Efficacy and Safety of PD-1 Inhibitor Monotherapy in Elderly Patients with Advanced Non-Small Cell Lung Cancer: An Exploratory Study (Postprint)

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Abstract

Background: Recent years have witnessed that immunotherapy represented by PD-1 blockades has gradually become the standard treatment of advanced non-small cell lung cancer (NSCLC), thus changing the therapeutic landscape. Unfortunately, most PD-1-related studies excluded elderly NSCLC patients over 70 or 75 years of age, resulting in relatively limited data on the efficacy and safety of PD-1 in elderly patients.

Full Text

Preamble

Exploratory Study Regarding the Efficacy and Safety of PD-1 Inhibitor Monotherapy for Elderly Patients with Advanced Non-Small Cell Lung Cancer

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Abstract

Background: Recent years have witnessed that immunotherapy represented by PD-1 blockades has gradually become the standard treatment of advanced non-small cell lung cancer (NSCLC), thus changing the therapeutic landscape. Unfortunately, most PD-1-related studies excluded elderly NSCLC patients over 70 or 75 years of age, resulting in relatively limited data on the efficacy and safety of PD-1 in elderly patients.

Objective: This study was to investigate the efficacy and safety of PD-1 blockades among elderly patients with advanced NSCLC.

Methods: Elderly patients with advanced NSCLC aged 65 years or older who received PD-1 blockades monotherapy from October 2018 to November 2021 were screened retrospectively, and a total of 63 elderly patients with NSCLC were eligible for inclusion ultimately. The PD-1 blockades in the study were the available PD-1 monoclonal antibodies that already approved for marketing in China, including camrelizumab, sintilimab and pembrolizumab. Efficacy and safety data of the patients were collected using the electronic medical record system of the hospital and all the subjects were followed up regularly to assess the long-term prognostic data. Additionally, association analysis between prognosis and baseline characteristic subgroups was performed to identify the potential risk factors for prognosis.

Results: The median age of the 63 elderly patients with advanced NSCLC was 71 years (range: 65-89 years). The best overall response during PD-1 blockades administration suggested that no patients were complete response, partial response was observed in 14 patients, stable disease was noted in 21 patients and 28 patients had progressive disease, yielding in an objective response rate (ORR) of 22.2% (95%CI: 12.7%-34.5%) and a disease control rate (DCR) of 55.6% (95%CI: 42.5%-68.1%). Furthermore, prognostic data exhibited that the median progression free survival (PFS) of the 63 patients with advanced NSCLC was 3.3 months (95%CI: 2.0-4.6) and the median overall survival (OS) was 10.2 months (95%CI: 6.1-14.3). Regarding the safety profile, a total of 46 patients were observed of the treatment related adverse reaction (73.0%) among the 63 elderly patients with NSCLC, and the incidence of grade 3 or above adverse reactions was 14.3%. Additionally, the most common adverse reactions were fatigue, diarrhea, rash and abnormal liver function with the incidence of 23.8%, 19.1%, 15.9% and 14.3%, respectively. Association analysis between PFS and baseline characteristic subgroups suggested that ECOG performance status and number of metastatic lesions might be independent factors to predict the PFS.

Conclusion: PD-1 blockades monotherapy demonstrated potential efficacy and acceptable safety for elderly patients with NSCLC. ECOG performance status and number of metastatic lesions might be potential risk factors to predict the PFS of the patients. And the conclusion should be confirmed in prospective clinical trials subsequently.

Key words: elderly; NSCLC; PD-1 blockades; efficacy; safety

Introduction

Lung cancer is one of the most common malignant tumors worldwide, with approximately 2.1 million new cases and 1.77 million deaths annually [1]. Chinese epidemiological data indicate approximately 815,000 new cases and 715,000 deaths per year [2]. Non-small cell lung cancer (NSCLC) is the most common type, accounting for about 85% of all lung cancer patients [3], resulting in 693,000 new NSCLC cases annually in China. In recent years, breakthrough advances have been achieved in advanced NSCLC treatment. Immunotherapy represented by PD-1 inhibitors has demonstrated remarkable and durable efficacy in advanced NSCLC patients with driver gene-negative disease, improving the 5-year survival rate from 5% to 20% [4]. Nevertheless, the overall prognosis for advanced NSCLC patients remains poor, necessitating further exploration to improve patient outcomes.

In clinical practice, the median age at NSCLC diagnosis is approximately 70 years [5]. However, most clinical trials have strict age eligibility criteria (typically <75 years), resulting in fewer than 10% of patients over 75 participating in clinical research [6]. Consequently, available clinical data for elderly NSCLC patients are limited. The exclusion of elderly patients from most studies may be attributed to several factors: advanced age, poor Eastern Cooperative Oncology Group (ECOG) performance status, insufficient support systems, cognitive impairment, multiple comorbidities, and inability to tolerate high-toxicity regimens [7]. These factors objectively limit elderly patient participation in clinical trials. PD-1 inhibitor monotherapy or combination chemotherapy has become the standard second-line or first-line treatment for advanced NSCLC [8]. PD-1 monotherapy demonstrates approximately 20% objective response rate, 3-6 months median progression-free survival (PFS), and 10-15 months median overall survival (OS) in advanced NSCLC patients [9], though most participants in these studies were younger. In the Keynote-010 study, the median age of 690 advanced NSCLC patients receiving pembrolizumab was 63 years [10]. In Checkmate-057, the median age of 292 non-squamous NSCLC patients receiving nivolumab was 61 years, while in CheckMate-017, the median age of 135 squamous NSCLC patients receiving nivolumab was 62 years [11, 12]. Therefore, current PD-1 monotherapy data in advanced NSCLC primarily focus on relatively younger patients, with limited efficacy and safety data for elderly NSCLC patients aged 65 and above.

Furthermore, a major challenge of PD-1 inhibitor monotherapy in clinical practice is its relatively low response rate. In patients with PD-L1 CPS expression <50%, the objective response rate (ORR) is below 20% [13]. It is necessary to investigate the association between baseline clinical characteristics and treatment efficacy and prognosis to better identify potential beneficiaries of PD-1 inhibitors.

Therefore, this study aims to explore the efficacy and safety of PD-1 inhibitor monotherapy in elderly patients with advanced NSCLC in the real-world setting.

1.1 Study Design and Inclusion/Exclusion Criteria

This study was designed as a retrospective analysis, enrolling elderly patients with advanced NSCLC who received PD-1 inhibitor monotherapy in the Department of Thoracic Surgery and Oncology at the Fourth Affiliated Hospital of Gansu University of Traditional Chinese Medicine between October 2018 and November 2021. The main inclusion criteria were: (1) age $ $65 years (WHO criteria for elderly population); (2) pathologically confirmed NSCLC with stage b or ; (3) ECOG performance status 0-2; (4) patients who received PD-1 inhibitor monotherapy after progression on prior systemic therapy; (5) at least one measurable target lesion according to immune-related Response Evaluation Criteria in Solid Tumors (irRECIST). The main exclusion criteria were: (1) history of autoimmune disease or current treatment with steroids or other immunosuppressive agents; (2) concurrent malignancy or serious comorbidities that might affect survival; (3) patients with substantial missing general or treatment information and no efficacy evaluation data, though those lost to follow-up during subsequent therapy could be included.

A total of 63 elderly patients with advanced NSCLC were ultimately enrolled. The therapeutic profiles are shown in Table 1 . The primary objectives were to investigate the efficacy and safety of PD-1 inhibitor monotherapy in elderly advanced NSCLC patients, including ORR, disease control rate (DCR), PFS, OS, and safety. The study was approved by the Ethics Committee of the Fourth Affiliated Hospital of Gansu University of Traditional Chinese Medicine (approval number: KY-2021036), and all enrolled patients provided informed consent.

1.2 Treatment Regimen and Efficacy/Safety Assessment Criteria

As a retrospective analysis, all enrolled patients were elderly advanced NSCLC patients who received PD-1 inhibitor monotherapy in clinical practice. The PD-1 monoclonal antibodies used were those approved for marketing in China, including camrelizumab (Jiangsu Hengrui Pharmaceuticals Co., Ltd.), sintilimab (Innovent Biologics (Suzhou) Co., Ltd.), and pembrolizumab (Merck Sharp & Dohme (China) Co., Ltd.). All three agents were administered at 200 mg intravenous infusion on day 1, with infusion duration exceeding 30 minutes, every three weeks as one treatment cycle, until disease progression or intolerable adverse reactions occurred.

Efficacy was assessed using irRECIST criteria. CT or MRI evaluations of target lesions were performed before treatment and every two cycles thereafter. Due to the retrospective nature of this study, not all patients underwent evaluation at exactly two-cycle intervals; some were assessed as clinically indicated. ORR and DCR were determined based on each patient's best overall response during

treatment. Adverse reactions during PD-1 inhibitor monotherapy were evaluated using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, with the highest grade of adverse reaction recorded for each patient.

Furthermore, since this study evaluated prognostic indicators (PFS and OS), all enrolled patients underwent regular follow-up. Patients were followed up monthly, primarily through telephone interviews, to document subsequent treatment after PD-1 inhibitor progression and monitor survival status. In cases of death, family members were contacted to record the exact date. The last follow-up date was March 15, 2022.

1.3 Statistical Analysis

All data were analyzed using SPSS version 25.0. Efficacy endpoints included ORR and DCR, defined as the proportion of patients with complete response (CR) or partial response (PR) (ORR), and the proportion with CR, PR, or stable disease (DCR), respectively. PFS was defined as the time from initiation of PD-1 inhibitor monotherapy to disease progression or death, while OS was defined as the time from treatment initiation to death from any cause. Kaplan-Meier curves for PFS and OS were generated using Stata version 14.0. The association between baseline clinical subgroups and PFS was analyzed using the log-rank test. Patients without disease progression or death at the last follow-up date were censored. Safety analysis presented the incidence of different adverse reactions using frequency data. $P<0.05$ was considered statistically significant.

2 Results

2.1 Baseline Clinical Characteristics of 63 Elderly NSCLC Patients

A total of 63 elderly NSCLC patients receiving PD-1 inhibitors were enrolled. Baseline clinical characteristics are presented in Table 1 . The median age was 71 years (range: 65-89). Patients were predominantly driver gene-negative advanced NSCLC, including 34 with adenocarcinoma and 29 with squamous cell carcinoma. The PD-1 inhibitors used were clinically approved agents for advanced NSCLC, comprising 25 cases of camrelizumab, 23 of sintilimab, and 15 of pembrolizumab. Additional baseline characteristics are shown in Table 1 .

2.2 Efficacy of PD-1 Inhibitors in 63 Elderly NSCLC Patients

All 63 enrolled patients had evaluable efficacy data. Best overall response during PD-1 inhibitor treatment was determined according to irRECIST criteria. No patients achieved complete response, 14 had partial response, 21 had stable disease, and 28 had progressive disease. Consequently, the ORR of PD-1 inhibitors in elderly advanced NSCLC patients was 22.2% [95% confidence interval (CI): 12.7%-34.5%], and the disease control rate (DCR) was 55.6% (95%CI: 42.5%-68.1%). Changes in target lesions after treatment are illustrated in Figure 2 [Figure 2: see original paper], showing significant tumor shrinkage in some

patients, with 14 achieving PR.

2.3 Prognosis of 63 Elderly NSCLC Patients Receiving PD-1 Inhibitors

All enrolled patients underwent regular follow-up. The data cutoff date was March 15, 2022, with a median follow-up duration of 10.5 months (range: 0.5-26 months). For PFS analysis, 46 patients had experienced disease progression or death by the cutoff date, yielding a PFS data maturity of 73.0%. The PFS curve is shown in Figure 3 [Figure 3: see original paper]. The median PFS for the 63 elderly NSCLC patients was 3.3 months (95%CI: 2.0-4.6). Additionally, the 6-month and 12-month PFS rates were 34.7% (95%CI: 23.2%-46.4%) and 26.5% (95%CI: 15.3%-39.1%), respectively. Nine patients achieved long-term PFS benefit exceeding 12 months.

Regarding OS, with sufficient follow-up duration, 42 patients had died by the cutoff date, resulting in an OS data maturity of 66.7%. The OS curve is shown in Figure 4 [Figure 4: see original paper]. The median OS was 10.2 months (95%CI: 6.1-14.3), with 12-month and 24-month OS rates of 48.0% (95%CI: 35.0%-60.0%) and 27.4% (95%CI: 16.0%-40.1%), respectively. Eight patients achieved OS benefit exceeding 20 months.

To explore the correlation between baseline clinical subgroups and PFS, association analysis was performed (Table 2). Univariate analysis indicated that elderly NSCLC patients across almost all clinical subgroups could benefit from PD-1 inhibitor monotherapy. However, ECOG performance status and number of metastatic lesions showed significant correlation with PFS. Patients with ECOG score 0-1 had significantly longer PFS than those with score 2 (median PFS: 3.9 months vs 1.9 months, P=0.018). Patients with $ $3 metastatic lesions had better PFS than those with >3 lesions (median PFS: 4.0 months vs 1.9 months, P=0.012). Multivariate Cox regression analysis including ECOG performance status and number of metastatic lesions showed both variables remained statistically significant (ECOG: HR=0.58, P=0.031; metastatic lesions: HR=0.54, P=0.021). These results indicate that ECOG performance status and number of metastatic lesions are independent predictive factors for PFS in elderly NSCLC patients receiving PD-1 inhibitor monotherapy.

2.4 Safety of PD-1 Inhibitors in 63 Elderly NSCLC Patients

Adverse reactions were retrospectively collected for the 63 elderly advanced NSCLC patients receiving PD-1 inhibitor monotherapy, with results shown in Table 3 . During treatment, 46 patients (73.0%) experienced adverse reactions of any grade, with grade $ $3 adverse reactions observed in 9 patients (14.3%). One patient died due to immune-related lung cancer (1.6%).

Common adverse events included fatigue (23.8%), diarrhea (19.1%), rash (15.9%), abnormal liver function (14.3%), nausea/vomiting (14.3%), reactive cutaneous capillary endothelial proliferation (RCCEP, 7.9%), pneumonitis

(7.9%), fever (6.3%), and stomatitis (3.2%). Grade $ $3 adverse reactions comprised abnormal liver function (AST or ALT elevation, 6.3%), diarrhea (4.8%), fatigue (3.2%), nausea/vomiting (1.6%), and pneumonitis (1.6%). Overall, adverse events were manageable and safety was acceptable.

3 Discussion

The results of this study provide real-world efficacy and safety data for PD-1 inhibitor monotherapy in elderly advanced NSCLC patients. Additionally, we analyzed factors influencing PFS, suggesting that ECOG performance status and number of metastatic lesions may be predictive factors for PFS with PD-1 inhibitor monotherapy. These findings offer reference data for clinical decision-making regarding drug selection in elderly advanced NSCLC patients.

This study defined elderly patients as those aged 65 years or older, following WHO criteria. Lung cancer incidence in China has been rising, with approximately 815,000 new cases annually [2]. The proportion of elderly lung cancer patients is increasing correspondingly. However, age-related changes such as decreased body fat, declining hepatic and renal function may affect the absorption, metabolism, and excretion of immunotherapeutic agents. Consequently, most clinical trials exclude elderly patients, resulting in limited clinical data for elderly NSCLC patients [7]. Therefore, effective and safe treatment options are urgently needed for the large population of elderly advanced NSCLC patients in clinical practice.

Among the 63 enrolled patients, 11 received PD-1 inhibitors as second-line therapy, while 52 received them as third-line or later. Given that PD-1 inhibitors have been approved for second-line monotherapy, their use in this study was ethically appropriate. The ORR and DCR were 22.2% and 55.6%, respectively, with a median PFS of 3.3 months. These results are consistent with the CheckMate-017 and CheckMate-057 studies of nivolumab in second-line treatment of advanced squamous and non-squamous NSCLC (ORR approximately 20%, median PFS around 3 months) [11, 14]. The Keynote-010 study of pembrolizumab in second-line advanced NSCLC showed an ORR of 18% and median PFS of 3.9 months, which is slightly better than our results. Several factors may explain this difference: first, the median age differed (63 years in Keynote-010 vs. 71 years in our study), and some research suggests older age is associated with poorer prognosis [15]. Second, Keynote-010 included predominantly patients with ECOG performance status 0-1, whereas 46% of our patients had ECOG score 2. ECOG score has been established as a prognostic factor for PFS and OS in advanced NSCLC [16], and our multivariate Cox analysis confirmed significantly worse outcomes for ECOG 2 patients. Third, as a retrospective study, patient management and compliance were likely inferior to those in rigorous phase III trials, potentially affecting prognosis, as demonstrated in previous retrospective studies [17]. These three factors may explain the inferior median PFS in our study compared to Keynote-010.

Additionally, Giulia G et al. conducted a retrospective study of immunotherapy in elderly advanced NSCLC patients in Italy, enrolling 180 patients under 70 and 110 patients aged 70 or older [18]. Patients over 70 achieved approximately 20% ORR, 3.5-month median PFS, and 11.3-month median OS, consistent with our efficacy and prognosis results. In the Chinese population, Shao et al. performed a retrospective study on the impact of age-adjusted Charlson comorbidity index on prognosis in 118 elderly advanced NSCLC patients over 70 receiving PD-1 inhibitors [19]. They reported an ORR of 22.9% and DCR of 76.3%, with median PFS of 6.1-10.6 months and median OS of 11.7-33.9 months. While their ORR and DCR were consistent with our study, their PFS and OS were significantly superior, possibly due to fewer ECOG 2 patients or heterogeneity in patient selection. Overall, these studies suggest elderly NSCLC patients can still benefit from PD-1 inhibitors. However, Shao's study did not evaluate safety data, leaving a gap in adverse event information for elderly patients receiving PD-1 inhibitors.

Our Cox analysis also identified ECOG performance status and number of metastatic lesions as independent risk factors for PFS, consistent with previous retrospective studies [20]. However, whether these factors can serve as predictive biomarkers for PFS requires validation in larger cohorts, as patients with poor performance status and numerous metastases inherently have higher tumor burden and poorer prognosis regardless of treatment.

Regarding safety, our analysis showed that 73.0% of elderly advanced NSCLC patients experienced adverse reactions of any grade, with 14.3% experiencing grade $ $3 adverse events. Overall, adverse events were manageable and consistent with previous retrospective studies of PD-1 inhibitor monotherapy in advanced NSCLC [21]. Notably, we observed abnormal liver function in 9 patients, including 4 with grade $ $3 AST/ALT elevation, which appears higher than in Keynote-010. This may be attributed to elderly patients' multiple comorbidities and relatively poorer hepatic and renal function, leading to more high-grade liver function abnormalities during PD-1 treatment. Overall, PD-1 monotherapy demonstrated manageable safety in elderly patients, though prospective validation is needed.

This study has several limitations. First, as a retrospective analysis with a relatively small sample size, results require validation in larger studies. Additionally, the maturity of some PFS and OS data was relatively low, and suboptimal patient management may have introduced bias. Second, PD-L1 expression was not assessed, precluding analysis of its association with PD-1 inhibitor efficacy. Nevertheless, this study preliminarily explored the efficacy and safety of PD-1 inhibitors in elderly advanced NSCLC patients, providing valuable reference data for clinical practice.

Figure 1 [Figure 1: see original paper] Therapeutic profiles of the study regarding 63 elderly patients with advanced NSCLC who received PD-1 blockades monotherapy

Figure 2 [Figure 2: see original paper] Waterfall plot for the best percentage change in target lesion size of the 63 elderly patients with non-small cell lung cancer who received PD-1 inhibitors

Figure 3 [Figure 3: see original paper] The Progression-Free Survival curve of the 63 elderly patients with advanced non-small cell lung cancer who received PD-1 inhibitors

Figure 4 [Figure 4: see original paper] The Overall Survival curve of the 63 elderly patients with advanced non-small cell lung cancer who received PD-1 inhibitors

Table 1 Baseline characteristics of the 63 elderly patients with NSCLC

Table 2 Univariate and multivariate analysis of baseline characteristics and PFS in 63 elderly patients with advanced NSCLC who were treated with PD-1 blockades

Table 3 Safety profile of the 63 elderly patients with advanced NSCLC who received PD-1 blockades monotherapy

Author Contributions: SONG Pingan: Conceptualized the study, designed the research protocol, and proposed the research topic and design. CHEN Xiaoliang, YAO Yuan, and GAO Jin: Managed study subjects and conducted follow-up. YANG Yang and CUI Hongchun: Collected, acquired, and cleaned data. ZHANG Yi: Performed statistical analysis and created figures. SONG Pingan: Drafted and wrote the manuscript, revised the final version, and took responsibility for the paper.

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Note: Figure translations are in progress. See original paper for figures.