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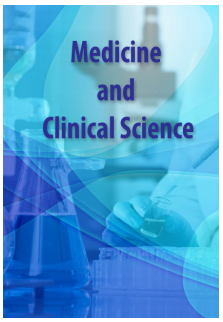

Efficacy and safety of camrelizumab in metastatic lung cancer: a single-center, prospective cohort study

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Abstract

Objective: To explore the efficacy and safety of camrelizumab in the treatment of patients with metastatic lung cancer in the real world.

Methods: A prospective cohort study was designed to include a total of 44 patients with metastatic lung cancer who received camrelizumab treatment in xx Hospital between July 2019 and May 2020, with a follow-up endpoint set on August 1, 2020. The primary endpoints were objective response rate (ORR) and safety. Secondary endpoint measures included progression-free survival (PFS), and overall survival (OS). Cox regression was used for the analysis of factors associated with PFS.

Results: The ORR of 44 patients was 27.3% (including 1 complete response and 10 partial responses), and 7 patients had disease progression. The PFS was 8 months (2-11 months), and the OS had not been reached. Multivariate Cox regression analysis showed that the number of metastatic sites ≤ 1 (HR = 0.202, 95% CI: 0.065-0.637, P < 0.01) was associated with PFS. The most common adverse event was anemia (47.7%, 21/44), all grade 1 to 2. Five patients (9.1%) had grade 3 adverse events, including 2 cases of neutropenia, 1 case of leukopenia, and 2 cases of immune pneumonitis. Other common adverse events included thrombocytopenia (18.2%), hemangioma (15.9%), and hypothyroidism (11.4%), all of which were grade 1-2. There were no deaths due to adverse events. Conclusion: In the real world, camrelizumab has definite efficacy and controllable toxicity in patients with metastatic lung cancer, with high safety. .

Introduction

Lung cancer is currently the malignancy with the highest incidence and mortality worldwide [1], and the 5-year survival rate of patients with advanced lung cancer is less than 5% [1]. Most lung cancers have progressed to the middle and advanced stages at the time of diagnosis, and surgical treatment is of great significance, which is also the primary reason for the high mortality rate of lung cancer. Thanks to the in-depth study and significant progress of pathogenesis at the level of tumor genes and molecular biology, the diagnosis, and treatment of lung cancer has been significantly improved [2]. Among them, immunotherapy has become a remarkable focus in the current field of lung cancer research [3,4]. Currently, programmed death 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors are proven to be effective cancer immunotherapies [5,6]. The PD-1/PD-L1 inhibitors nivolumab [7], pembrolizumab [8] and atezolizumab [9] have recently been approved by the Food and Drug Administration (FDA) for the treatment of patients with advanced metastatic squamous cell carcinoma of the lung, metastatic non-small cell lung cancer (NSCLC) and other lung cancers. More studies on the use of PD-1/PD-L1 inhibitors in the treatment of lung cancer are still in full swing.

Camrelizumab, a PD-1/PD-L1 inhibitor independently developed in China, is a humanized IgG4κ anti-PD-1 monoclonal antibody obtained using recombinant technology in Chinese hamster ovary (CHO) cell line [10]. It blocks the PD-1/PD-L1 pathway by binding to PD-1, thereby activating T cells and producing sustained antitumor effects [11]. A recent single-arm phase II clinical trial [12] used camrelizumab to treat classical Hodgkin's lymphoma with encouraging results. Based on this study, camrelizumab was recently approved by the China Food and Drug Administration (CFDA) for the treatment of relapsed or refractory classical Hodgkin's

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lymphoma after at least two lines of systemic chemotherapy. Clinical trials of Camrelizumab in the treatment of other solid tumors are also being widely conducted. A phase 1b study (NCT03083041) [13] that included 15 patients with advanced non-scaly non-small cell lung cancer who had previously received intensive treatment and were treated with camrelizumab in combination with apatinib showed that the overall response rate and disease control rate were 41.2% and 94.1%, respectively. Another study [14] also achieved an ORR of 33.33% using camrelizumab combined with microwave in the treatment of advanced cancer. However, there is still a lack of sufficient studies on the efficacy and safety of camrelizumab in the treatment of lung cancer, especially in the real world, the difference in efficacy for different types of lung cancer is not clear.

In this study, we included 44 patients with metastatic lung cancer to clarify the efficacy and safety of camrelizumab in the treatment of lung cancer in the real world by analyzing the treatment response rate, occurrence of adverse events, and survival.

Materials and methods

Patients

A total of 44 patients with metastatic lung cancer treated with camrelizumab admitted to our hospital between July 2019 and May 2020 were included in the study. Inclusion criteria 1) Patients admitted to the hospital with imaging and pathological examination confirmed the diagnosis of lung cancer, and at least 1 site of metastasis. 2) Expected survival > 3 months. 3), all of whom received camrelizumab or combination therapy. Exclusion criteria : 1) Patients with mental illness such as cognitive dysfunction or pregnant or lactating women; 2) Patients who are intolerant to camrelizumab drugs. 3) Patients with incomplete follow-up data.

Ethical statement

The study followed the tenets of following the Declaration of Helsinki and was approved by the Ethics Committee of our hospital for conduct. Informed consent was obtained from all patients.

Camrelizumab treatment

All patients were treated with 200 mg camrelizumab (Jiangsu Hengrui Medicine Co., Ltd., China, strength 200 mg) intravenously every 2 weeks until intolerable toxicity or disease progression occurred.

Efficacy assessments

Best Overall Response (BOR): Patients were evaluated for a clinical response using Response Evaluation Criteria in Solid Tumors version 1.1 [15], which was classified as follows: complete response (CR): complete disappearance of tumor lesions on imaging; partial response (PR): reduction in the diameter of tumor lesions by more than 30%; stable disease (SD): tumor shrinkage, but < 30%; progressive disease (PD): increase in the diameter of tumor lesions by ≥ 20%, or the appearance of new lesions. Objective response rate (ORR) was defined as the percentage of patients with CR and PR. Disease control rate (DCR) was defined as the percentage of patients with CR, PR, and SD.

Progression-free survival (PFS) is defined as the time interval from the start of treatment with camrelizumab to the occurrence of disease progression or death. Overall survival (OS) was defined as the interval from the start of treatment with camrelizumab to the occurrence of death from any cause.

Assessment of adverse events (AEs)

National cancer institue-common terminology criteria for adverse events (NCI-CTC 4.0) were used for determination and classified into grades 1 to 5.

Observation indicators

Primary endpoints included objective response rate (ORR) and safety. Secondary endpoint measures included factors associated with progression-free survival (PFS), overall survival (OS), and patient PFS.

Statistical analysis

SPSS version 23.0 (SPSS, Inc., Chicago, IL, USA) software was applied for statistical analysis. Enumeration data were expressed as an example (percentage) [n (%)], and $\chi 2$ test or Fisher's exact test was performed. Patient age is presented as mean (range). Kaplan-Meier curves for PFS and OS of patients were plotted using GraphPad 7.0 and compared using the log-rank t-test. Multivariate Cox regression analysis was used to evaluate the influencing factors of PFS in patients. The test level was $\alpha = 0.05$, and $P < 0.05$ was considered statistically significant.

Table 1. *Baseline data of patients*

Item	Number of patients (n = 34)
Age, mean (range)	63.8 (32-83)
Gender, n (%)	
Male	37 (84.1)
Female	7 (15.9)
ECOG score	
1	35 (79.6)
2	8 (18.2)
3	1 (2.3)
Tumor type, n (%)	
Squamous cell carcinoma of lung	19 (43.2)
Lung adenocarcinoma	21 (47.7)
Small cell lung cancer	4 (9.1)
First-line medication or not, n (%)	
Yes	16 (36.4)
No	28 (63.6)
Combination therapy drugs, n (%)	
None	5 (11.4)
Apatinib	5 (11.4)
Anlotinib	5 (11.4)
Nab-paclitaxel	9 (20.5)
Platinum drugs	21 (47.7)
Docetaxel	4 (9.1)
Gemcitabine	5 (11.4)
Pemetrexed	4 (9.1)
Other chemotherapy drugs	4 (9.1)
Number of chemotherapy lines after recurrence, n (%)	
0	17 (38.6)
1	6 (13.6)
2	8 (18.2)
≥ 3	13 (29.6)

Item	Number of patients (n = 34)
Number of metastatic sites, n (%)	
1	18 (40.9)
2	13 (29.6)
≥ 3	13 (29.6)
Metastatic site, n (%)	
Brain	5 (11.4)
Lung	21 (47.7)
Liver	5 (11.4)
Bone	20 (45.6)
Lymph nodes	23 (52.3)
Other	5 (11.4)

ECOG: Eastern Cooperative Oncology Group

Results

Baseline data of patients in the two groups

A total of 44 patients with a mean age of 63.8 years were included in the study, most of whom (84.1%) were male. One patient had an ECOG score of 3. The main types of lung cancer were lung squamous cell carcinoma (43.2%) and lung adenocarcinoma (47.7%). There were 16 patients (36.4%) on the first-line camrelizumab. Nearly half of the patients (47.7) were combined with platinum therapy, and 10 patients (5 apatinib and 5 anlotinib) had dual-target therapy (Table 1). Other clinical baseline data 1.

Efficacy

All 44 patients with lung cancer were evaluated for efficacy as of the follow-up by August 1, 2020. After camrelizumab treatment, 2 patients achieved CR, 10 patients achieved PR, 25 patients had SD, and 7 patients had PD. The ORR was 27.3% (including 1 CR and 10 PR) and the DCR was 84.1% (including 1 CR and 10 PR and 25 SD patients). A total of 23 PFS events were reported, with a PFS of 8 months (range, 2 to 11 months) (Figure 1). 4 patients died, OS was 2 months, and median OS had not been reached.

Analysis of camrelizumab treatment

In camrelizumab treatment, there were no significant differences in ORR among different lung cancer types, the different number of lines of medication, whether combined with platinum therapy, the different number of chemotherapy lines after recurrence and metastasis, and the different number of metastases (Table 2).

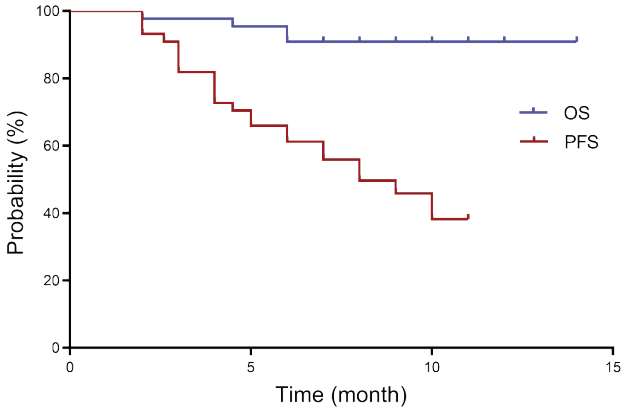

Figure 1. *Kaplan-Meier curves of PFS and OS for all patients. PFS of 8 months (2-11 months) was not reached.*

We further analyzed the difference in PFS of lung cancer patients with different number of chemotherapy lines after recurrence and metastasis and the different number of metastasis. Figure 2 shows that PFS was significantly prolonged in patients with chemotherapy lines ≤ 1 compared with patients with chemotherapy lines > 1 after recurrence and metastasis (HR = 0.403, 95% CI: 0.173 – 0.939, P < 0.05). Compared with patients with > 1 metastasis, PFS was significantly longer in patients with ≤ 1 metastasis (HR = 0.391, 95% CI: 0.165 – 0.928, P < 0.05).

In multivariate analysis, the number of metastatic sites ≤ 1 (HR = 0.202, 95% CI: 0.065-0.637, P < 0.01) remained statistically significant and was associated with PFS in patients excluding the potential mixer factor (Table 3). In the multivariate analysis, after excluding potential confounding factors, the number of metastatic sites ≤1 (HR=0.202, 95%CI: 0.065-0.637, P<0.01) remained statistically significant, which was related to longer PFS (Table 3).

Adverse Events

SForty-four patients were evaluable for safety. AEs were observed in 93.2% (41/44) of patients. The most common AEs were anemia (47.7%, 21/44), all of which were grade 1 to 2. Five patients (9.1%) experienced grade 3 AEs, including 2 cases of neutropenia, 1 case of leukopenia, and 2 cases of immune pneumonitis. One of the patients with immune pneumonitis interrupted camrelizumab treatment. Other common adverse events also included: thrombocytopenia (18.2%), hemangioma (15.9%), hypothyroidism (11.4%), and elevated transaminases (9.1%), all of which were grade 1-2 (Table 4). There were no deaths related to AEs. .

Discussion

We retrospectively analyzed the clinical data of 44 metastatic lung cancer patients treated with camrelizumab. As of follow-up through August 1, 2020, the ORR for metastatic lung cancer treated with camrelizumab was 27.3% (including 1 CR and 10 PRs). The DCR was 84.1% (including 1 CR and 10 PR and 25 SD patients). Thirty patients are still on treatment. At a follow-up of 8.2 months, a total of 23 PFS events and 3 OS events were reported, the PFS of patients was 8 months (2-11 months), and the OS has not been reached.

Compared with a previous phase 1b study (NCT03083041) [13], patients in this study achieved reduced ORR (27.3% vs 41.2%) and DCR (84.1% vs 94.1%). The reason for this may be that the patients in phase Ib study were strictly screened, the baseline data of the patients were relatively consistent, and the treatment regimen was unified (all camrelizumab combined with apatinib treatment). In our observational study, the clinical characteristics of patients were different, and the treatment regimens were complex and diverse, most obviously including the combination regimens of more than 5 chemotherapeutic drugs. However, a recent multicenter prospective cohort study [16] involving 97 cases of advanced lung cancer showed that camrelizumab or combined chemotherapy or combined anti-angiogenic drug therapy had an ORR of 21.2% and a DCR of 92.3% for advanced lung cancer. This is similar to our findings. Both of these studies were early stage data analyses and no patient PFS data are available. Before camrelizumab, pembrolizumab and atezolizumab are two more promising PD-1/PD-L1 inhibitors for the treatment of advanced lung

Table 2. *Analysis of ORR, n (%)*

Group	N	CR	PR	SD	PD	ORR (%)
Type of lung cancer						
Lung adenocarcinoma	21	0 (0.0)	4 (19.1)	15 (71.4)	2 (9.5)	19.0
Squamous cell carcinoma of lung	19	2 (10.5)	5 (26.3)	9 (47.4)	3 (15.8)	36.8
1st line or not						
Yes	16	2 (12.5)	4 (25.0)	10 (62.5)	0 (0.0)	33.3
No	28	0 (0.0)	6 (21.4)	15 (53.6)	7 (25.0)	21.4
Combination Platinum						
Yes	21	1 (4.8)	3 (14.3)	13 (61.9)	4 (19.1)	19.1
No	23	1 (4.4)	7 (30.4)	12 (52.2)	3 (13.0)	34.8
Number of chemotherapy lines after recurrence and metastasis						
≤ 1	23	2 (8.7)	5 (21.7)	14 (60.9)	2 (8.7)	30.4
> 1	21	0 (0.0)	5 (23.8)	11 (52.4)	5 (23.8)	23.8
Number transferred						
≤ 1	18	2 (11.1)	4 (22.2)	10 (55.6)	2 (11.1)	33.3
> 1	26	0 (0.0)	6 (23.1)	15 (57.7)	5 (19.2)	23.1

Table 3. *Univariate and multivariate Cox regression analysis of progression free survival (PFS) (n = 44, 23 events)*

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age (years 60 ≤ vs > 60 years)	0.938	0.665-1.326	0.392			
Gender (male vs female)	1.175	0.859-2.318	0.238			
ECOG (≤ 1 vs > 1)	0.903	0.498-1.286	0.485			
Lung adenocarcinoma (vs squamous)	1.085	0.536-1.692	0.126			
1st line of medication (yes vs no)	0.892	0.663-1.352	0.208			
In combination with platinum (yes vs no)	1.215	0.973-1.825	0.177			
Number of metastatic sites (≤ 1 vs > 1)	0.391	0.165-0.928	0.033	0.202	0.065-0.637	**0.003**
Number of chemotherapy lines after recurrence and metastasis (≤ 1 vs > 1)	0.403	0.173-0.939	0.035	0.687	0.219-1.226	0.096
Brain metastases (yes vs no)	1.272	0.802-1.336	0.195			
Lung metastases (yes vs no)	0.963	0.498 to 1.295	0.464			
Liver metastases (yes vs no)	0.873	0.593-1.874	0.193			
Bone metastasis (yes vs no)	1.203	0.786-2.034	0.085			
Metastases to lymph nodes (yes vs no)	1.122	0.932-1.709	0.265			

Important P values are shown in bold.

Table 4. *Incidence of adverse events [n (%)]*

AEs	Grading		
	Grade 1-2	Grade 3-4	Total
Hematologic Adverse Reactions			
Anemia	21 (47.7)	0 (0.0)	21 (47.7)
Neutropenia	4 (9.1)	2 (4.6)	6 (13.6)
Thrombocytopenia	8 (18.2)	0 (0.0)	8 (18.2)
Leukopenia	3 (6.8)	1 (2.3)	4 (9.1)

AEs	Grading		
Other adverse reactions			
Nausea	3 (6.8)	0 (0.0)	3 (6.8)
Hemangioma	7 (15.9)	0 (0.0)	7 (15.9)
Reactive cutaneous capillary angiomatosis	3 (6.8)	0 (0.0)	3 (6.8)
Immune pneumonitis		2 (4.6)	2 (4.6)
Asthenia	1 (2.3)	0 (0.0)	1 (2.3)
Hypothyroidism	5 (11.4)	0 (0.0)	5 (11.4)
Transaminases increased	4 (9.1)	0 (0.0)	4 (9.1)
Hand-foot syndrome	1 (2.3)	0 (0.0)	1 (2.3)
Peripheral neuritis	2 (4.6)	0 (0.0)	2 (4.6)

AEs: adverse events

cancer. Compared with the phase III clinical study by Gandhi et al. [17], the results of our study showed that camrelizumab had a PFS comparable to pembrolizumab (8 months vs 8.8 months). Compared with atezolizumab [18], camrelizumab appeared to be associated with PFS (8 months vs 6.3 months). However, considering that in this group of cohorts, the pathological types and treatment regimens of lung cancer in patients are not uniform, whether camrelizumab alone has equivalent efficacy to previous PD-1/PD-L1 inhibitors needs further clinical trial validation.

In the analysis, we found that PFS was significant in patients with chemotherapy lines ≤ 1 after recurrence and metastasis (HR = 0.403, 95% CI: 0.173 – 0.939) and in patients with metastases ≤ 1 (HR = 0.391, 95% CI: 0.165 – 0.928). In multivariate COX analysis, exclusion of potential confounding factors, and metastasis number ≤ 1 were associated with PFS, which was consistent with most study conclusions [19].

In terms of safety, the results of this study suggest that camrelizumab has a high safety profile in the treatment of metastatic lung cancer in the real world, with overall manageable toxicity. In the study. AEs were observed in 93.2% (41/44) of patients, with the most common AE being anemia (47.7%, 21/44), all of which were grade 1 – 2. This is similar to the results of a previous study [12]. Grade 3 AEs occurred in 5 patients, with an incidence of 9.1%, which seems to be lower than the incidence of camrelizumab in esophageal cancer (27.5%) and hepatocellular carcinoma (22.5%) [12]. Compared with nivolumab [20], camrelizumab also had lower grade 3 or higher AEs in lung cancer treatment (9.1% vs 45%). This indicates a significant advantage in the safety of camrelizumab in the treatment of lung cancer.

There are several limitations to this study, the most important of which is the small sample size, which makes our results likely to be quite biased. Also, the follow-up time was short, and the long-term outcome of patients could not be further analyzed. Future larger cohort studies with follow-up time are needed to further clarify the effect of camrelizumab in the treatment of lung cancer.

In summary, the current study shows that camrelizumab has definite efficacy in the treatment of metastatic lung cancer in the real world, can effectively prolong PFS in patients with metastatic lung cancer, and has high safety, which is worthy of a clinical citation for further study and evaluation of the application effect in patients with a wide range of lung cancer.

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