Fig.2). The patient was without treatment for the following 3 months (Following disease progression, the patient did not return for further follow-up appointments at the clinic).

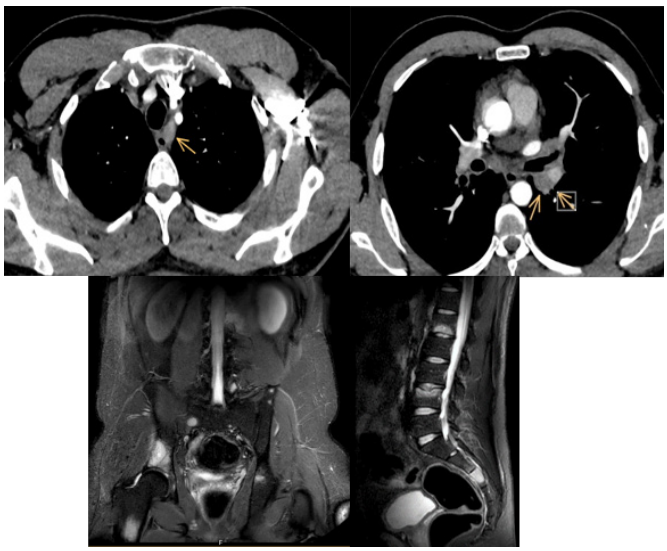

Figure 1: Small, enhancing mass in the right middle lobe, border of 4 and 5 segments, adjacent to the pleura. In size 15/12 mm. Enlarged paratracheal, subcarinal, pre-pericardial and bilateral hilar lymph nodes. Maximum size 16/14 mm (left hilar), Multiple, osteolytic metastatic lesions in cervical and lumbar vertebra, pelvic bones.

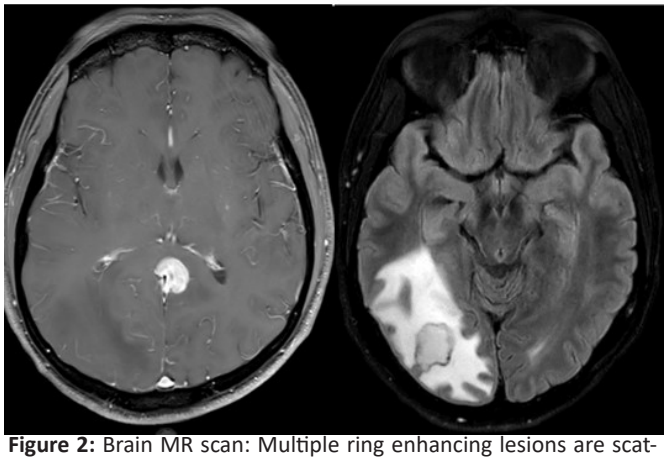

Figure 2: Brain MR scan: Multiple ring enhancing lesions are scattered at both cerebral hemispheres. They elicit intermediate or isointense signal at T2/FLAIR and marginal post contrast enhancement with no diffusion restriction, they are surrounded by vasogenic edema. Max. size 24/20 mm in right occipital lobe.

When the patient admitted to our hospital (01.2023), second opinion molecular testing confirmed lacking of driver mutations (EGFR/ALK). Subsequently, the patient underwent palliative radiotherapy with a total dose of 30 Gy (Whole Brain irradiation, L2-L5 vertebra, pelvic bone). The case was discussed by the multidisciplinary team (MDT), given the metastatic nature of the NSCLC (PD-L1=3%, no driver mutations), it was advised to start the second-line treatment, using anti-PD-1 immunotherapy in combination with Cisplatin/Pemetrexed. Taking into account patient's age, lack of comorbidities, treatment free interval and previous regimen without pemetrexed (Cisplatin/pemetrexed is the standard of care for NSCLC adenocarcinoma histology in our institution). After palliative radiotherapy patient's PS was ECOG 2. From 03.2023 immunochemotherapy was started with pembrolizumab (200 mg every 3 weeks), cisplatin (75 mg/m² q21), and pemetrexed (500 mg/m² q21). After three cycles, the patient underwent brain MRI and chest/abdomen/pelvic CT scans (05.2023), which revealed a partial response. The whole-body FDG PET/CT (09.2023) scan revealed medium intensity FDG uptake in the right lung subpleural node. Additionally, there were multiple sclerotic and lytic lesions throughout the bones, with mild intensity FDG uptake. The Brain MRI scan: indicating no significant progression or regression compared to previous scans. During treatment patient's general condition was improved, patient became fully active and disease was controlled. After 4 cycles using platinum compound regimen, the treatment was continued with maintenance pemetrexed/pembrolizumab, until disease progression or unacceptable toxicity. The whole-body FDG PET/CT (01.2024) scan showed a favorable response, with a decrease in FDG uptake. (FIG.3).

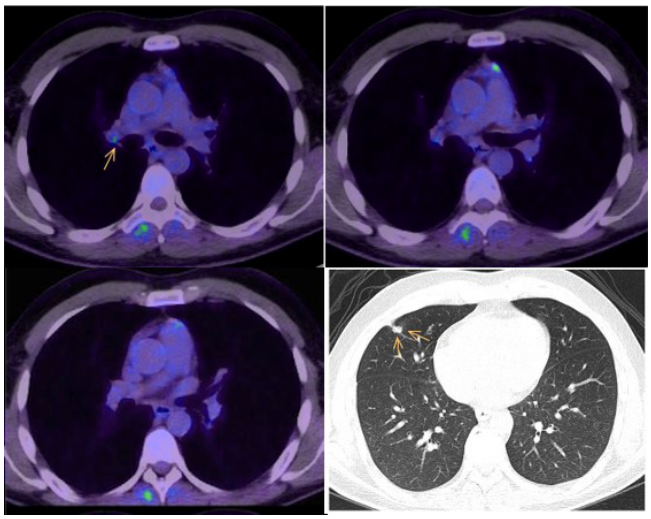

Figure 3: The nodule in the middle lobe of the right lung is reduced in size. Its size is 9/7 mm (was 15/15 mm). The size of mediastina and hilar lymph nodes is also significantly decreased. Most of them doesn't appear anymore. Metastatic pulmonary nodules in both lungs no longer differentiate.

Now the patient is on treatment, with durable excellent response on immunochemotherapy without any complaints, maintaining a high quality of life. (09.2024) (FIG 4.)

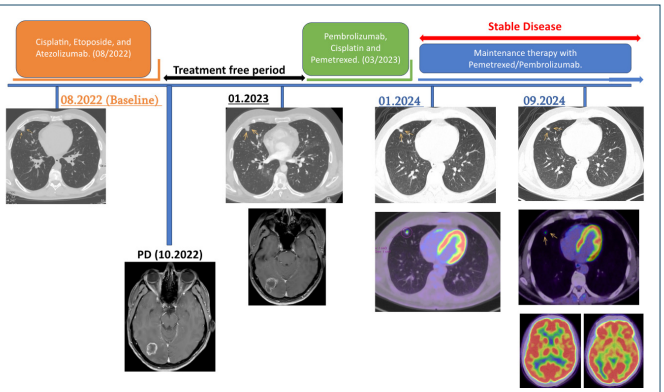

Figure 4: Short summarizing of radiological images.

Discussion

Here, we reported the case of a patient who responded to combination of PD-1 inhibitor and platinum-based chemotherapy in the second line of treatment, which had previously failed with a PD-L1 inhibitor and cytotoxic chemotherapy. Immune checkpoint inhibitors (ICIs), including anti-programmed cell death-1 (PD-1) and anti-programmed cell death ligand-1 (PD-L1) antibodies, have changed the treatment landscape for patients with advanced NSCLC [21-23]. The phase 3 KEYNOTE-189 and KEYNOTE-407 [16,24]. studies found that pembrolizumab, an anti–PD-1 monoclonal antibody combined with standard platinum-doublet chemotherapy significantly improved overall and progression-free survival compared to chemotherapy alone in patients with metastatic non-squamous and squamous NSCLC, regardless of PD-L1 TPS. Pembrolizumab plus chemotherapy may be more effective than pembrolizumab alone, especially in patients with lower PD-L1 expression. Updated data from the KN-189 trial indicated that overall survival (OS) outcomes were similar across PD-L1 TPS groups: ≥50% (HR, 0.59; 95% CI, 0.39-0.88), 1% to 49% (HR, 0.62; 95% CI, 0.42-0.92), and <1% (HR, 0.52; 95% CI, 0.36-0.74) [25]. Still now, for advanced NSCLC that progresses after platinum-based chemotherapy and immunotherapy, treatment options are limited to chemotherapy, regardless of actionable genomic alterations or PD-L1 status [26].

Currently, after progression to immunotherapy, the effectiveness of ICI rechallenge remains controversial for aNSCLC patients. Post-hoc analyses of the Keynote 010 study [27] found that 14 patients retreated with pembrolizumab after disease progression achieved an overall response rate (ORR) of 42.9%. Additionally, in the OAK study [28], 51% of patients in the atezolizumab arm who experienced disease progression continued atezolizumab treatment beyond progression. The OS for this group was longer than for those who switched to non-protocol anti-cancer therapies or received no follow-up treatment (12.7 months vs. 8.8 months vs. 2.2 months). These findings suggest that re-administering PD-1 inhibitors may still offer benefits after tumor progression.

A real-world study involving over 4,000 aNSCLC patients in the USA found that those receiving immunotherapy beyond progression (IBP) had longer OS compared to non-IBP patients (11.5 months vs. 5.1 months, $p < 0.001$) [29]. Similarly, a study by Ge et al. with 125 aNSCLC patients reported an OS of 26.6 months for the IBP group compared to 9.5 months for non-IBP patients ($p < 0.001$) [30]. Another study by Tian et al. also showed longer OS in the IBP group (15.7 vs. 5.0 months, $p < 0.001$) [31].

A study by Ziyi Xu et al. suggested that ICI rechallenge could be a viable option for NSCLC patients who progress after immunotherapy. In this research, the median progression-free survival (PFS) with initial immunotherapy was 5.8 months, compared to 6.8 months with ICI rechallenge [32]. In a retrospective study by Min Wang et al. assessing the efficacy of immunotherapy beyond progression, 121 patients with DP were divided into two groups: the IBP and non-IBP groups. OS and PFS showed no significant differences between the two groups across the entire population. The authors concluded that the clinical outcomes for the IBP group were similar to those for the non-IBP group in advanced NSCLC patients following first-line immunotherapy [33]. However, several studies have reported conflicting results. A study by Enomoto et al. [34] found no significant benefits from continuing nivolumab in aNSCLC patients. Similar findings were observed in two smaller studies [35,36], that reported no advantages from ICI re-challenge. Some studies suggest that NSCLC that is resistant to initial ICI therapies may show limited responses to ICI rechallenge, providing clinical benefits to only a small subset of patients. The ORR ranged from 0% to 8.5%, with a median PFS of 1.5 to 2.9 months and a median OS of 6.5 to 11.0 months [35,37, 38].

Our patient had excellent and durable response on PD-1 inhibitor and chemotherapy after failure of combination of PD-L1 inhibitor and cytotoxic chemotherapy. To date, limited published data is available about the efficacy and safety of using of PD-1 inhibitors after failure of anti PD-L1 agents. Although PD-1 and PD-L1 inhibitors operate through similar mechanisms, they exhibit differences in efficacy. Comparative analysis using half-maximal effective concentration (EC50) values from functional assays showed that PD-L1 antibodies have significantly lower EC50 values than PD-1 antibodies, indicating that PD-L1 inhibitors may be more effective [39]. Practically, PD-1 and PD-L1 inhibitors are considered equally effective, despite a lack of direct comparisons. Mechanistically, PD-1 inhibitors block the interaction between PD-1 and its ligands, PD-L1 and PD-L2, which negatively regulate T cell activation. In contrast, PD-L1 inhibitors prevent PD-L1 from engaging with its receptors, PD-1 and CD80. While CD80 is generally a co-stimulatory receptor, it can also negatively regulate T cells, and its overexpression may contribute to resistance against PD-1 inhibitors [40, 41].

In this case, our patient exhibits a partial, durable response despite having a low PD-L1 TPS of 3%. Some studies indicate that PD-L1 expression is not a reliable indicator of sensitivity to immunotherapy. Immune checkpoint inhibitors (ICIs) may also benefit individuals with negative PD-L1 expression, and their ability to predict responses to immunotherapy is not particularly strong [11,42]. Despite this, PD-L1 is still considered an inadequate biomarker, as some individuals with high PD-L1 expression do not respond to treatment, while those with negative or low expression often show a positive response [43]. While pembrolizumab based therapy can lead to significant and lasting tumor responses, the lack of reliable biomarkers to predict individual prognosis presents a significant challenge for its broader clinical application. Another potential biomarker, tumor mutational burden (TMB), shows promise, but its predictive value remains debated [44]. In referring back to our case, after progression on atezolizumab/cisplatin-based chemotherapy, the patient was started on pembrolizumab combined with cisplatin/pemetrexed, along with vitamin B12 and folic acid supplements. The carboplatin and pemetrexed chemotherapy regimen is widely recognized as the standard first-line treatment for adenocarcinoma histology. Molecular findings showed that the patient's tumor was negative for EGFR, BRAF, and immunohistochemistry showed no ALK rearrangements and 3% PD-L1 expression. Lab results showed normal creatinine levels and liver function.

When selecting a combination of PD-1 inhibition and chemotherapy, various factors must be considered. Our patient presented with a significant symptom burden, including fatigue, cough, dyspnea, anorexia, weight loss, and pain. Considering the patient's age, absence of comorbidity, treatment-free interval, and previous treatment regimen, chemotherapy was added to anti-PD-1 therapy for fast effect considered symptoms improvement alongside survival. The selection of the second-line systemic therapy also based by a network meta-analysis that indirectly indicated that pembrolizumab combined with chemotherapy resulted in prolonged overall survival compared to the atezolizumab chemotherapy group [45]. It is well-estab-

lished that chemotherapy agents possess immunomodulatory properties, which can directly and indirectly stimulate immune responses and enhance tumor immunogenicity. Additionally, chemotherapy may boost the anti-tumor effects of immunotherapy, potentially increasing the chances of clinical benefit from pembrolizumab, irrespective of tumor PD-L1 expression [46,47].

In our case, the patient exhibited an unexpected, partial, and long-lasting response to ICI rechallenge. It is well recognized that patients who previously responded well to immunotherapy tend to derive greater survival benefits from second-line ICI-based treatments. While the exact mechanism for this observation remains unclear, one possible explanation is that patients who had favorable responses to prior immunotherapy developed immune memory cells [48,49], allowing for a quicker restoration of the immune system during subsequent rounds of treatment. The patient fully tolerated both the chemotherapy agents and the anti-PD-1 therapy, experiencing no serious side effects. This is noteworthy considering that the incidence of grade 5 treatment-related adverse events was higher in the pembrolizumab plus chemotherapy group compared to the chemotherapy-only group [50,51]. This case may indicate the potential effectiveness of re-challenging ICI in selected patients with advanced NSCLC who have progressed on prior ICI treatment. However, further research is needed to confirm the efficacy and safety of this approach in NSCLC patients.

Conclusion

To summarize, this case report shows the potential role of switching to anti-PD-1 treatment in selected patients with NSCLC who were non-responsive to PD-L1 inhibition. Clinical trials investigating this strategy would be highly beneficial for this cohort of patients.

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Conflict of Interest: Other authors declare no conflicts of interest.

Author Contributions: LC, AG and IK: conceptualization and study design. LC, AG and MV: data collection. LC, AG and IK: literature research. LC, AG and IK: manuscript drafting. LC, AG and IK: revision. All authors contributed to the article and approved the submitted version.

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