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CASE REPORT

Crossing the River by Feeling the Stones: Experiences with PD-1 Inhibitors in Geriatric Oncology People, a Case Report and Literature Review

Hang Yin[1,*], Xia Zhang[2,*], Manjie Zhang[1], Hong Tang[1], Chunxia Zhang[1], Jia Li[1]

[1]Oncology Department, The First Affiliated Hospital of Dalian Medical University, Dalian, 116000, People's Republic of China; [2]Oncology Department, Dalian Fifth People's Hospital, Dalian, 116000, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jia Li; Chunxia Zhang, The First Affiliated Hospital of Dalian Medical University, Dalian, 116000, People's Republic of China, Email lijia_211@hotmail.com; qm1210@hotmail.com

Abstract: Currently, lung cancer remains one of the deadliest cancers, with a very high mortality rate, accounting for approximately 18% of all cancer-related deaths. Non-small cell lung cancer (NSCLC) accounts for 80% of all lung cancer deaths. In particular, elderly patients generally have poor tolerance to chemotherapy or cannot tolerate chemotherapy. This case analysis focuses on an elderly patient with non-small cell lung cancer stage IV. The patient was an 86-year-old female with poor nutritional status and low body weight (27 kg) and could not tolerate platinum-based dual-drug first-line chemotherapy. This patient had tumour cells in alveolar lavage fluid without conditions examined for pd-l1 expression. However, the efficacy of previous first-line immunotherapy was positive, and the patient and his family members agreed to apply it, so there was no contraindication to apply anlotinib + pembrolizumab. Results were reviewed after two cycles, and CR was used to evaluate the efficacy. After four cycles, the efficacy was evaluated as complete remission (CR), the patient developed immune-related side effects, immunotherapy was suspended, and maintenance therapy with anlotinib was used. The most recent review was in 2023-6-9, and PET/CT indicated that the patient had sustained CR. In general, this case provides support for the successful possibility of a treatment strategy for elderly patients with poor physical fitness who cannot tolerate platinum-based doublet chemotherapy and who have driver gene-negative squamous cell lung cancer (PS>0-1).

Keywords: pembrolizumab, immune checkpoint inhibitors, non-small cell lung cancer, case report, anlotinib

Introduction

Cancer incidence and mortality rates in China both increased with age and peaked in the age group of 80–84 years and 85+ years for males and females.[1] The SEER database reports that 50% of lung cancer cases are found in individuals aged 70 and above, with 15% of cases diagnosed in patients over 80 years old, where the highest mortality rates are observed within these age groups.[2] Despite significant advances in cancer treatment over the past decade, there is currently a lack of consensus on the optimal treatment for elderly patients with driver gene-negative non-small cell lung cancer (NSCLC).[3] These patients often have comorbid conditions, poor performance, and low tolerance to chemotherapy, which likely contributes to the lower rates of guideline-concordant lung cancer treatment in the elderly tumor population.[4]

Recently, the combination of immune checkpoint inhibitors (ICIs) with chemotherapy has been shown to improve the survival rates of patients with squamous non-small cell lung cancer, regardless of PD-L1 expression.[5] Unfortunately, in clinical trials that could potentially change clinical practice, older individuals are often underrepresented. In most clinical practices, the median age of ICI clinical trials is 60–65 years old. In the CheckMate 078 study, only 2% of the study were 75 years or older,[6] so the research on ICIs in patients older than 85 years is limited. Combining ICIs with chemotherapy is unsuitable for geriatric

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oncology patients. So, this case report an elderly driver gene-negative non-small cell lung cancer patients who benefit from first-line treatment with immunotherapy and anlotinib agents. Hope to provide a reference for the treatment plan of such patients.

The report has been communicated to the patient's family and has received their consent. It has also been approved by the First Affiliated Hospital of Dalian Medical University.

Case Presentation

An 86-year-old female presented with chest pain, chest tightness, and shortness of breath for one month and sought medical attention in December 2021. Her body surface area (BS) was 1.1m^2, her weight was 27 kg, and her ECOG performance status was 1. She had no comorbid conditions, no smoking history, and no family history of lung cancer.

A chest CT scan on December 17, 2021 (Figure 1A), revealed a soft tissue mass with a disrupted bronchus in the left lower hilar area. The mass had well-defined borders and measured approximately 2.9×1.3 cm with a CT value of approximately 46 Hounsfield units (HU).

A PET/CT scan on December 23, 2021 (Figure 1B), showed increased FDG metabolism in a mass in the left lower hilar area with a maximum standardized uptake value (SUVmax) of 11.2, measuring 3.1×1 cm.

The patient underwent tracheoscopy in January 2022. Immunohistochemical staining revealed the following results: CD56 (NK-1)(-), CgA(-), CK7(-), Napsin-A(-), P40(+), Syn(-), TTF-1(-), Ki-67(+25–50%), and CK5/6(+). Combining the cytological findings with the immunohistochemistry results supported the diagnosis of poorly differentiated non-small cell carcinoma, with a tendency towards squamous cell carcinoma (Figure 1C).

CT, PET/CT, and bronchoscopy supported the diagnosis of left lung squamous cell carcinoma cT4NxM1a stage IV with obstructive lung atelectasis, lung metastasis (AJCC staging method). Continued NGS gene testing detected no gene mutations or PD-L1 expression due to insufficient sample material.

The patient did not tolerate chemotherapy because of their elderly age and low weight. This patient had no clear pd-l1 expression, the efficacy of pembrolizumab monotherapy is uncertain, combination therapy is needed to ensure the curative effect and patients are not suitable for combined chemotherapy. Combined antiangiogenic drugs is a better option and anlotinib was administered as convenient, and the patient had good compliance with oral administration. The incidence of side effects such as proteinuria and hypertension was low, and considering that the patient was weak, the antiangiogenic+anlotinib dose was limited to 8 mg every day. Combined treatment with anlotinib and pembrolizumab was proposed until disease progression or intolerance. The specific dosages were as follows: 8mg anlotinib was administered once daily on Days 1–14 of

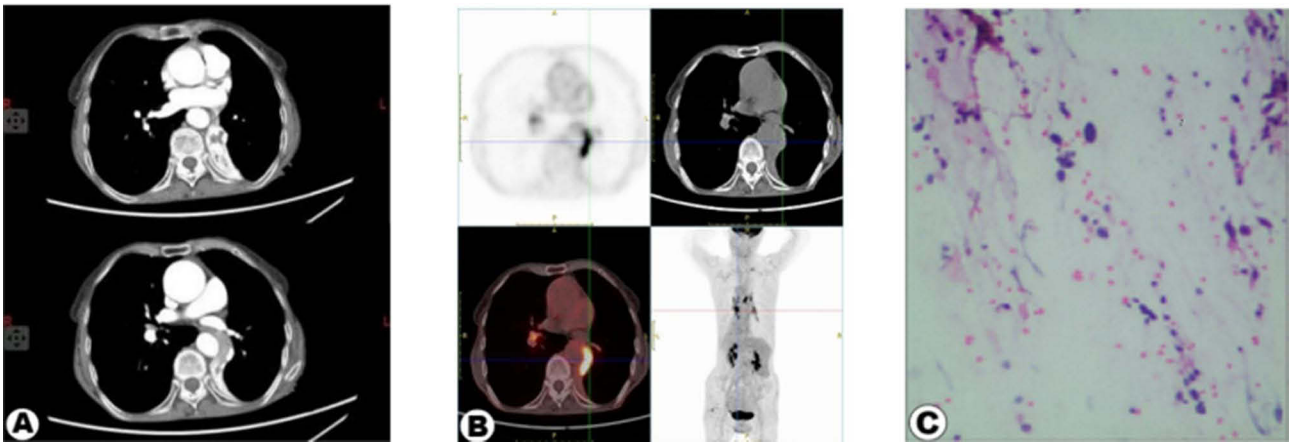

Figure 1 Pathological and image findings of the patient on the first visit. (**A**) A chest CT scan on December 17, 2021 (**A**) revealed a soft tissue mass with a disrupted bronchus in the left lower hilar area. The mass had well-defined borders and measured approximately 2.9×1.3 cm with a CT value of approximately 46 Hounsfield units (HU). The arterial phase enhancement showed CT values of 105 HU and 122 HU, respectively. Atelectasis was observed in the left lower lobe. Multiple nodular opacities were found in both lungs, with miliary opacities and a larger opacity measuring approximately 0.7 cm in diameter in the right upper lung, showing spiculation and adjacent pleural traction. (**B**) A PET/CT scan on December 23, 2021 (**B**) showed increased FDG metabolism in a mass in the left lower hilar area with a maximum standardized uptake value (SUVmax) of 11.2, measuring 3.1×1 cm. This was suggestive of central-type lung cancer in the left lung with associated atelectasis in the left lower lobe. A small nodule measuring 0.8 cm in the right upper lobe showed increased FDG metabolism (SUVmax of 7.5). (**C**) depicts the pathological slide of the patient's tumor tissue stained with hematoxylin and eosin. (×400).

a 21-day cycle, and 200mg pembrolizumab was administered for 3 weeks. The patient was closely monitored for immune-related adverse events. Before the second cycle of treatment, an enhanced CT scan was performed. Assessing treatment response according to the RECIST 1.1 criteria. The patient showed a complete response (CR). The patient developed hypothyroidism and fatigue symptoms after three cycles, thyroxine tablets were supplemented, and regular review was performed. The patient had hypokalaemia and a prolonged QT interval caused by hypokalaemia and was given potassium supplementation. The diet was poor during the treatment period, and the patient had poor nutritional status. Low potassium is associated with this effect. The patient could not tolerate the fatigue, the immunotherapy was stopped, and the QT interval was normal. The subsequent treatment was maintained with tolerable and effective drugs. The patient had no abnormal blood routine during the double-drug treatment, so anlotinib maintenance therapy was selected. (Figure 2) April 2022, followed by maintenance treatment with anlotinib. For maintenance treatment, 8 mg anlotinib was administered once daily on Days 1–14 of a 21-day cycle.

After potassium supplementation, the QTc interval returned to normal. QTc prolongation and kaliopenia were considered to be related to the patient's poor appetite and immunotherapy with checkpoint inhibitors. Immunotherapy with checkpoint inhibitors was temporarily discontinued, and close follow-up was advised. Followed by maintenance treatment with anlotinib. During this period, the patient underwent multiple follow-up examinations at the hospital, and the results are shown in Figure 3. The latest follow-up was conducted on June 9, 2023, with a chest PET/CT scan that showed sustained CR. This old patient benefited from combination therapy. (Figure 4)

Discussion

Several prospective and retrospective studies have determined the efficacy of immune checkpoint inhibitors and anlotinib in elderly patients through the analysis of multiple experimental groups. Monotherapy with immune checkpoint inhibitors with anlotinib has shown comparable effectiveness between elderly patients and younger patients. Combination treatment regimen may be a better treatment option for elderly patients who are intolerant to chemotherapy. A study included all patients aged 70 years or older with advanced non-small cell lung cancer (NSCLC) who received first-line pembrolizumab monotherapy or combination therapy with chemotherapy at Thoraxklinik Heidelberg between January 2016 and May 2021. Compared to pembrolizumab monotherapy (10 out of 61 patients or 16%), treatment-related adverse events were more frequent with chemoimmunotherapy (82 out of 95 patients or 86%, $P < 0.001$). In this context, treatment discontinuation due to toxicity occurred in 49 cases (31%), and 68 cases (44%) required hospitalization for the management of side effects, with a significant correlation between the two (42 out of 156 patients experienced both,

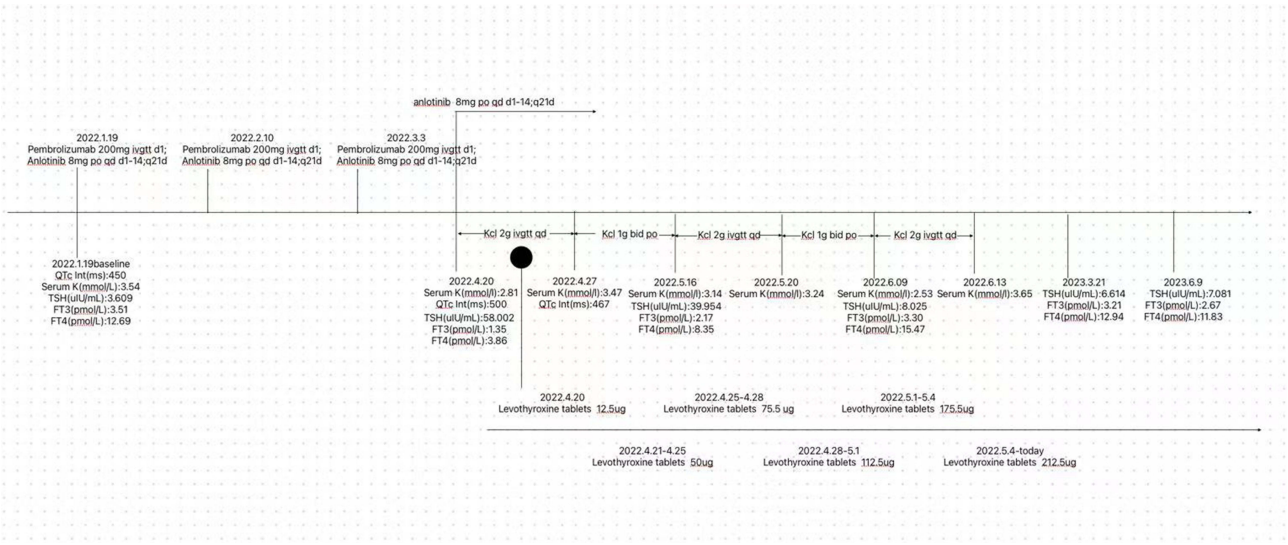

Figure 2 Illustrates the treatment process of the patient, including therapeutic medications and relevant examination results.

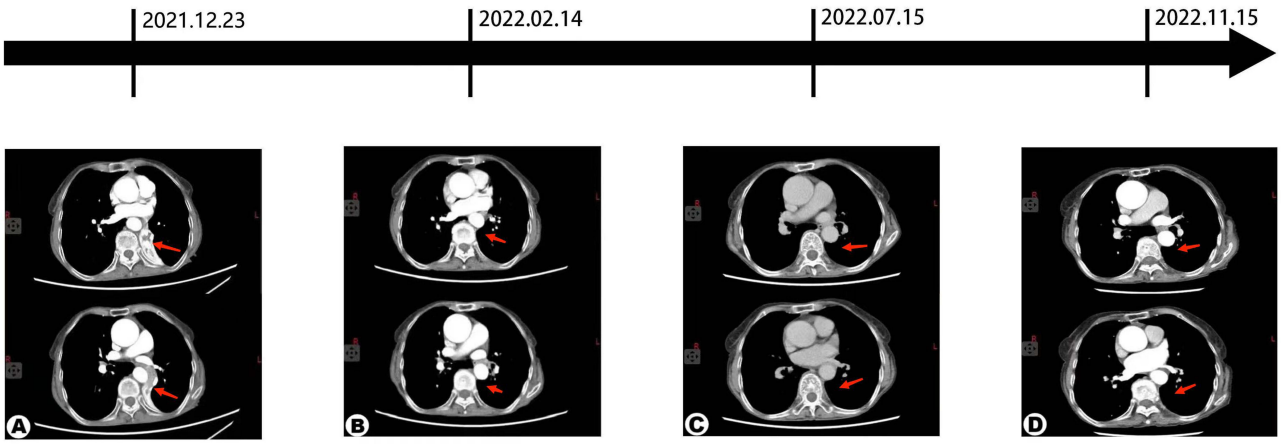

Figure 3 The image shows the lesion presentation on the same level of the patient's follow-up CT scan. The upper half of each image shows the most prominent area of lung atelectasis (indicated by the red arrow), while the lower half of each image depicts the largest site of the lesion (marked by the red arrow). (**A**) The upper part was atelectatic, and the lower part was a tumorous. (**B**) Comparison of patients treated with pembrolizumab combined with anlotinib after one cycle. The scan revealed bilateral subpleural linear opacities, irregularity of the left lower lobar bronchus, multiple nodular opacities, and miliary opacities, with the largest one measuring approximately 0.7 cm in the right upper lobe, presenting spiculation and adjacent pleural traction. (**C**) The patients were re-examined eight months after the diagnosis of lung cancer. (**D**) The patients were re-examined twelve months after the diagnosis of lung cancer.

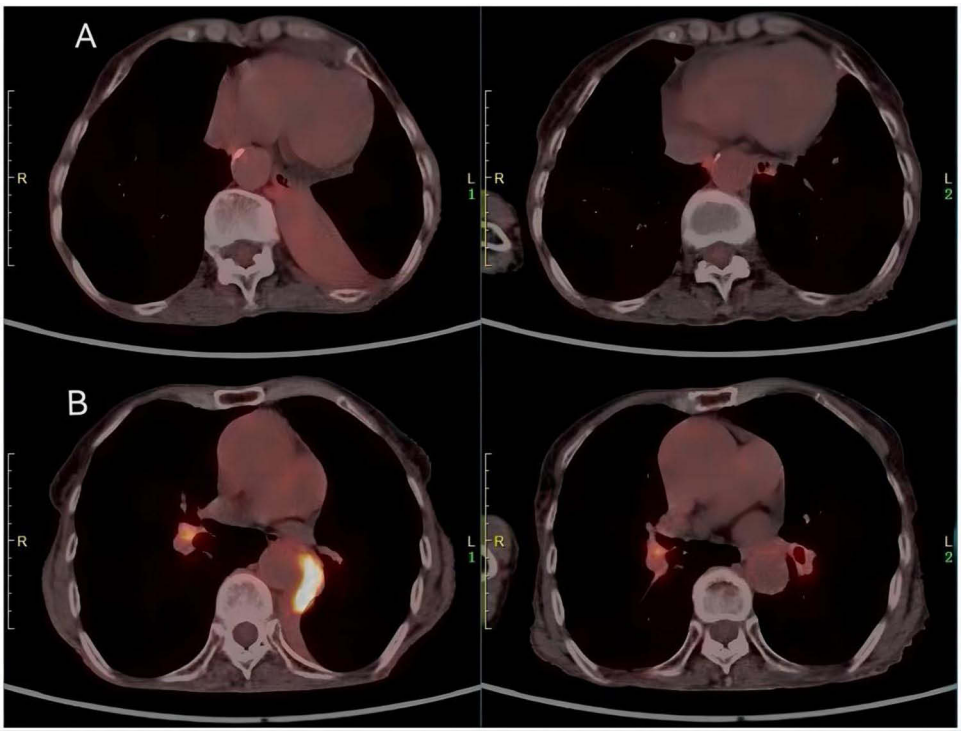

Figure 4 (**A**) This image shows the most severely compressed region of the lungs, with the left side depicting the PET/CT results obtained on December 23, 2021, and the right side displaying the PET/CT results obtained on June 9, 2023. (**B**) This image shows the area of highest metabolic activity in the lung lesions, with the left side showing the PET/CT results from December 23, 2021, and the right side showing the PET/CT results from June 9, 2023.

and 81 out of 156 experienced neither, $P < 0.001$).[7] This indicates that the adverse reactions of immunotherapy are indeed much lower than those of chemotherapy, especially for elderly patients.

For PD-L1 negative or low expressors, immune combination therapy has been demonstrated to improve the survival rates of advanced non-small cell lung cancer (NSCLC) patients compared to platinum-based chemotherapy. The KEYNOTE-407 study, which included 559 newly diagnosed metastatic squamous cell lung cancer patients, showed that pembrolizumab combined with chemotherapy significantly extended progression-free survival (median 6.4 months

vs 4.8 months, HR < 0.1) and overall survival (median 15.9 months vs 11.3 months, HR 0.56, p < 0.001), with no significant increase in adverse reactions. Subgroup analysis suggests that regardless of whether PD-L1 expression high or low, all benefit from combination therapy.[8] The Phase II ALTN-AK105-II-01 study aims to explore the efficacy and safety of pembrolizumab in combination with anlotinib for the treatment of various advanced tumours. The study included platinum-resistant metastatic head and neck squamous cell carcinoma patients who had not received antiangiogenic therapy or immunotherapy, with 20% of them having lung cancer. These patients received anlotinib 12 mg on Days 1–14 every 3 weeks and pembrolizumab 200 mg on Day 1 every 3 weeks until disease progression or unacceptable toxicity. The overall response rate was 28%. An open-label, dose-escalation, and expansion study indicated that anlotinib, as a second-line or beyond treatment for non-small cell lung cancers (especially in the 12 mg cohort), exhibits good efficacy and manageable toxicity.[9] Anlotinib In the treatment of non-small cell lung cancer, not only single drug application, but also combination administration, has its definite efficacy.

The efficacy and safety of pembrolizumab in combination with anlotinib as a first-line treatment for elderly patients with squamous cell lung cancer have not been reported previously. We reviewed the relevant literature and found that patients with PS2 NSCLC are a group of patients with unmet therapeutic needs in a single-arm, Phase 2 trial. The PePS2 trial demonstrates that pembrolizumab can be safely administered to these patients without increasing the risk of immune-related or other toxicities. The efficacy outcomes are at least as promising as in patients with PS0-1, providing us with confidence in incorporating pembrolizumab into the treatment approach for PS2 non-small cell lung cancer patients.[10] In a Phase 3, global, multicenter, open-label, randomized controlled study, first-line treatment with atezolizumab as a monotherapy was shown to improve overall survival, double the two-year survival rate, maintain quality of life, and demonstrate good safety compared to monotherapy chemotherapy.[11] These data support the use of atezolizumab monotherapy as a potential first-line treatment option for advanced non-small cell lung cancer patients who are not suitable for platinum-based chemotherapy. These findings give us confidence in the treatment regimen. In this case, an 86-year-old elderly patient with low body weight received anlotinib in combination with 200 mg pembrolizumab for 3 cycles, achieving a complete remission after 2 cycles. The patient continued anlotinib maintenance therapy, and the disease remained stable for 18 months. The patient continued to benefit from immunotherapy, surpassing the progression-free survival reported in previous studies for patients with low or unknown PD-L1 expression receiving immune combined chemotherapy and approaching the PFS benefits seen in the high PD-L1 expression population. The patient is currently taking anlotinib regularly and maintaining long-term disease control.

Currently, the majority of clinical trials for immune checkpoint inhibitors (ICIs) include a population of elderly patients aged ≥65, accounting for 35–50% of the total study population. However, there is a lack of data specifically for patients aged ≥75. The management of safety during the use of immune checkpoint inhibitors in elderly patients determines the benefits of anticancer treatment in this population. When receiving ICI treatment, a baseline risk assessment for immune-related adverse effects (irAEs) is needed, including evaluation of thyroid function and screening for cardiovascular toxicity risk. Monitoring of indicators should be conducted during each treatment cycle to detect irAEs early. In this patient, after completing the third cycle of anlotinib + pembrolizumab treatment, a prolonged QTc interval with hypokalaemia was observed, with a maximum QTc interval of 512 ms. The most common acquired cause of QT interval prolongation is drug-related factors, with electrolyte imbalances such as hypokalaemia being a common trigger for QT prolongation. The primary treatment-related adverse effects in this patient include grade 2 hypothyroidism, hypokalemia, and prolonged QT interval. According to the recommendations from the "Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update", it is advised to continue immunotherapy in the presence of grade 2 hypothyroidism while actively supplementing thyroid hormone. However, considering the patient's poor tolerance to adverse reactions and the potential for worsened prognosis with exacerbated adverse events, the decision was made to discontinue immunotherapy. Following the cessation of immunotherapy, the patient did not experience further deterioration in thyroid function. ICI-related cardiovascular adverse reactions are rare, accounting for approximately 6.3% of all irAEs. In 90% of cases of myocarditis, abnormal electrocardiogram findings are observed. In this patient, the QT interval recovered without the use of steroids after correcting hypokalaemia. Endocrine toxicity includes thyroid dysfunction and acute pituitary inflammation. The incidence of thyroid dysfunction during PD-1/PD-L1 monotherapy is approximately 5–10%. ICI-induced thyroid dysfunction rarely exceeds grade 2, and with timely monitoring and symptomatic or supportive treatment, it rarely leads to fatal thyroid crisis.[12]

This patient could continue immunotherapy, but the patient could not tolerate the fatigue symptoms caused by hypothyroidism. Although both drugs have been reported to cause hypothyroidism, for elderly tumour patients, immune side effects are uncertain, considering the patient's poor tolerance to adverse reactions and the potential for worsened prognosis with exacerbated adverse events. A study reveals that it encompasses all advanced non-small cell lung cancer (NSCLC) patients who underwent PD-(L)1 inhibitor treatment at Thoraxklinik Heidelberg from October 2012 to June 2020. Among stage IV patients, 232 immune-related adverse events (irAEs) were documented, with 14% (27/198) of patients experiencing involvement of multiple organs (median of 2). The most frequently affected organs were the endocrine glands, accounting for 4.9% (44/894) of patients. The article points out that patients experiencing irAEs may have a longer survival period. This could be attributed to the fact that patients with irAEs are more sensitive to immunotherapy, regardless of treatment efficacy or side effects. In clinical practice, many patients who stop immunotherapy due to immune-related adverse reactions may experience a sustained therapeutic effect, which could be one of the reasons for the benefits observed in the patients in this study. It is hoped that this article can provide an example to support subsequent related research.[13] So first, immunization and oral Ann Luo maintenance treatment were suspended. During treatment, the patient's hypothyroidism improved after treatment, so Ann did not aggravate the adverse effects of hypothyroidism.

Although there are limited data supporting immunotherapy in elderly patients, ICIs are still considered a low-toxicity and effective treatment compared to chemotherapy, with manageable side effects. To determine the best treatment strategy for specific populations, the effectiveness and safety of immunotherapy in elderly patients need to be evaluated based on clinical characteristics, accumulated experience, and improvements in the survival of elderly cancer patients through clinical practice. In general, it is evident that the benefits of PD-1/PD-L1 immune checkpoint inhibitors, regardless of whether they are high-expression inhibitors, are clear for specific patient populations.

Ethics and Consent Statement

All the therapeutic measures and matters related to the publication of this article comply with the relevant regulations of the "Management Measures for Academic Ethics and Integrity of the First Affiliated Hospital of Dalian Medical University". The patient has provided written informed consent for the publication of case details and all relevant images.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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