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Pembrolizumab or Bevacizumab Plus Chemotherapy as First-Line Treatment of Advanced Nonsquamous Nonsmall Cell Lung Cancer: A Retrospective Cohort Study

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Abstract

Objective: Pembrolizumab and bevacizumab both have antitumor activity. According to NCCN updated guideline the benefit of pembrolizumab or bevacizumab as a first line in management of advanced nonsmall cell lung cancer (NSCLC) is documented in randomized controlled studies. The study aimed to evaluate the response and complications of patients with advanced NSCLC treated with pembrolizumab or bevacizumab plus chemotherapy. **Methods:** This study was a retrospective cohort study of patients with advanced nonsquamous NSCLC who received cisplatin with pemetrexed combined with pembrolizumab (A group) or bevacizumab (B group) from 07/02/2018 to 07/03/2021 at Peking University Cancer Hospital. Progression-free survival (PFS) was the primary outcome. The secondary outcomes included overall survival (OS), objective response rate (ORR), disease control rate (DCR), duration of response (DoR), and adverse events (AEs). **Results:** This study included 66 patients, 34 in A group and 32 in B group. There were no differences in median PFS (7.6 vs 9.9 months, $P = .601$). There were no differences in median OS (23.1 vs 24.2 months, $P = .782$). There were no differences in ORR (57.6% vs 41.9%, $P = .211$) and DCR (93.9% vs 100.0%, $P = .164$) between 2 groups. The occurrence of AEs was similar. No new safety signals were observed. Grade 3 to 4 treatment-related AEs occurred in 17 (50.0%) patients of A group and in 12 (37.5%) of B group ($P > .05$). **Conclusion:** The addition of pembrolizumab or bevacizumab to pemetrexed plus cisplatin was well tolerated and resulted in a clinically meaningful treatment benefit in advanced nonsquamous NSCLC. When pembrolizumab is not suitable, bevacizumab plus chemotherapy may be an option.

Keywords

bevacizumab, chemotherapy, nonsquamous nonsmall cell lung cancer, pembrolizumab, response to treatment

Abbreviations

ABCP, bevacizumab plus carboplatin plus paclitaxel; ACP, atezolizumab plus carboplatin plus paclitaxel; AEs, adverse events; ASCO, American Society of Clinical Oncology; BCP, bevacizumab plus carboplatin plus paclitaxel; CR, complete response; CT, Computed tomography; DCR, disease control rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; MRI, magnetic resonance imaging; NSCLC, nonsmall cell lung cancer; ORR, objective response rate; PD, progression disease; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PR, partial response; SAiL, Safety of Avastin in Lung; SD, stable response

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Introduction

Lung cancer is the main cause of cancer-related death in the world.[1,2] Lung cancer is also the disease with the highest

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mortality rate, with annual age-standardized mortality of 27.1 per 100,000 men and 14.3 per 100,000 women.[2] Smoking is the main risk factor.[3,4] Environmental pollution and genetic factors may be other causes. 85% to 90% of malignant diseases of lung are nonsmall cell lung cancers (NSCLC).[3,4] NSCLC can be classified as squamous and nonsquamous (adenocarcinoma and large cell carcinoma, etc).[4,5] Most patients are in advanced stage at the time of diagnosis and cannot be acceptance of surgery. The standard treatment for advanced NSCLC without sensitive mutations is chemotherapy with platinum-based regimens.[3–7] Due to the low efficiency and short overall survival (OS) time of chemotherapy, it is still necessary to explore more effective treatments.[4,8]

Bevacizumab is an angiogenesis inhibitor. Three randomized phase III clinical trials (ECOG4599, AVAIL, and Beyond) confirmed that bevacizumab combined with chemotherapy had advantages over single chemotherapy. The treatment of bevacizumab plus chemotherapy had longer progression-free survival (PFS) and OS.[9–11]

Inhibitors of programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) are approved as the first line treatment for advanced NSCLC without sensitive mutations.[4,12,13] Immunotherapy combined with chemotherapy significantly increased OS, PFS, and duration of response (DoR) and a higher response rate compared with single chemotherapy.[4,12–14.]

In the randomized phase 3 IMpower150 trial, there were 3 treatment group. ABCP was used atezolizumab in combination with bevacizumab plus carboplatin plus paclitaxel. ACP was used atezolizumab plus carboplatin plus paclitaxel. BCP was used bevacizumab plus carboplatin plus paclitaxel. The 4 drugs treatment group (ABCP) significantly increased PFS and OS, but the PFS and OS of BCP and ACP group were similar.[15]

Our study wanted to evaluate the response and adverse events (AEs) of patients with advanced nonsquamous NSCLC treated with pembrolizumab plus chemotherapy versus bevacizumab plus chemotherapy. The results could provide evidence for a future clinical trial.

Materials and Methods

Study Design and Patients

This study was a retrospective cohort study of patients with advanced nonsquamous NSCLC who received chemotherapy plus pembrolizumab or bevacizumab from July 2, 2018 to July 03, 2021, at the Thoracic Oncology Department of Peking University Cancer Hospital. This study was approved by the medical ethics committee of Beijing Cancer Hospital (Beijing, China; 2019-KT43). All patients provided written informed consent for the acceptance of chemotherapy plus pembrolizumab or bevacizumab.

The inclusion criteria were (1) ≥18 and <75 years of age, (2) histologically or cytologically confirmed stage IIIB/IV nonsquamous NSCLC based on examination of specimens obtained by bronchoscopy, mediastinoscopy, or computed tomography (CT)-guided percutaneous lung biopsy, according to the American Joint Committee on Cancer 8th criteria,[4,16] (3) without EGFR gene sensitive mutations, ALK gene rearrangement, and ROS-1 positive tumor, (4) naïve to platinum-containing doublet chemotherapy or targeted therapy, (5) could be received immunotherapy or targeted anti-angiogenesis therapy, and (6) life expectancy >3 months when they chemotherapy was started. The exclusion criteria were (1) uncontrolled brain metastases or meningeal metastases, (2) incomplete clinical data, or (3) received other chemotherapy or investigational agents during first-line induction therapy.

Treatment

All patients received 4 or 6 3-week cycles of cisplatin (75 mg/m^2, Qilu Pharmaceutical Co. Ltd) plus pemetrexed (500 mg/m^2, Jiangsu Haosen Pharmaceutical Co. Ltd), followed by pemetrexed (500 mg/m^2) every 3 weeks. All patients received premedication with folic acid (400 μg/d, oral), vitamin B12 (1 mg every 3 months, intramuscular injection), and dexamethasone (3.75 mg/bid, oral) for pemetrexed use. The patients who received pembrolizumab (Merck Frosst) plus pemetrexed and cisplatin were grouped as the A group. Pembrolizumab was administered at 200 mg on day 1 of each 3-week cycle. The patients who received bevacizumab plus pemetrexed and cisplatin were grouped as the B group. Bevacizumab (Roche) was administered at 7.5 mg/kg on day 1 of each 3-week cycle. After the induction phase, the patients continued to receive pembrolizumab or bevacizumab until the occurrence of unmanageable toxicity (including bone marrow suppression and impaired liver and kidney function) or disease progression. Continuation of pembrolizumab after the occurrence of disease progression was allowed if evidence of clinical benefit was observed.

Follow-up

Follow-up was conducted through the outpatient clinic on the first day of each cycle. Every 2 cycles, the patients were examined by cranial magnetic resonance imaging (MRI), chest CT, and abdominal CT. Follow-up was censored on July 03, 2021.

Outcomes

PFS was the primary outcome. PFS was calculated from the start of treatment until the date of disease progression (assessed according to the RECIST 1.1 criteria) or death from any cause or the last follow-up. The secondary outcomes included OS, the objective response rate (ORR) (complete response [CR] + partial response [PR]), disease control rate (DCR) (CR + PR + stable disease [SD]), DoR and AEs. Tumor response was assessed by imaging every 2 cycles until disease progression. The tumor response was evaluated according to the RECIST 1.1 criteria,[17] including CR, PR, SD, and progressive disease (PD). OS was calculated from the start of treatment until the

date of death or the last follow-up. DoR was calculated from the occurrence of PR or CR until disease progression or death from any cause or the last follow-up. The AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.[18]

Tumor response was calculated in eligible patients who underwent tumor evaluation for at least 2 cycles of treatment. AEs were evaluated in all patients who received at least one cycle of treatment.

Data Collection

Pretreatment evaluation in both groups included patient history, physical examination, complete blood count, serum chemistry, bronchoscopy, chest CT, abdominal ultrasound or CT, bone scan, and brain MRI were collected from clinical medical records.

Statistical Analysis

All statistical analyses were performed with Prism 6 (Graph Pad Software Inc.). Continuous data are presented as medians (range) and were analyzed using the Mann–Whitney *U*-test. Categorical data are presented as n (%) and were analyzed using the chi-square test or Fisher's exact test. The actuarial survival curves were computed using the Kaplan–Meier method and analyzed using the log-rank test. Variables with *P* values <.05 in univariable analyses were included in a Cox multivariable analysis to determine the independent factors associated with survival. Two-sided *P* values <.05 were considered statistically significant.

Results

Characteristics of the Patients

This study included 66 patients: 34 in the A group and 32 in the B group. The median age was 62 years (range 36-75). There were 49 men (74.2%) and 17 women (25.8%). The demographic characteristics are shown in Table 1.

Table 1. Demographic and Disease Characteristics of the Patients at Baseline (n = 66).

Characteristics	A group (n = 34)	B group (n = 32)	*P*
Age, years, median (range)	62.0 (47.0-72.0)	61.0 (36.0-75.0)	.432
Sex, n (%)			.675
Male	26 (76.5)	23 (71.9)	
Female	8 (23.5)	9 (28.1)	
ECOG PS, n (%)			.222
0	22 (64.7)	9 (28.1)	
1	12 (35.3)	23 (71.9)	
Smoking status, n (%)			.719
Current or former	19 (55.9)	19 (59.4)	
Never	15 (44.1)	13 (40.6)	
Staging, n (%)			.599
IIIb	2 (5.9)	3 (9.4)	
IV	32 (94.1)	29 (90.6)	
Brain metastases, n (%)	9 (26.5)	12 (37.5)	.344
Liver metastases, n (%)	5 (14.7)	3 (9.4)	.515
Mutation, n (%)			.548
Negative	21 (61.8)	23 (71.9)	
EGFR nonsensitive	3 (8.8)	3 (9.4)	
KRAS	7 (20.6)	2 (6.3)	
Other	3 (8.8)	4 (12.5)	
PD-L1 TPS, n (%)			.333
<1%	1 (2.9)	4 (12.5)	
1-49%	3 (8.8)	1 (3.1)	
≥50%	4 (11.8)	2 (6.3)	
Unknown	26 (76.5)	25 (78.1)	

A group, pembrolizumab plus pemetrexed and cisplatin; B group, bevacizumab plus pemetrexed and cisplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; TPS, tumor proportion score.

Survival and Cox Multivariable Analysis

The median follow-up time was 24.2 months (range, 12.8-36.6 months). The median PFS was 8.3 months (95% confidence interval [CI]:5.2-11.4). By the last follow-up, 49 patients (74.2%) had a disease progression, 25 (73.5%) in A group, and 24 patients (75.0%) in B group. The median PFS for patients treated with A group and B group was 7.6 months (95% CI: 5.0-9.8) and 9.9 months (95% CI: 5.0-13.0), respectively (Figure 1), without significant difference between the 2 groups ($P = .601$). The median OS for patients with A group and B group was 23.1 months (95%CI: 16.6-32.8) and 24.2 months (95%CI: 16.2-32.2) (Figure 2). There was no significant difference between 2 groups ($P = .782$).

Supplemental Tables 1 and 2 shows the multivariable analysis for factors associated with PFS and OS. Sex was the only factor independently associated with PFS (HR = 3.255, 95%CI: 1.195-8.870, $P = .021$). No factors were associated with OS ($P > .05$).

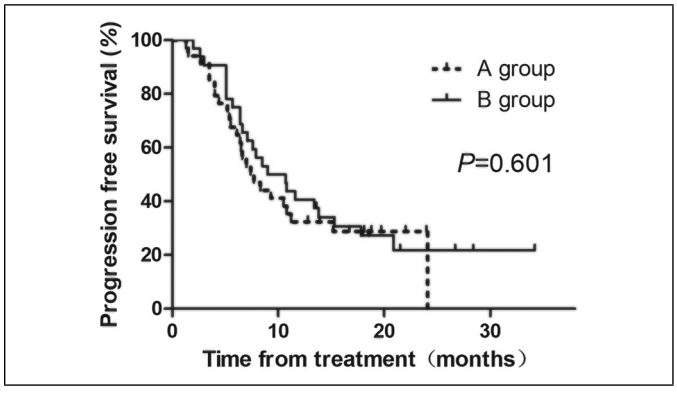

Figure 1. Kaplan–Meier curves of progression-free survival (PFS) in the pembrolizumab plus chemotherapy group and the bevacizumab plus chemotherapy group.

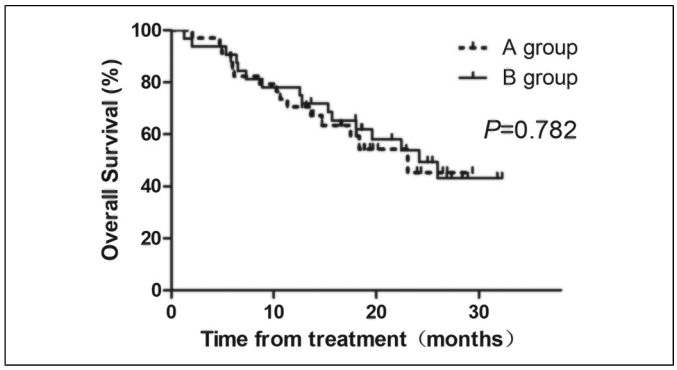

Figure 2. Kaplan–Meier curves of overall survival (OS) in the pembrolizumab plus chemotherapy group and the bevacizumab plus chemotherapy group.

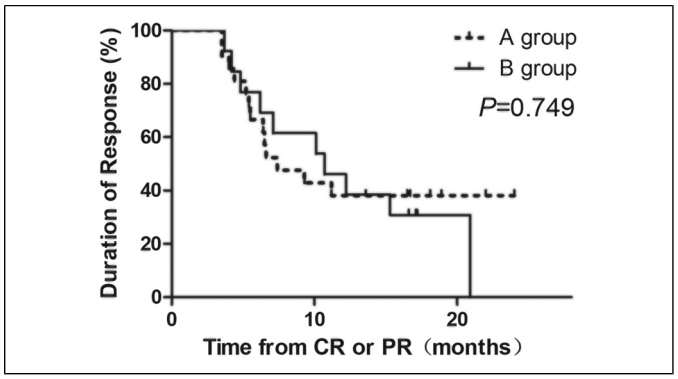

Figure 3. Kaplan–Meier curves of duration of response (DoR) in the pembrolizumab plus chemotherapy group and the bevacizumab plus chemotherapy group.

Tumor Response

The efficacy of each treatment regimen is detailed in Table 2. Of the 66 patients who began the treatment, 64 (97.0%) completed at least 2 treatment cycles and were assessed for response. No patients in each treatment group had a CR. In group A, there were 19 cases of PR and 12 of SD, for an ORR of 57.6% and DCR of 93.9%. Of the 34 patients who originally had pembrolizumab plus chemotherapy, maintenance therapy with pemetrexed plus pembrolizumab was performed in 9 (26.5%). Treatment was discontinued in 2 patients because of toxicities, 3 patients because of economic reasons, and 6 patients because of COVID-19. In group B, there were 13 cases of PR and 18 of SD, for an ORR of 41.9% and DCR of 100.0%. Of the 32 patients who originally had bevacizumab plus chemotherapy, maintenance therapy with pemetrexed plus bevacizumab was performed in 16 (50.0%). Treatment was discontinued in 4 patients because of economic reasons and 8 because of COVID-19. The ORR and DCR of the 2 groups were not significantly different ($P = .211$ and $P = .164$, respectively). The median DOR in A and B group was 7.44 months (95% CI: 3.2-11.6) and 10.7 months (95% CI: 4.7-16.7), respectively (Figure 3), with no statistically significant difference ($P = .749$).

Table 2. Summary of Treatment Efficacy in Patients who Underwent Tumor Evaluation.

Treatment efficacy, n (%)	A group (n = 34)	B group (n = 32)	*P*
Complete response	0	0	
Partial response	19 (55.9)	13 (40.6)	
Stable disease	12 (35.3)	18 (56.3)	
Progressive disease	2 (5.9)	0	
Could not be evaluated	1 (2.9)	1 (3.1)	
Objective response rate	19/33 (57.6)	13/31 (41.9)	.211
Disease control rate	31/33 (93.9)	31/31 (100.0)	.164

A group, pembrolizumab plus pemetrexed and cisplatin; B group, bevacizumab plus pemetrexed and cisplatin.

Adverse Events

All AEs are listed in Table 3. No patients in 2 groups had grade 5 AE. Grade 3 to 4 treatment-related AEs occurred in 17 (50.0%) patients in group A and in 12 (37.5%) in group B ($P > .05$). AEs that led to discontinuation of treatment occurred in 2 (5.9%) patients in A group and 2 (6.3%) patients in B group ($P > .05$). The most frequent treatment-related AEs were leukopenia (29.4%) and neutropenia (29.4%) in the pembrolizumab group and leukopenia (37.5%) and neutropenia (37.5%) in the bevacizumab group. One patient (2.9%) had severe immune-mediated ventricular arrhythmia in A group. One patient (3.1%) had deep venous thrombosis in B group.

Discussion

Most lung cancer patients are advanced or locally advanced at the time of diagnosis.[4] Platinum-containing 2 drug chemotherapy was the standard treatment for advanced lung cancer in past time, the survival period and treatment efficiency were not ideal.[3–7] The median OS is approximately 1 year,[19–21] especially for NSCLC patients without actionable driver mutations.[22,23] Pembrolizumab and bevacizumab both have antitumor activity, their benefits in treatment of advanced nonsquamous NSCLC are confirmed.[15] Therefore, our study wanted to evaluate the response and AEs of patients with advanced nonsquamous NSCLC treated with pembrolizumab plus chemotherapy versus bevacizumab plus chemotherapy. We wanted to explore which of the 2 treatments has more advantages. The results suggested that pembrolizumab or bevacizumab plus pemetrexed and cisplatin was well tolerated and may both have had advantages for advanced nonsquamous NSCLC. For patients with immunotherapy contraindications, we can choose bevacizumab plus chemotherapy treatment.

Bevacizumab combined with chemotherapy in the treatment of advanced nonsquamous NSCLC can improve OS and treatment efficiency.[9,10,24] The E4599 study confirmed that Bevacizumab combined with chemotherapy had more advantages in OS time. The E4599 and AVAiL study confirms the

Table 3. Adverse Events of 2 Groups.

Adverse events, n (%)	A group		B group		*P*
Treatment-related AEs					
Any grade	28 (82.4)		23 (71.9)		.317
Grade III-V	17 (50.0)		12 (37.5)		.330
Serious AEs	1 (2.9)		1 (3.1)		.966
Led to discontinuation	2 (5.9)		2 (6.3)		.951
Led to death	0		0		-
Treatment-related AEs in either arm	I-II	III-IV	I-II	III-IV	
Fatigue	8 (23.5)	0	11 (34.4)	0	.331
Anorexia	7 (20.6)	0	6 (18.8)	0	.851
Leukopenia	10 (29.4)	5 (14.7)	12 (37.5)	4 (12.5)	.609
Neutropenia	10 (29.4)	6 (17.6)	12 (37.5)	5 (15.6)	.622
Anemia	6 (17.6)	2 (5.9)	9 (28.1)	0	.110
Thrombocytopenia	3 (8.8)	1 (2.9)	3 (9.3)	1 (3.1)	1.000
Nausea/vomiting	3 (8.8)	1 (2.9)	2 (6.3)	0	.439
Arrhythmia	1 (2.9)	1 (2.9)	0	0	.328
Diarrhea	1 (2.9)	0	0	2 (6.3)	.965
Hepatitis	2 (5.9)	1 (2.9)	5 (15.6)	0	.199
Thrombus	0	0	0	1 (3.1)	.299

AE, adverse event; A group, pembrolizumab plus pemetrexed and cisplatin; B group, bevacizumab plus pemetrexed and cisplatin.

benefits of PFS.[9,10] SAiL study suggested that bevacizumab combined with chemotherapy may be effective to Asian populations.[25] The phase III BEYOND trial confirmed that bevacizumab combined with carboplatin/paclitaxel compared with single chemotherapy had achieved better clinical benefits, and the toxicity was tolerable in the Chinese population.[11] A phase II study in Japan, used bevacizumab combined with cisplatin and pemetrexed followed by maintenance therapy in patients with wild-type EGFR advanced nonsquamous NSCLC showed that the median PFS was 12.0 months and OS was 31.0 months, and ORR was 70%.[26] In our study, the median PFS of using bevacizumab combination group was 9.9 months, the median OS was 24.2 months and ORR was 41.9%, similar to these previous studies.

Immunomodulatory agents targeting PD-1 or PD-L1 have recently been introduced and are in the process of being integrated into standard treatment.[27,28] The phase III KEYNOTE-189 study have confirmed that pembrolizumab plus pemetrexed and platinum compared with chemotherapy alone in patients with nonsquamous metastatic NSCLC significantly prolonged OS and PFS at different levels of PD-L1 expression..[14] Many other studies have also confirmed the significant clinical benefits of pembrolizumab combination therapy.[4,12–14] In the IMPOWER 150 study, the median PFS was 6.7 months versus 6.8 months in the ACP and BCP groups.[15,29] In our study, the median PFS of using pembrolizumab group was 7.6 months. Besides, the ORR in patients with metastatic nonsquamous NSCLC in the pembrolizumab combination group compared with those of the bevacizumab combination group was similar. The results were consistent with these previous studies.

Indeed, the KEYNOTE-001 study[30] showed that at a median follow-up of 23.1 months, the median OS was 22.1 months in the overall population for treatment-naïve patients.[31] In the KEYNOTE-101 study, pembrolizumab compared with docetaxel had significant benefits in OS except for EGFR mutation and squamous subgroups.[32] KEYNOTE-024 study showed that anti-PD-1 monotherapy compared with platinum-containing chemotherapy as first-line treatment in patients with advanced NSCLC had OS benefit.[33] In our study, the median OS of anti PD-1 plus chemotherapy was almost 2 years. It has been previously reported that the median survival of platinum-containing chemotherapy was almost 1 year. We can see that combined immunotherapy prolonged the OS.

Currently, immunotherapy brings survival benefits for advanced NSCLC. In KEYNOTE-024, KEYNOTE-042, KEYNOTE-021, KEYNOTE-189, KEYNOTE-407 study, the data showed that pembrolizumab plus chemotherapy as a first-line treatment for all patients with advanced NSCLC without sensitive mutations could have OS benefits compared with single platinum doublet chemotherapy. Immunotherapy as a first-line therapy might have a long-term effect on the outcomes. Regardless of the expression of PD-L1, pembrolizumab plus chemotherapy all had survival benefits. Many studies showed that PD-1 or PD-L1 plus chemotherapy had no significant advantages in PFS. It may suggest that immunotherapy could influence the effectiveness of subsequent therapies or had long-term advantages.[34–39] In our study, the median follow-up time was 24.2 months, the median OS for patients with pembrolizumab combination group was 23.1 months (95%CI: 16.6-32.8). It is almost 2 years.

This study suggested that the AEs observed in the 2 groups were manageable. The occurrence and severity of the AEs were consistent with those previous studies.[33] There were no treatment-related deaths occurred in our study. And there was no evidence of cumulative toxicity. The use of pembrolizumab or bevacizumab plus with pemetrexed and platinum did not appear to increase the frequency of AEs. Most of the treatment-related AEs were defined as grade 1 or 2, leading to

underreporting. The rates of death or treatment discontinuation were not different between the 2 groups.

There may have predictors of immunotherapy. In the KEYNOTE-001 trial, patients with a PD-L1 tumor proportion score of 50% or greater who were treated with immunotherapy have a 5-year OS rate of 25%.[40] Different randomized clinical trials had different results, whether PD-L1 expression level could be used as an ideal biomarker of predicting immunotherapy efficacy remained to be explored.[41] Other better biomarkers were needed. Only a small number of patients have been tested for PD-L1 in our study. The selection of patients most likely to benefit from immunotherapy is necessary to avoid exposure to potentially toxic and ineffective drugs and prevent inappropriate allocation of health resources. It is also very important to explore the predictive biomarkers of antiangiogenic drugs. Further studies are needed to improve our understanding of the mechanisms of immunotherapy and antiangiogenic drugs in vivo, to find suitable predictive biomarkers.

This study has some limitations. First, the number of patients was relatively small, the number of enrolled people needed to be expanded to validate our findings. Second, we need a longer follow-up to evaluate the OS effect of pembrolizumab plus chemotherapy. Finally, this is a retrospective study in a single center, and the generalizability of the findings is unknown.

Updated NCCN guidelines recommend pembrolizumab as a first line regimen for advanced nonsquamous NSCLC without actionable mutation. Bevacizumab is recommended for those who have contraindication to PD-1, PD-L1 inhibitors. Clinically, there are patients with pulmonary interstitial fibrosis, or active autoimmune system diseases, or economic difficulties, we will choose bevacizumab adding platinum doublet treatment regimen. In our study, we found bevacizumab plus chemotherapy was not worse than pembrolizumab plus chemotherapy.

Conclusions

Pembrolizumab or bevacizumab plus chemotherapy with pemetrexed and cisplatin and with pemetrexed maintenance therapy resulted in similar PFS, OS, ORR and AEs in patients with advanced nonsquamous NSCLC without sensitizing EGFR or ALK mutations. The use of pembrolizumab or bevacizumab plus pemetrexed and cisplatin was well tolerated and resulted in a treatment benefit in advanced nonsquamous NSCLC. When pembrolizumab is not suitable, bevacizumab plus chemotherapy may be an option.

Authors' Note

Jian Fang designed this study. Ziran Zhang, Jie Zhang, Di Wu, Guangming Tian, and Jindi Han collected the data. Xiaoling Chen, Xiangjuan Ma, Weiheng Hu, Jieran Long, and Yang Wang analyzed the data and interpreted the results. Jie Zhang wrote the manuscript. Jun Nie and Ling Dai modified the manuscript. All authors read and approved the final manuscript. The study was approved by the medical ethics committee of Beijing Cancer Hospital (Beijing, China; 2019-KT43). All patients provided written informed consent.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

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