Immune Checkpoint Inhibitor without Pemetrexed for First-line Maintenance Therapy in Advanced Lung Adenocarcinoma: A real-world retrospective study

Ming Gao  
Fifth Medical Center of PLA General Hospital

Wenyu Yang  
Nankai University, Fifth Medical Center of PLA General Hospital

Ting Wang  
Nankai University, Fifth Medical Center of PLA General Hospital

Fangfang Jing  
First Medical Center of PLA General Hospital

Fan Zhang  
Fifth Medical Center of PLA General Hospital

Haitao Tao  
Fifth Medical Center of PLA General Hospital

Junxun Ma  
Fifth Medical Center of PLA General Hospital

Yi Hu  
Fifth Medical Center of PLA General Hospital

Lijie Wang  (wljznk123@163.com)  
Fifth Medical Center of PLA General Hospital

Research Article

Keywords: Immune checkpoint inhibitor, Pemetrexed, Maintenance therapy, Lung adenocarcinoma

Posted Date: August 25th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3181154/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Objective

To explore the efficacy and safety of immune checkpoint inhibitor (ICI) without pemetrexed as first-line maintenance therapy in driver-gene negative advanced lung adenocarcinoma.

Methods

A retrospective analysis was performed on patients with advanced lung adenocarcinoma treated with chemotherapy combined with ICI at the PLA General Hospital from January 2019 to June 2022. Clinical data of the patients were collected and followed up. SPSS (version 26.0) was used to analyze the clinical characteristics and survival of the patients.

Results

A total of 30 patients with ICI maintenance therapy and 39 patients of pemetrexed combined with ICI were included in this study. The median follow-up time was 23.2 months. PFS of ICI monotherapy maintenance group and pemetrexed combined ICI (P + ICI) maintenance group were 15.8 months (95%CI 7.6–23.9) and 22.6 months (95%CI 8.9–36.3). There was no statistical difference between the two groups (P = 0.42), and the median OS of both groups was not reached. ORR of ICI group was 60.0% (95%CI 42.5–77.5) and that of P + ICI group was 69.2% (95%CI 54.7 ~ 83.7). The incidence of treatment-related adverse reactions (TRAEs) was 90.0% and 92.3%, and the incidence of ≥ 3 grade events was 23.3% and 23.1%. No grade 5 adverse reactions occurred.

Conclusion

The maintenance treatment of ICI shown good therapeutic efficacy and controllable adverse events, which can be used as the first-line maintenance therapy for patients with driver-gene negative advanced lung adenocarcinoma.

Introduction

Lung cancer is one of the most common malignant tumors in the world, its high morbidity and mortality have aroused great attention. According to the statistics of the Global Cancer Report of 2020 by IARC/WHO, the incidence of lung cancer ranks second to breast cancer and the mortality ranks first worldwide\(^1\). Lung cancer can be divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) according to histopathologic types. NSCLC accounts for about 85% of lung cancer, among which lung adenocarcinoma is the most common pathological type, accounting for about 63%\(^2\).
Surgery is usually first considered for early-stage lung adenocarcinoma, and adjuvant chemotherapy should be determined according to the postoperative stage. As for unresectable advanced lung adenocarcinoma, molecular genetic testing is an important approach for precision therapy. Driver-gene positive patients can have a chance for targeted therapy, while pemetrexed combined with platinum-based chemotherapy has been the preferred treatment to negative. For patients who respond to chemotherapy, whether maintenance therapy is required after chemotherapy was explored. Two Phase clinical trials of pemetrexed versus placebo maintenance in NSCLC showed significant survival benefits in the pemetrexed maintenance group\(^3\text{--}^5\). Therefore, pemetrexed plus platinum followed by pemetrexed maintenance therapy has become the standard first-line treatment for driver-gene negative advanced lung adenocarcinoma.

In recent years, with the advent of immune checkpoint inhibitor (ICI), ICI combined with systemic chemotherapy has achieved gratifying results. In a number of large clinical trials, pemetrexed and platinum plus ICIs achieved a breakthrough both in the efficacy of PFS and OS in the first-line treatment of advanced non-squamous NSCLC without driver genes\(^6,^7\). In KEYNOTE-189 study, 5-year follow-up showed that ORR and OS doubled in combination with Pembrolizumab compared with chemotherapy alone. Therefore, the CSCO guidelines recommend pemetrexed plus platinum-based chemotherapy combined with ICIs as the standard first-line treatment for driver-gene negative advanced lung adenocarcinoma, followed by pemetrexed combined with ICI maintenance therapy.

Pemetrexed is a folic acid analogue which has high affinity for elements involved in folic acid membrane transport in mammals\(^8\). Reduced Folate Carrier (RFC) is an important membrane transporter for folic acid synthesis. The affinity of the RFC-mediated anion exchange for pemetrexed is twice of that for methotrexate and about 100 times the affinity for folic acid. Pemetrexed acts as a folic acid antagonist by disrupting the normal folate dependent metabolic process in cells, inhibiting cell replication, and thus inhibiting tumor growth. However, pemetrexed can also affect normal cells, causing a series of adverse reactions such as myelosuppression and gastrointestinal toxicity. Folic acid and vitamin B12 supplement are needed, and dexamethasone is taken orally to prevent rash\(^9\).

Due to the toxic of pemetrexed and resistance to chemotherapy, some patients show poor compliance to pemetrexed. With the advent of the era of immunotherapy, the long-term efficacy of immune checkpoint inhibitor therapy combined with chemotherapy has shown a good advantage. It is still unknown whether ICI monotherapy can also continue to benefit in the maintenance stage after first-line chemotherapy combined with immunotherapy for patients with advanced lung adenocarcinoma, and there is no relevant study on the comparison of efficacy of pemetrexed combined with ICI and ICI monotherapy. Therefore, this study retrospectively analyzed patients with advanced driver-gene negative lung adenocarcinoma admitted to the General Hospital of the People's Liberation Army, aiming to explore the difference in efficacy and safety between ICI monotherapy and ICI combined pemetrexed maintenance therapy after the treatment of advanced lung adenocarcinoma with pemetrexed plus platinum combined with ICI.
Methods

Patients and data collection

Patients with histologically or cytologically confirmed advanced lung adenocarcinoma who received first-line chemotherapy combined with ICI in PLA General Hospital from January 2019 to June 2022 were collected. The clinical stages ranged from B to  with driver-gene negative. Pemetrexed and platinum plus ICI were used as first-line therapy for 4–6 cycles, and the Eastern Cooperative Oncology Group (EGOG) score is 0–1. Exclusion criteria: combined with secondary primary tumor; Serious systemic disease; Present with autoimmune disease; Long-term oral immunosuppressant. Clinical data of the patients were collected including age, gender, smoking history, brain metastasis status, ECOG score, pathological type, PD-L1 expression level and treatment regimen.

Treatment

Patients enrolled in the study received pemetrexed (500mg/m2) and platinum (cisplatin 75mg/m2; Carboplatin AUC 5; Nedaplatin 80 ~ 100mg/m2) chemotherapy combined with immune checkpoint inhibitor (standard dose) was treated every 3 weeks as a treatment cycle, and the efficacy was evaluated every 2 cycles. A total of 4 ~ 6 cycles of treatment were performed. Patients with no progress were subsequently put into ICI combined pemetrexed or ICI monotherapy maintenance treatment stage. Premedication with folic acid, vitamin B12, and corticosteroids was administered according to guidelines.

Assessments

Imaging data within 4 weeks were retained as baseline data before treatment, and CT or MRI was reviewed every 2 cycles for efficacy evaluation. According to RECIST 1.1 efficacy evaluation criteria for solid tumors, patients were divided into complete response (CR), partial response (PR), stable disease (SD), and disease progression (PD). During the treatment phase, adverse events were reviewed. Blood routine, biochemistry, thyroid, adrenal function and other indicators were examined before each cycle. Treatment-related adverse events (TRAEs) were graded according to CTCAE 5.0 evaluation criteria.

Statistical analysis

Statistical analysis was conducted using the SPSS 26.0 statistical software. The distribution of patients and baseline clinical characteristics were described using frequency analysis. PFS refers to the time from the beginning of tumor therapy to the onset of disease progression or death, in terms of the event that occurred before, and the time until the last follow-up for patients who did not progress. OS refers to the time from the start of treatment to death from all causes or the last follow-up. The survival curves were estimated using the Kaplan-Meier method, while differences in the variables were calculated using the log-rank test. P value < 0.05 was considered statistically significant.

Results
Patients’ characteristics

From January 2019 to June 2022, a total of 93 patients who received first line chemotherapy combined with ICI were collected, including 39 patients receiving pemetrexed combined with ICI maintenance treatment, 30 patients receiving ICI monotherapy maintenance treatment, and 24 patients who failed to enter the maintenance treatment stage due to progress in the treatment process or patients refusing maintenance treatment. Based on the analysis of the basic data of 69 patients included in this study, the median age of ICI maintenance group was 62 (42 ~ 81) years old, and that of pemetrexed combined with ICI (P + ICI) maintenance group was 63 (35 ~ 74) years old. Male patients in the two groups accounted for 66.7% (20/30) and 79.5% (31/39). Patients with a history of smoking were 63.3% (19/30) and 74.4% (29/39) respectively. Brain metastases at initial diagnosis was 10% (3/30) and 23.1% (9/39) in both groups. The baseline demographic and disease characteristics were generally well balanced between the groups (P > 0.05). (Table 1)

<table>
<thead>
<tr>
<th>clinical factors</th>
<th>ICI(n = 30)</th>
<th>P + ICI(n = 39)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.23</td>
</tr>
<tr>
<td>male</td>
<td>20(66.7)</td>
<td>31(79.5)</td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>10(33.3)</td>
<td>8(20.5)</td>
<td></td>
</tr>
<tr>
<td>Age, median(range),years</td>
<td>62 (42 ~ 81)</td>
<td>63 (35 ~ 74)</td>
<td>0.98</td>
</tr>
<tr>
<td>ECOG Status</td>
<td></td>
<td></td>
<td>0.60</td>
</tr>
<tr>
<td>0</td>
<td>2(6.7)</td>
<td>4(10.3)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>28(93.3)</td>
<td>35(89.7)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td>0.32</td>
</tr>
<tr>
<td>Former or current</td>
<td>19(63.3)</td>
<td>29(74.4)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>11(36.7)</td>
<td>10(25.6)</td>
<td></td>
</tr>
<tr>
<td>Brain metastases</td>
<td>3(10.0)</td>
<td>9(23.1)</td>
<td>0.16</td>
</tr>
<tr>
<td>PD-L1 status(TPS)</td>
<td></td>
<td></td>
<td>0.69</td>
</tr>
<tr>
<td>1%</td>
<td>9(30.0)</td>
<td>9(35.9)</td>
<td></td>
</tr>
<tr>
<td>1%~49%</td>
<td>6(20.0)</td>
<td>11(28.2)</td>
<td></td>
</tr>
<tr>
<td>≥ 50%</td>
<td>10(33.3)</td>
<td>10(25.6)</td>
<td></td>
</tr>
<tr>
<td>Not detected</td>
<td>5(16.7)</td>
<td>9(23.1)</td>
<td></td>
</tr>
</tbody>
</table>

Efficacy
The follow-up data of 69 patients were statistically analyzed. Until March 31, 2023, the median follow-up time was 23.2 months. The median PFS was 15.8 months (95%CI 7.6–23.9) in ICI maintenance group and 22.6 months (95%CI 8.9–36.3) in pemetrexed combined with ICI maintenance group. There was no statistically significant difference between the two groups (P = 0.42) (Fig. 1A). The OS of both groups was not reached (Fig. 1B).

Figure 1A K-M survival of PFS Fig. 1B K-M survival of OS

**Figure 1 Kaplan-Meier survival curve of PFS and OS**

According to RECIST 1.1 solid tumor efficacy evaluation criteria, ORR of ICI maintenance group was 60.0% (95%CI 42.5–77.5), among which 18 cases achieved partial response (PR) and 12 cases were stable (SD). The ORR of pemetrexed combined with ICI group was 69.2% (95%CI 54.7 ~ 83.7), with PR in 27 cases and SD in 12 cases (Table 2).

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>ICI (n = 30)</th>
<th>P + ICI (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>SD</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>ORR(%)</td>
<td>60 (95%CI 42.5–77.5)</td>
<td>69.2 (95%CI 54.7 ~ 83.7)</td>
</tr>
</tbody>
</table>

**PD-L1 status**

Patients with definite PD-L1 expression were divided into three groups (TPS < 1%, 1–49%, and ≥ 50%) according to expression states. With the increase of PD-L1 expression, the median PFS was gradually extended (8.8m vs.10.8m vs.22.8m). The therapeutic efficacy between the two groups was analyzed respectively and the results showed that there was no statistical significance in PFS of different PD-L1 expression states. (Fig. 2)

**Figure 2 Kaplan-Meier survival curve of PFS under different PD-L1 status**

**Treatment related adverse events (TRAEs)**

TRAEs were graded according to CTCAE 5.0 evaluation criteria. The incidence of TRAEs at any grade was 90% in the ICI group and 92.3% in the pemetrexed combined with ICI group. The most common adverse reactions were anemia, nausea, fatigue, and leukopenia. The incidence of grade 3–5 adverse reactions in the two groups was 23.3% (7/30) and 23.1% (9/39), mainly due to neutropenia and leukopenia. Immune-related adverse events include hypothyroidism, pneumonia, adrenal insufficiency, hypophysitis, type 1 diabetes, peripheral neuropathy and reactive capillary hyperplasia. Grade 3–5 immune-related adverse event is pneumonia. (Table 3)
Table 3  
Treatment-related adverse events of patients

<table>
<thead>
<tr>
<th>TRAEs</th>
<th>ICI (n = 30)</th>
<th>P + ICI (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3–5</td>
</tr>
<tr>
<td>Any event</td>
<td>27 (90.0)</td>
<td>7 (23.3)</td>
</tr>
<tr>
<td>Anemia</td>
<td>15 (50.0)</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>14 (46.7)</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12 (40)</td>
<td>0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>11 (36.7)</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>9 (30.0)</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>9 (30)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>8 (26.7)</td>
<td>0</td>
</tr>
<tr>
<td>Elevated aminotransferase</td>
<td>5 (16.7)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Immune-related adverse events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hypothyroidism</td>
<td>4 (13.3)</td>
<td>0</td>
</tr>
<tr>
<td>pneumonia</td>
<td>3 (10.0)</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>hypophysitis</td>
<td>1 (3.3)</td>
<td>0</td>
</tr>
<tr>
<td>myocarditis</td>
<td>1 (3.3)</td>
<td>0</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>1 (3.3)</td>
<td>0</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>1 (3.3)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Reactive capillary hyperplasia</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Discussion**

Lung cancer is malignant tumor with the highest mortality rate in the world, and the 5-year survival rate of advanced lung cancer is less than 10%\(^{10}\). In the past, traditional platinum-based double-drug chemotherapy was the standard treatment for advanced lung adenocarcinoma without driver gene. In recent years, with the continuous progress in the field of immunotherapy, the application of immune checkpoint inhibitors represented by PD-1/PD-L1 and CTLA-4/CD28 has become more and more extensive, and the exploration of different treatment modes has become more diversified.
Tumor immunotherapy refers to stimulating or mobilizing the body's immune system to enhance the anti-tumor immunity of the tumor microenvironment, so as to control and kill tumor cells. Tumor growth is influenced by both cancer cells and surrounding immune cells. In order to prevent the damage of activated T cells to the surrounding normal tissues after the presentation of tumor neoantigen by APC, the immune system has a variety of internal mechanisms or "checkpoints" to regulate the duration and amplitude of immune response, and suppress immune response and prevent the damage caused by inflammation and autoimmunity by upregulating the "co-inhibitory" receptors of T cells. Therefore, the combined action of co-stimulatory and co-inhibitory signals determines T cell activation\[11\]. PD-1/PD-L1, CTLA-4/CD28 and other immune checkpoints express co-inhibitory signals through the combination and immune checkpoint inhibitors can block immune checkpoints and enhance the activation of T cells, so as to better play the anti-tumor role\[12\].

ICI can enhance the antitumor effect synergistically with a variety of treatments. The synergistic effect of immunotherapy combined with chemotherapy has been explored. A study of Emens et al. showed that chemotherapy can induce immunogenic tumor cell death and enhance antigen presentation by up-regulating the expression of tumor antigen or MHC bound to the antigen and enhance the activity of effector T cells by up-regulating co-stimulatory molecules/down-regulating co-inhibitory molecules\[13,14\]. Therefore, with the breakthrough of immunotherapy in clinical application, the combined treatment mode of chemotherapy and ICIs has received great attention.

In a number of large clinical trials, chemotherapy combined with ICIs has made a breakthrough in the first-line treatment of driver negative advanced lung adenocarcinoma, with significant extension of PFS and OS\[7,15,16\]. In the population with PD-L1 TPS ≥ 50%, Atezolizumab and Pembrolizumab monotherapy have also been included in the guidelines as grade I recommendations\[17,18\]. The survival curve of OS in the combined immunotherapy group showed favorable advantages and a long tail effect, and the 2-year and 5-year OS rate was significantly better than that in the control group, indicating that the long-term benefit was greater in the population who are responding to immunotherapy. In addition, in advanced patients after multilime therapy, immunotherapy has also shown considerable long-term efficacy\[19\]. In KEYNOTE-189 and other large clinical trials, the maintenance treatment was pemetrexed combined with ICIs. Some patients had relatively poor compliance due to adverse reactions such as bone marrow suppression and gastrointestinal toxicity caused by chemotherapy. Therefore, for the group of advanced lung adenocarcinoma who are effectively treated by ICI combined with chemotherapy, it is still unknown whether pemetrexed is necessary in maintenance treatment and whether ICI maintenance treatment can also achieve long-term survival.

In this study, advanced lung adenocarcinoma patients who received first-line chemotherapy combined with ICI immunotherapy were selected in the real world. Among them, 30 patients received ICI maintenance treatment, 39 patients received pemetrexed and ICI maintenance treatment. PFS of ICI maintenance group and P+ICI maintenance group were 15.8 months and 22.6 months. The PFS of P+ICI maintenance group seems longer than that of ICI group in numerical terms, but the difference between
the two groups was not statistically significant. In the subgroups of PD-L1 expression status, there was also no statistical difference in PFS. In addition, some patients could still achieve a stable state of disease for a long time in ICI group even though immunotherapy was terminated due to adverse reactions, which proved that ICI maintenance treatment could also produce long-term sustained benefits.

In terms of adverse reactions, the adverse reactions of the two groups were similar. Grade 3–5 adverse reactions were mainly manifested as neutropenia and leukopenia, mostly caused by chemotherapy, which were improved after dose adjustment. Immune-related adverse events mainly manifested in endocrine system adverse events and pneumonia. Endocrine system adverse events include hypothyroidism, adrenal insufficiency, hypophysitis and type 1 diabetes. Hormone replacement and symptomatic treatment can be given. In addition, one patient developed immune-associated myocarditis. The severe adverse reactions were mainly immune-related pneumonia, and one patient was discontinued as a result.

In summary, maintenance treatment of ICI followed by chemotherapy combined with immunotherapy for advanced lung adenocarcinoma still achieves good efficacy. Since all the enrolled people in this study have entered the maintenance treatment stage, the results of PFS and OS studies are longer than those of other large clinical studies. In addition, the deficiencies of this study lie in the small number of enrolled patients and certain bias in statistical data results. Further clinical studies and the support of large sample data are needed.

**Conclusion**

The discovery and wide application of immune checkpoint inhibitors are of great significance to the treatment of malignant tumors. For driver-gene negative advanced lung adenocarcinoma, ICI maintenance therapy without pemetrexed has shown good efficacy and can be a choice for first-line maintenance treatment.

**Declarations**

**Funding**

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

**Competing interests**

The authors have no relevant financial or non-financial interests to disclose.

**Author Contributions**

All authors contributed to the study conception and design. Ming Gao, Wenyu Yang, Ting Wang and Lijie Wang conceived and designed the study. Fangfang Jing, Fan Zhang, Haitao Tao collected and analyzed
Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

The study was approved by the ethics committee of PLA General Hospital.

Consent to participate

Informed consent was obtained from all individual participants included in the study. All methods were carried out in accordance with relevant guidelines and regulations.

Consent to publication

Not applicable

Availability of data and material

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Acknowledgements

Not applicable

References


Figures

Fig 1A K-M survival of PFS

Fig 1B K-M survival of OS

Figure 1

Kaplan-Meier survival curve of PFS and OS

A K-M survival of PFS

B K-M survival of OS
Figure 2

Kaplan-Meier survival curve of PFS under different PD-L1 status

Fig 2A

Fig 2B

Fig 2C