OncoTargets and Therapy

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ORIGINAL RESEARCH

Anlotinib Hydrochloride and PD-1 Blockade as a Salvage Second-Line Treatment in Patients with Progress of Local Advanced Non-Small Cell Lung Cancer in Half a Year After Standard Treatment

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Purpose: As for local advanced non-small cell lung cancer (NSCLC), synchronous radiotherapy and chemotherapy is the standard treatment mode. But for patients with progress in half a year, which means the second-line chemotherapy effect is not ideal for them. We observed the efficacy and safety of anlotinib hydrochloride combined with PD-1 blockade as the second-line treatment for those patients in this trial.

Patients and Methods: From January 2018 to December 2019, 57 patients with the progress of local advanced NSCLC treated with anlotinib plus PD-1 blockade until disease progression or intolerance as a result of adverse events. Patients have been assessed using computed tomography prior to treatment and during follow-up every 2 months until disease progression or death. The primary endpoint was objective response rate (ORR). The secondary endpoints included overall survival (OS), progression-free survival (PFS) and safety. Survival curves were created using the Kaplan–Meier method.

Results: 57 patients were enrolled. The median age was 64 years, and 61.4% of the patients were men. The ORR was 50.9% with a median OS time of 14 months and the 1-year OS rates and PFS rates were 81.8% and 33.3%, respectively. The patients with squamous cell carcinoma, no brain or liver metastases had longer PFS than patients with liver metastasis. When the PFS was calculated from the time of second treatment, the median PFS was 9 months. Most adverse events (AEs) were grade 1–3, one drug-related death was noted.

Conclusion: The expected outcome of this study is that anlotinib combined with PD-1 blockade has tolerable toxicity and better ORR, OS than second-line chemotherapy. The results may indicate additional treatment options for patients with progress of local advance NSCLC in half a year after standard treatment.

Keywords: anlotinib, PD-1 blockade, local advanced non-small cell lung cancer, angiogenesis, immunotherapy

Introduction

Lung cancer is the leading incident cancer and cause of cancer mortality worldwide.[1] Non-small cell lung cancer (NSCLC) accounts for approximately 80% of lung cancer cases. About 30% of lung cancer patients are locally advanced lung cancer at the initial diagnosis.[2,3] For stage I to III NSCLC treated with surgery or radiotherapy with curative intent, the current literature does not provide evidence that suggests a survival benefit from adding immunotherapy (excluding checkpoint inhibitors) to conventional curative surgery or radiotherapy, but immune checkpoints inhibitors (PD-1/PD-L1) have made significant advances in lung cancer.[4,5] For locally advanced NSCLC, synchronous radiotherapy and chemotherapy is the standard of care, but some patients will make progress in half a year after chemoradiotherapy.[6] For those patients, docetaxel, pemetrexed, and checkpoint blockade blockers are considered standard second-line therapies based on several randomised controlled trials.[7–10] As for those patients, the median PFS of second-line chemotherapy was only 3 months.

Received: 4 July 2022
Accepted: 1 October 2022
Published: 17 October 2022

Anlotinib hydrochloride is a multitarget tyrosine kinase inhibitor that targets vascular endothelial growth factor receptor, fibroblast growth factor receptor, platelet-derived growth factor receptor, c-Kit, and c-MET, which was approved as a third-line treatment for stage IV NSCLC on May 9, 2018 in China.[11,12] However, the objective response rate (ORR) was only 9.2% and the overall survival (OS) time was prolonged only 5.4 months, which was better than the results of other line treatment schemes. Immune checkpoint inhibitors (ICIs) are a novel class of drugs for the treatment of NSCLC.[13,14] ICIs activate the host's immune cells, especially T cells, to target specific tumor cells. Many Phase 3 clinical trials have confirmed anti-PD-1 treatments in advanced NSCLC patients, either as a second-line[15–17] or first-line treatment,[18] which provided improved efficacy and survival, but not increased the infection risk.[19] Compared with second-line docetaxel chemotherapy, treatment with nivolumab or pembrolizumab provided a better ORR and OS.[20–22]The combination of anlotinib hydrochloride and Immune checkpoint inhibitors is effective and well-tolerated in patients with NSCLC.[23] Therefore, we assessed the efficacy and safety of anlotinib combined with immune checkpoint inhibitors as salvage treatment in patients with progress of local advance NSCLC in half a year after standard treatment and investigated the predictors of therapeutic efficacy.

Materials and Methods

Patients and Methods

This clinical study was designed to evaluate the efficacy and safety of anlotinib and immunotherapy in patients with progress of local advanced NSCLC after standard treatment. From January 2018 to December 2019, 57 patients were included in this study in Peking University Cancer Hospital (PUCH). This study was approved by the Research Ethics Committee of PUCH complies with the Declaration of Helsinki. Patients' demographics and clinical characteristics such as age, sex, smoking history, and performance status were reviewed using a lung cancer cohort. All patients received radiological assessment of tumor response by computed tomography (CT) every 8 weeks. The response to therapy was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The confirmation of treatment results were response to immunotherapy and anlotinib. PFS was defined as the time from the start of treatment to disease progression or death. OS was defined as time from the start of treatment to death from any cause. Liver and kidney function, blood routine test, myocardial enzyme spectrum and thyroid function were reviewed before each immunotherapy. The safety of treatment was assessed using Common Terminology Criteria for Adverse Events version 4.0.

Treatment

All patients received anlotinib (one cycle of 12 mg daily for 14 days, discontinued for 7 days, and repeated every 21 days). Doses were reduced when patients experienced intolerable adverse events (AEs). Patients continued anlotinib until disease progression or intolerance as a result of AEs. Immunotherapy (tislelizumab, 200 mg/3 week; or toripalimab injection, 200 mg/3week) was administered intravenously every 3 weeks until withdrawal of consent, unacceptable toxicity, disease progression at the discretion of the physician, or for 1 year.

Statistical Analysis

Statistical analysis was processed using SPSS version 22.0. The Overall Survival curves and PFS were created using the Kaplan–Meier method using the Log rank test, and a Cox proportional hazards model was used for multivariable survival analysis. Objective response rate and disease control rate was compared using Pearson χ^2or Fisher exact test when appropriate. Statistical significance was defined as $P < 0.05$.

Results

As a result, a total of 57 patients were included in this study. Clinical characteristics of initial treatment are detailed in Table 1, indicating that 30 patients (52.6%) were initially diagnosed in stage IIIA, while the others were stage IIIB. Tislelizumab injection were used in 27 patients. No patient was lost during the follow-up. The median follow-up time was 18 months for the surviving patients and 14 months for the whole group. 40 patients died by the end of the follow-up.

The objective effective rate is shown in Table 2. There was a complete response in 17 (29.8%) patients, a partial response in 12 (21.1%) patients, making an ORR of 50.9%. Table 3 shows the case data after progression. In total, 4

Table 1 Patient Characteristics

Characters	Adenocancinoma N(%)	Squamous Cell Cancinoman(%)
Age (mean, range)	62.9±8.8	61.6±8.3
Gender, n (%)		
Male	14(35.0)	21(60.0)
Female	13(59.1)	9(40.9)
Stage, n (%)		
IIIA	8(26.7)	22(73.3)
IIIB	19(70.4)	8(29.6)
EGFR mutation (%)	3(11.1)	5(16.7)
Location (%)		
Upper lobe	9(33.3)	9(30.0)
Middle lobe	7(25.9)	12(40.0)
Lower lobe	11(40.7)	9(30.0)
History of chemotherapy		
PP	26(92.8)	0 (0.0)
TP	2(7.1)	29(100.0)
Radiotherapy, n(%)	28(100.0)	29(100.0)
ECOG score, n(%)		
0	24(88.9)	24(80.0)
1	3(11.1)	6(20.0)
PD-L1expression PD-L1(22C3)		
<50%	23(85.1)	23(76.7)
≥50%	4(14.8)	7(23.3)

Abbreviations: PP, Pemetrexed cisplatin; TP, Paclitaxel cisplatin.

Table 2 Treatment Response

Best Overall Response	N=57
CR, Complete response	29.8%
PR, Partial response	21.1%
SD, Stable disease	36.8%
PD, progressive disease	12.3%
ORR, Objective response rate	50.9%
DCR	87.7%

patients had known brain metastases, 30 patients recurred in primary tumor and nodal areas, 14 patients failed in distant areas, 13 patients failed in new nodal areas, and 4 patients failed in liver. The clinical stage of 16 patients was improved compared with the initial treatment.

For all patients, the median PFS and OS were 10 and 14 months, respectively. The survival curves were depicted in Figure 1. the 1-year OS rates was 81.8%. As shown in Figure 2, the progression-free survival rate for 1 year was 33.3% and the median time of treatment failure is 9 months.

The side effects of treatment are given in Table 4, Two patients (3.5%) were off treatment due to toxicity, one patient was grade 5. Drug-related adverse events were reported in 38 patients (66.7%). Typical toxicities included hypertension (36.8%), thyroid-stimulating hormone (26.3%), hand-foot syndrome (35.1%), fatigue (22.8%), impairment of liver function and kidney function (17.5%).

Discussion

Lung cancer, which is the most common type of cancer worldwide[24] has historically been associated with poor outcomes. At present, a large number of clinical studies have confirmed that immunotherapy alone, combined with chemotherapy in

Table 3 Stage at Recurrence

Intrathoracic Metastases Only (M1a) vs Extrathoracic Metastases (M1b)		
	LI R(M1a)	**DR(M1b)**
n	43	14
Age (mean,SD)	62.6±9.2	61.0±6.1
Gender, n (%)		
Male	25(58.1%)	9(64.3%)
Female	18(41.9%)	5(35.7%)
Stage, n (%)		
IIIA	18(41.9%)	1(7.1%)
IIIB	25(58.1%)	1(7.1%)
IV	0	12(85.8%)
Histology		
Adenocancinoma	20(46.5%)	8(57.1%)
Squamous cell cancinoma	23(53.5%)	6(42.9%)
ECOG score, n(%)		
0	20(46.5%)	5(35.7%)
1	23(53.5%)	9(64.3%)
PD-L1 expression PD-L1(22C3)		
<50%	24(55.8%)	5(35.7%)
≥50%	19(44.2%)	9(64.3%)

Abbreviations: LIR, Local or intrathoracic recurrence; DR, Distant recurrence.

the treatment of lung cancer has good effects.[25–28] However, identifying the patients in this population who are most likely to achieve long-term survival with immunotherapy is a key challenge. Associations of baseline characteristics and biomarker status with overall survival in previously treated patients who received PD-1 or PD-L1 inhibitor therapy for unresectable local advanced NSCLC have been explored previously.[25–27] The PACIFIC study have proved that durvalumab consolidation after standard therapy showed superior PFS and OS compared to the observation group in a real

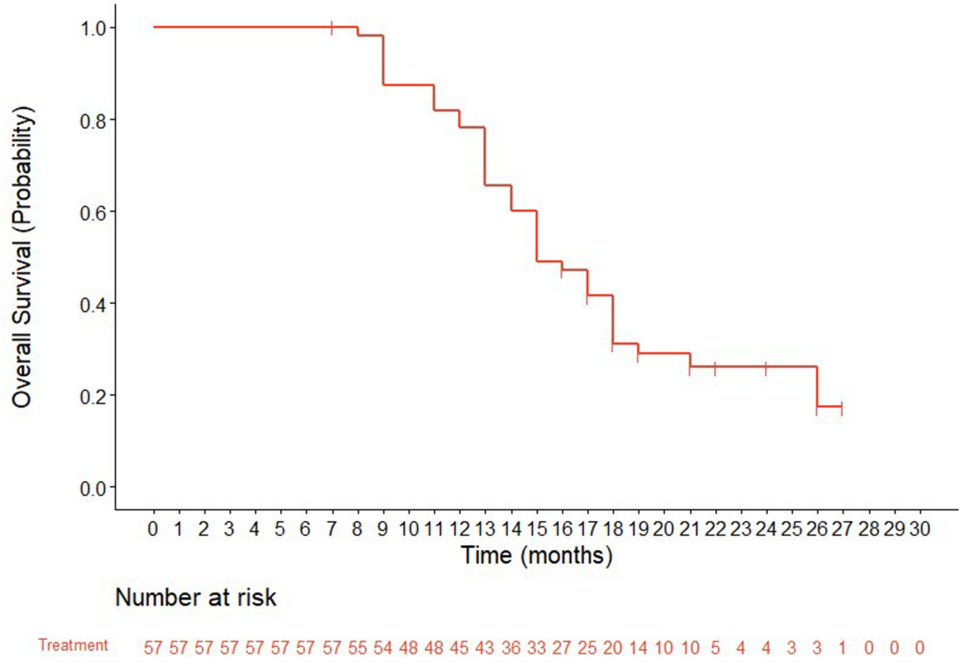

Figure 1 The overall survival rate for patients.

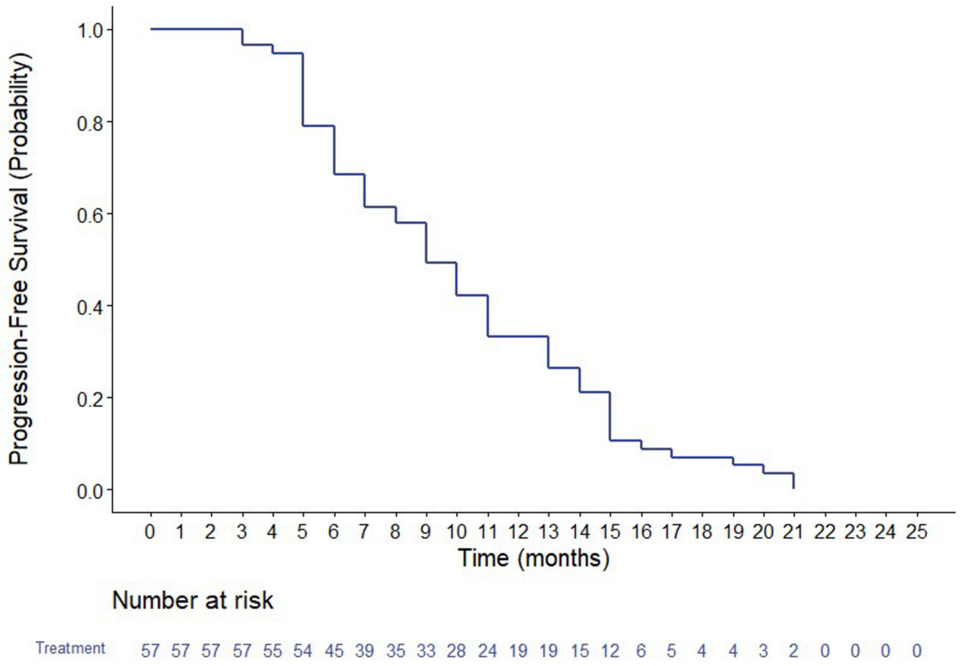

Figure 2 The progression-free survival rate for patients.

world setting and randomization clinical trial.[29] Therefore, immunotherapy as a second line therapy may be effective. It has been reported that second-line immunotherapy is effective in non-small cell lung cancer, which is better than that of second-line single drug chemotherapy and it's PFS was 12 months, which is better than single drug chemotherapy.[30–32]

Anti-angiogenic therapy combined with immunotherapy has been proved to be a good combination therapy mode. Anti-angiogenic drugs can change the immune microenvironment, which is conducive to immunotherapy. As a multi-target and small molecule anti-angiogenic drug, anlotinib has shown good efficacy in the second-line treatment of non-small cell lung cancer.[11] The research using first-line treatment of non-small cell lung cancer with anti-angiogenesis drugs show that anti-angiogenesis drugs have a good foundation in changing the immune microenvironment, which is also the theoretical basis of combined therapy. As a domestic approved small molecule multi-target tyrosine kinase inhibitor, anlotinib plays an important role in inhibiting angiogenesis and anti-tumor. Combined with immunotherapy, it can change the immune microenvironment as well as inhibiting angiogenesis in animal trial.[33]

The results showed that patients with advanced NSCLC who received anlotinib and immunotherapy as second-line had better OS, PFS, and objective response rate compared with patients who received second chemotherapy.[34,35] This therapy mode was well tolerated, and the patients maintained a reasonable quality of life. The objective response rate was significantly higher than previous report treated with second line chemotherapy.[21,36]

Table 4 Treatment-Related Adverse Events

Safety	**n=57**
Treatment-Related Adverse Events,n(%)	38(66.7)
Serious Treatment-Related Adverse Events,n(%)	6(10.5)
Therapy discontinued, n(%)	2(3.5)
Most common Treatment-Related Adverse Events,n(%)	
Hypertension	21(36.8)
Hand-foot syndrome	20(35.1)
Fatigue	13(22.8)
Thyroid Function	15(26.3)
Liver function and kidney function	10(17.5)

To our knowledge, this study is the first Phase 2 trial in the second-line treated anlotinib and immunotherapy to show an OS and PFS benefit. This study has shown that liver metastases might be negative predictors of OS in lung cancer patients. For example, we know that the median PFS and OS of second-line chemotherapy in the treatment of non-small cell lung cancer were only 5.7 and 13.6 months.[37] As for the second-line treatment, the previous study in patients with locally advanced NSCLC has evaluated the effects of immunotherapy and show that the median PFS and OS were ranged from 5 to 8.9 months and from 9.3 to 16 months in different cohorts.[30,31] For locally advanced non-small cell lung cancer that progresses within half a year after standard radiotherapy and chemotherapy, no matter second-line chemotherapy or immunotherapy, it can not obtain good clinical efficacy. As a small molecule anti-angiogenesis targeted drug, anlotinib is effective in the second-line or third-line treatment of non-small cell lung cancer.[11,38,39] In previous studies, anlotinib and immune drugs were used in the first-line treatment of non-small cell lung cancer and found to be effective,[39] but this treatment combination model is not the standard treatment model after all. In order to improve the efficacy of second-line treatment of non-small cell lung cancer, the combination of anlotinib and immune drugs was used in this study. Our results showed that the combination of anlotinib and immunotherapy had good efficacy, with median PFS and OS reaching 10 and 14 months respectively, which is significantly higher than that reported in the previous literature for second line chemotherapy.[21,34]

Regarding toxicity in study, the overall incidence of treatment-related AEs was 66.7%, The most common AEs during treatment were hypertension(36.8%),which is higher than that of previous reported.[40,41] Hypertension is a common adverse effect in patients treated with VEGF-targeted agents. The other common AEs were thyroid-stimulating hormone (26.3%), hand-foot syndrome (35.1%), Fatigue (22.8%), Liver function and kidney function (17.5%). Only one patient was found to death due to treatment. In addition, only two patients off treatment due to oral mucositis. Compared to the AEs associated with anlotinib and immunotherapy reported in previous studies,[23,42] no new AEs were observed in the present study. Our results show that anlotinib and immunotherapy is well tolerated in patients with the locally advanced NSCLC.

The limitation of this study is the retrospective analysis of small number of enrolled cases, but it is still the first one trying to evaluate the efficacy of arotinib and immunotherapy as the second-line in the treatment of lung cancer. This study has shown that anlotinib combined with PD-1 blockade has tolerable toxicity and better result than second-line chemotherapy. PFS should be chosen as the primary endpoint in the further research which helped to provide a more rigorous and comprehensive conclusion while the protocol also needs to be verified by multicenter prospective clinical studies.

Conclusion

In this study we demonstrated that anlotinib combined with PD-1 blockade as a salvage second-line treatment has good clinical efficacy and high safety than that of second-line chemotherapy in the treatment of patients with the progress of local advanced non-small cell lung cancer in half a year after standard treatment.

Ethics Approval and Informed Consent

This research was approved by the ethics committee of the Ethics Committee of Peking University Cancer Hospital and Institute. All participants are informed consent to the study.

Consent for Publication

All authors confirm that the details of any images, videos, recordings, etc can be published, and that the person(s) providing consent have been shown the article contents to be published.

Acknowledgments

We are thankful to the investigators and patients enrolled in this clinical trial.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the National Natural Science Foundation of China (No. 81672969, 81472814), a grant from the Health scientific and technological achievements and appropriate technology promotion project of Beijing Municipal Health Commission.

Disclosure

The authors report no conflicts of interest in this work.

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