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ORIGINAL RESEARCH

Feasibility and Safety of Anlotinib Plus Docetaxel versus Docetaxel Monotherapy in Patients with Previously Immunotherapy-Treated NSCLC: A Retrospective Exploratory Study

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Objective: This study aims to evaluate the efficacy and safety of anlotinib plus docetaxel in patients with advanced non-small cell lung cancer (NSCLC) who have previously treated with immunotherapy.

Methods: This retrospective analysis was conducted on 86 previously immunotherapy-treated patients with advanced NSCLC from December 2018 to October 2024 in clinical practice. Those who received anlotinib plus docetaxel were assigned to experimental group (EG, N=43), while those who were treated with docetaxel monotherapy were deemed as control group (CG, N=43) in clinical practice. Efficacy and safety of both regimens were compared with regular follow-up for survival data collection. The primary endpoints included overall survival (OS) and secondary endpoints were progression-free survival (PFS), objective response rate (ORR) and disease control rate (DCR).

Results: ORR in the experimental and control groups was 30.2% (95% CI: 17.2–46.1%) and 13.9% (95% CI: 5.3–27.9%), respectively, showing a trend towards significance (P=0.069). DCR was significantly higher in the EG at 79.1% (95% CI: 63.9–89.9%) compared to 51.2% (95% CI: 35.5–66.7%) in the CG (P=0.007). After a median follow-up of 12.8 and 8.5 months, respectively, the median PFS was 6.5 months (95% CI: 4.08–8.92) in the EG, compared to 2.9 months (95% CI: 2.53–3.27) in the CG (P=0.019). The median OS was 13.5 months (95% CI: 10.49–16.51) in the EG, compared to 9.2 months (95% CI: 5.73–12.67) in the CG (P=0.007). Adverse events of all grades occurred in 93.0% of patients in the EG and 83.7% in the CG. Grade 3 or above adverse events were detected in 51.2% and 44.2%, respectively, with similar safety profiles between the groups.

Conclusion: Anlotinib plus docetaxel demonstrated preliminary efficacy and a tolerable safety profile in patients with previously immunotherapy-treated advanced NSCLC, providing a potential therapeutic option in the post-immunotherapy setting. The conclusion should be confirmed in prospective clinical trials subsequently.

Keywords: NSCLC, previously immunotherapy-treated, anlotinib, docetaxel, efficacy, safety

Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide with over 2.48 million new cases and approximately 1.82 million deaths each year.[1] Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases and majority of NSCLC patients present with advanced disease at diagnosis, which significantly limits treatment options and reduces survival rates.[2] In the past decade, the advent of immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 axis has revolutionized first-line therapy, achieving durable responses in 20–30% of

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patients. Currently, over 8 PD-1/PD-L1 blockades have been approved for the first-line treatment of advanced NSCLC in China. However, only approximately 20–30% of patients with NSCLC have durable benefit from ICIs,[3] creating a critical therapeutic void in the post-ICI setting. The mechanisms behind immunotherapy resistance are complex, involving tumor microenvironment alterations, upregulation of alternative immune checkpoints and immune evasion strategies, which remain a significant challenge in the clinical management of advanced NSCLC.[4]

Among patients with advanced NSCLC, approximately 15–50% in East Asian populations and 40–55% in Western populations are negative for actionable driver gene mutations. Thus, this subgroup represents a significant portion of clinical practice, and the post-immunotherapy landscape is particularly bleak. Docetaxel monotherapy has long been established as the standard second-line treatment for advanced NSCLC patients without actionable driver gene mutations.[5] This standard is largely based on previous treatment paradigms where patients receive only platinum-based chemotherapy instead of immunotherapy in the first-line setting, followed by docetaxel upon progression. However, the landscape of NSCLC treatment has evolved significantly in recent years. With the increasing use of ICIs combined with chemotherapy in the first-line treatment of advanced NSCLC, the patient population that progresses after receiving immunotherapy has shifted. These patients now represent a new cohort with distinct treatment needs, and docetaxel's efficacy as a second-line option has become increasingly questioned.[6] Therefore, the management of immune-refractory NSCLC remains a formidable challenge, with limited evidence guiding post-ICI therapeutic decisions. Despite the widespread adoption of PD-1/PD-L1 inhibitors in frontline settings, fewer than 20% of patients derive durable benefit, and retreatment with ICIs yields dismal outcomes [objective response rate (ORR): 4–7%, median overall survival (OS): 6–8 months].[7] A 2023 pooled analysis of 12 studies progressing on prior immunotherapy revealed that ramucirumab plus docetaxel achieved an ORR around 20%, a median progression-free survival (PFS) of only 3.8 months and a median OS of 13.5 months, underscoring the inadequacy of current standards.[8] Consequently, no high-level medical evidence exists for post-ICI therapy in driver gene-negative NSCLC, leaving clinicians to rely on individualized approaches with suboptimal outcome.

As a result, there is a critical need to explore new therapeutic strategies for this cohort, especially those who have failed first-line treatment with ICIs or other systemic therapies. Multi-targeted tyrosine kinase inhibitors (TKIs) such as anlotinib have emerged as a promising addition to the armamentarium for advanced NSCLC. Anlotinib is a small-molecule, multi-targeted TKI that inhibits angiogenesis through targeting vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR), and c-KIT.[9] The ALTER0303 trial demonstrated that anlotinib significantly improved PFS and OS compared to placebo in patients with advanced or refractory NSCLC, highlighting its potential as an effective treatment for this patient population.[10] The combination of anlotinib with other therapeutic agents, such as chemotherapy, had shown promising synergistic effects. Several studies demonstrated that anlotinib might enhance the efficacy of chemotherapy by inhibiting tumor angiogenesis, thereby improving the delivery and effectiveness of chemotherapeutic agents within the tumor microenvironment.[11] Additionally, anlotinib might also alter the tumor microenvironment in ways that enhanced immune responses, offering potential benefits for patients who undergone prior immunotherapy treatment. This made anlotinib a particularly intriguing option in the context of patients who had previously been treated with immunotherapy.

While the efficacy of anlotinib combined with docetaxel was explored in previous studies, the results in the specific subgroup of immunotherapy-treated advanced NSCLC patients remained sparse. Previous trials demonstrated that combining anlotinib with chemotherapy agents like paclitaxel offered enhanced treatment efficacy, but the evidence for its benefit in an immunotherapy-treated cohort was still limited.[12] Despite these advances, no prospective data existed on anlotinib-chemotherapy combinations after ICI progression. Current evidence was limited to subgroup analysis in small sample size study. For instance, a multicenter analysis by Pu et al investigated anlotinib plus docetaxel in patients with NSCLC who failed first-line treatment. Of the 15 patients who underwent immunotherapy previously, anlotinib plus docetaxel yielded a median PFS of 7.8 months and a median OS of 16.2 months.[13] The preliminary results suggested that anlotinib combined with docetaxel might provide significant survival benefits for previously immunotherapy-treated advanced NSCLC.

Therefore, this study aimed to evaluate the efficacy and safety of combining anlotinib with docetaxel in patients with previously immunotherapy-treated advanced NSCLC.

Materials and Methods

Study Design and Eligibility Criteria

This study was designed as a retrospective analysis, screened patients diagnosed with advanced NSCLC from December 2018 to October 2024 at the First Affiliated Hospital of Heilongjiang University of Chinese Medicine consecutively. The main inclusion criteria were: (1) histologically or pathologically confirmed diagnosis of NSCLC; (2) stage of IIIb or IV disease based on the TNM staging system; (3) Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 score; (4) failure of previous treatment with immunotherapy (disease progression or intolerance to immunotherapy-related systemic treatment), previous treatment defined as first-line or subsequent therapy with ICIs; (5) after failure of previous immunotherapy therapy, patients received anlotinib combined with docetaxel or docetaxel monotherapy as subsequent treatment in clinical practice; (6) availability of complete demographic and clinical baseline data. Exclusion criteria included: (1) presence of multiple tumors or other serious concurrent diseases that might compromise survival of the patients; (2) patients received additional systemic antitumor treatments (including other targeted therapies or immunotherapy) besides the assigned treatment of anlotinib plus docetaxel or docetaxel alone; (3) patients with positive EGFR mutation or ALK rearrangement; (4) substantial unavailability of baseline and follow-up data. Patients in the experimental group (anlotinib plus docetaxel) were screened between December 2018 and October 2024. The control group (docetaxel monotherapy) was selected based on the included experimental group patients. Once a similar or equal number of control group patients was reached, no additional screening for control group patients was conducted. The flowchart of this study was illustrated in Figure 1. Ultimately, a total of 86 patients with previously immunotherapy-treated advanced NSCLC were enrolled.

This study primarily investigated the efficacy and safety of anlotinib plus docetaxel compared to docetaxel monotherapy in patients with previously immunotherapy-treated advanced NSCLC. The primary endpoint was OS, other endpoints included ORR, disease control rate (DCR), PFS and safety profile. The study was approved by the ethics committee of the First Affiliated Hospital of Heilongjiang University of Chinese Medicine. Informed consent was waived due to retrospective design. The entire study process was performed according to the recommendations of the Declaration of Helsinki.

Therapeutic Regimens

Patients were divided into two groups according to the therapeutic regimens they received in clinical practice: the experimental group (EG) received a combination of anlotinib and docetaxel (n=43), and the control group (CG) received docetaxel monotherapy (n=43). EG: The treatment regimen consisted of anlotinib (8–12 mg) and docetaxel (75 mg/m² intravenously on day 1 of each 21-day cycle). Anlotinib was administered orally, either before or after meals for 14 days, followed by a 7-day rest period. Docetaxel (75 mg/m^2) was administered via intravenous infusion on day 1, every 21-day cycle. Treatment continued until disease progression or intolerable toxicity occurred. In cases where patients could not tolerate both drugs, monotherapy with either anlotinib or docetaxel was permitted. CG: Patients in the control group received docetaxel monotherapy, with the same dosage and schedule as described in the EG.

Efficacy and Safety Profile Assessment

Efficacy was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria.[14] Tumor response was evaluated by radiological imaging (CT or MRI) every two treatment cycles, or as clinically indicated after patients treated with anlotinib plus docetaxel or docetaxel therapy. The efficacy endpoints included: ORR: Defined as the proportion of patients achieving a complete response (CR) or partial response (PR). DCR: Defined as the proportion of patients achieving CR, PR, or stable disease (SD) at the time of evaluation. PFS: Defined as the time from the treatment until disease progression or death from any cause, whichever occurred first. OS: Defined as the time from the treatment to death from any cause.[15]

Safety profile was assessed by collecting adverse reactions throughout the treatment period. Adverse reactions were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The incidence and severity of adverse reactions were recorded, and the grade of each adverse reactions was determined by the investigator.

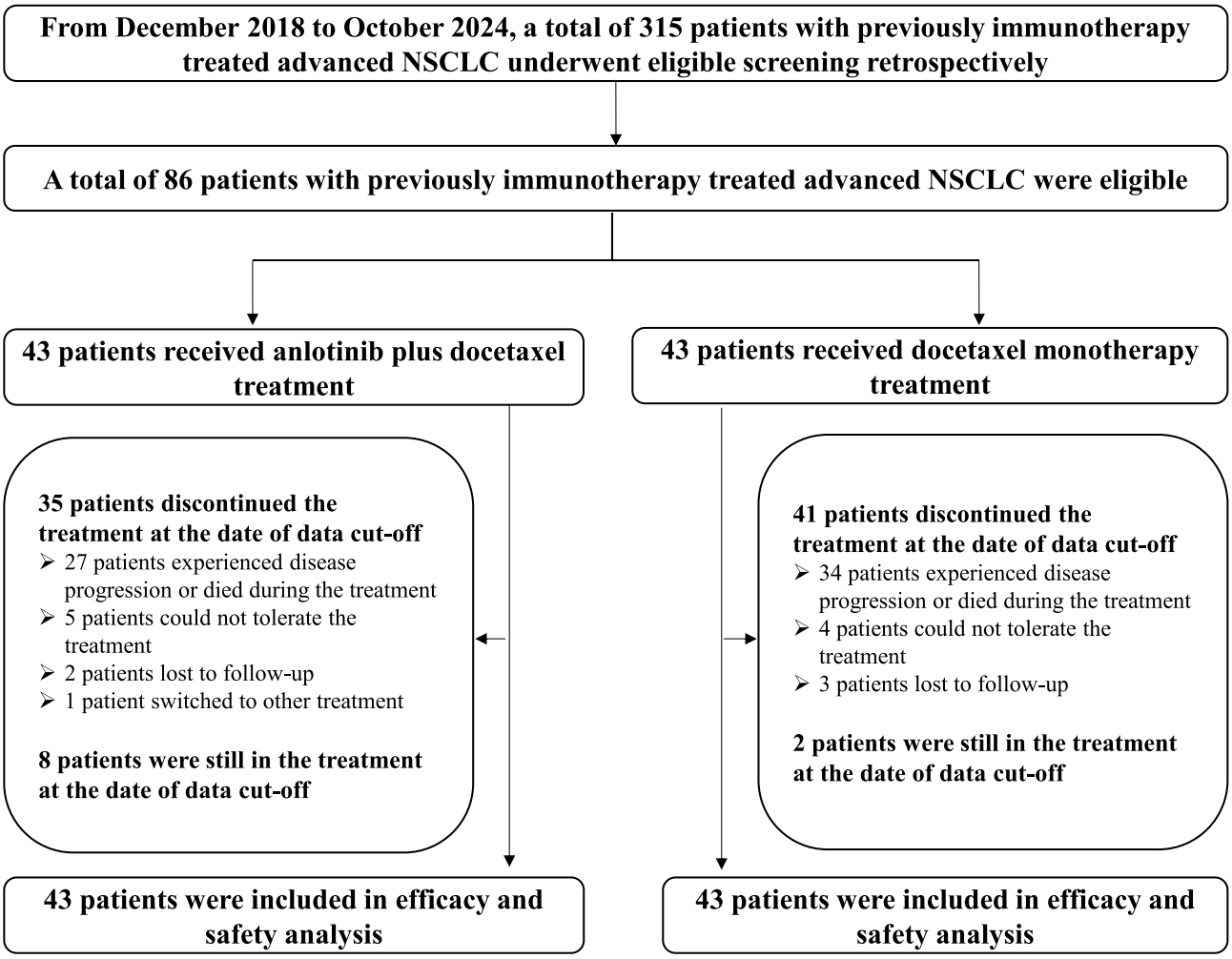

Figure 1 Flowchart of this retrospective study (NSCLC: non-small cell lung cancer).

Safety profile of each patient who was treated with anlotinib plus docetaxel or docetaxel monotherapy was documented and the maximum toxicity of the patients was recorded as detailed as possible to present the safety profile of the assigned regimens. The main safety endpoints included: Incidence of adverse reactions: Proportion of patients who experienced any grade of adverse reactions. Grade ≥3 adverse reactions: Proportion of patients who experienced grade 3 or higher adverse reactions.

Data Collection and Follow-up Protocol

Baseline characteristics and treatment information were collected and recorded from the departmental medical records and the hospital's electronic medical record system. Since OS was the primary endpoint of this study, patients were followed up periodically after disease progression of anlotinib plus docetaxel or docetaxel treatment. Follow-up visits were conducted monthly via telephone or in-person visits to monitor disease progression, adverse events and survival status. The data cut-off data of this study were January 10, 2025.

Statistical Analysis

Statistical analysis was performed using SPSS software version 25.0 (IBM, Armonk, NY, USA). Continuous variables were expressed as median values with ranges, and categorical variables were presented as frequencies and percentages. The Kaplan–Meier method was used to estimate survival outcomes, including PFS and OS, which was defined as the previous study.[16] Differences in survival between the two groups were assessed using the Log rank test. The comparison

of ORR and DCR between the two groups was analyzed using the chi-square test. Descriptive statistics were used to summarize safety profile. To adjust for potential confounders, we estimated hazard ratios (HRs) using Cox proportional hazards models and performed stepwise multivariable Cox regression analysis with predefined baseline characteristics to assess the effect of treatment after adjusting for significant prognostic factors. Statistical significance was defined as $P<0.05$ based on individual hypothesis tests without adjustment for multiple comparisons.

Results

Baseline Characteristics

A total of 86 patients with previously immunotherapy-treated advanced NSCLC were included in this study. Forty-three patients were assigned to the EG (anlotinib combined with docetaxel), and 43 patients were assigned to the CG (docetaxel monotherapy). The baseline characteristics of the patients in both groups were shown in Table 1. The two groups were well balanced in terms of age, gender, ECOG performance status, pathological staging, smoking status, histological subtype, number of metastatic lesions, lines of previous treatment, previous immunotherapy regimen and failure type of previous immunotherapy. Majority of patients in both groups had stage IV disease (88.4% in the EG and 93.0% in the CG). All the patients in EG and CG were treated with ICI-based regimen

Table 1 Comparison of the Baseline Characteristics Between Experimental Group and Control Group

Baseline Characteristics	Experimental Group (N=43)	Control Group (N=43)	χ^2	*P*
Age (year)				
Median (range)	59 (41–77)	58 (43–74)	NA	0.516
Gender				
Male	32 (74.4)	31 (72.1)	0.059	0.808
Female	11 (25.6)	12 (27.9)		
ECOG performance status				
0–1	28 (65.1)	26 (60.5)	0.199	0.655
2	15 (34.9)	17 (39.5)		
Pathological staging				
IIIb	5 (11.6)	3 (7.0)	0.551	0.458
IV	38 (88.4)	40 (93.0)		
Smoking status				
Non-smoker	14 (32.6)	11 (25.6)	0.508	0.476
Former smoker	29 (67.4)	32 (74.4)		
Histological subtype				
Adenocarcinoma	28 (65.1)	26 (60.5)	0.199	0.655
Squamous cell carcinoma	15 (34.9)	17 (39.5)		
Number of metastatic lesions				
≤3	33 (76.7)	35 (81.4)	0.281	0.596
>3	10 (23.3)	8 (18.6)		
Lines of previous treatment				
First-line	31 (72.1)	32 (74.4)	0.059	0.808
Second-line	12 (27.9)	11 (25.6)		
Previous immunotherapy regimen				
ICI monotherapy	6 (14.0)	5 (11.6)	0.104	0.747
ICI combination	37 (86.0)	38 (88.4)		
Failure type of previous immunotherapy				
Intolerance	5 (11.6)	4 (9.3)	0.124	0.725
Progression	38 (88.4)	39 (90.7)		

previously. No significant differences between the two groups in any baseline characteristics were observed (P>0.05).

Comparison of Efficacy Between the EG and CG

In the EG, 43 patients with previously immunotherapy-treated advanced NSCLC received the treatment of anlotinib plus docetaxel. The efficacy evaluation results showed that no patient achieved CR, 13 patients had PR, 21 patients had SD, 5 patients experienced progression disease (PD), and 4 patients were not available for the efficacy (unevaluable radiological scans 2 patients, lost to follow-up 1 patient, early death 1 patient). In the CG, 43 patients received docetaxel monotherapy, and the efficacy evaluation results showed no patients with CR, 6 patients with PR, 16 patients with SD, 16 patients with PD and 5 patients were not available for the efficacy (early death 2 patients, lost to follow-up 2 patients, unevaluable radiological scans 1 patient), and waterfall plot of the response in the EG and CG was shown in Figure 2. Obviously, patients received anlotinib plus docetaxel experienced a remarkable reduction of target lesion than those who received docetaxel monotherapy (mean: −14.75% vs 7.98%). Additionally, as shown in Figure 3, the ORR in the EG and CG was 30.2% (95% CI: 17.2–46.1%) and 13.9% (95% CI: 5.3–27.9%), respectively. While this difference did not reach statistical significance, it suggested a trend towards significance (P=0.069). The DCR was 79.1% (95% CI: 63.9–89.9%) in the EG and 51.2% (95% CI: 35.5–66.7%) in the CG, with a statistically significant difference (P=0.007).

Comparison of PFS and OS Between the EG and CG

The cut-off date for this study was January 10, 2025. The median follow-up duration in the EG and CG were 12.8 months (range: 0.5–33.5 months) and 8.5 months (range: 0.3–30.8 months), respectively. The PFS curves for both groups were shown in Figure 4. The median PFS for patients in the EG receiving anlotinib plus docetaxel was 6.5 months (95% CI: 4.08–8.92), compared to 2.9 months (95% CI: 2.53–3.27) in the CG receiving docetaxel monotherapy. And the 12-month PFS rate was 26.5% (95% CI: 14.21–40.42%) and 14.3% (95% CI: 5.51–27.01%), which showed a statistically significant difference [χ^2=5.53, HR=0.59 (95% CI: 0.36–0.95), P=0.019].

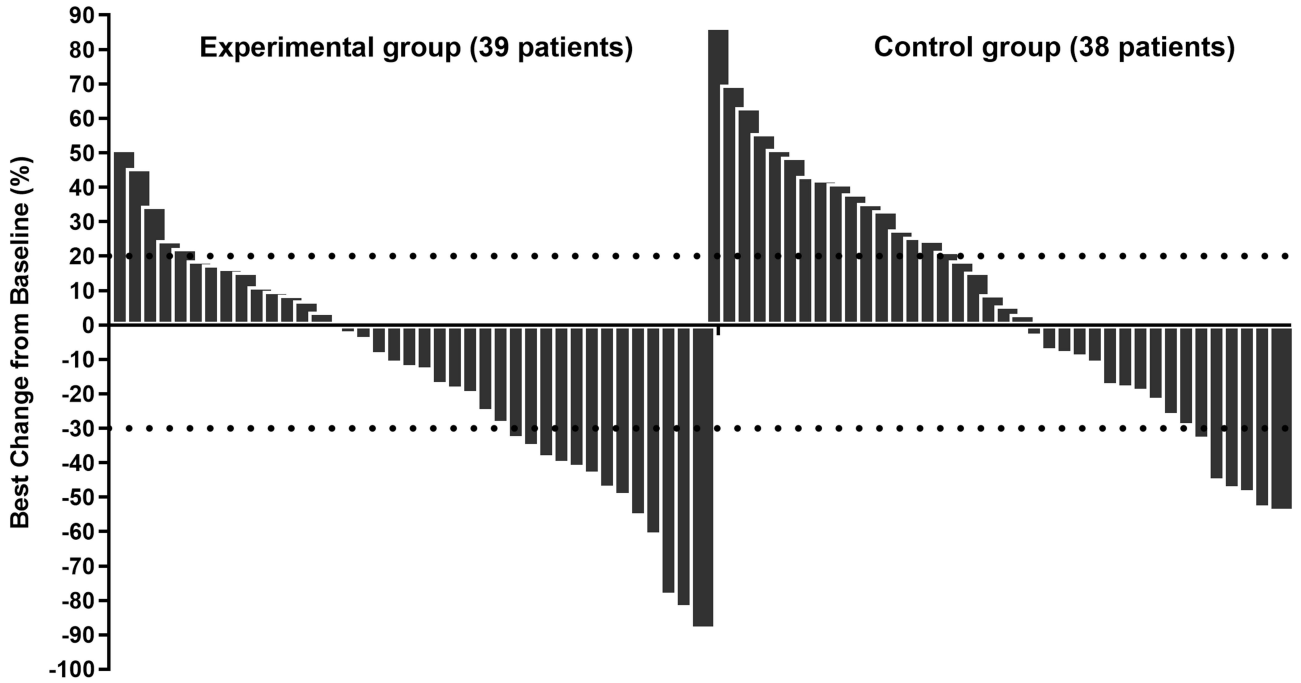

Figure 2 Waterfall plots of the best changes in target lesions of patients with previously immunotherapy-treated advanced non-small cell lung cancer (NSCLC) in experimental group (EG) and control group (CG).

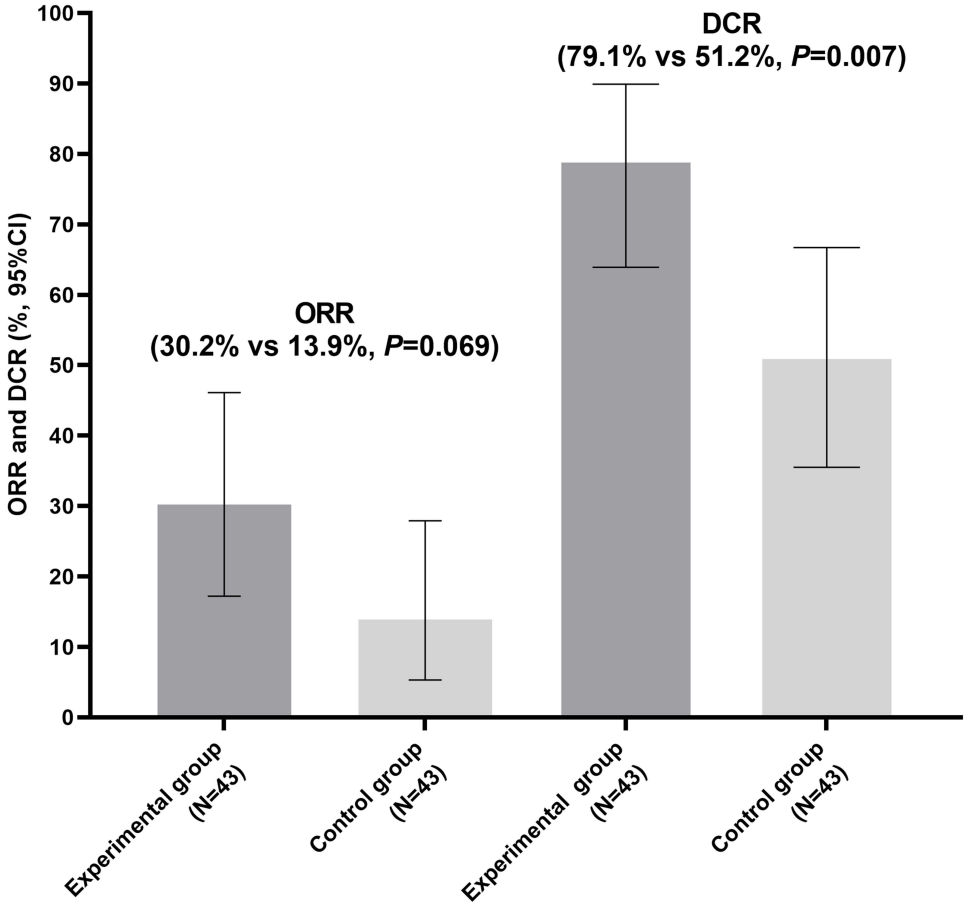

Figure 3 Comparison of objective response rate (ORR) and disease control rate (DCR) between experimental group (EG) and control group (CG).

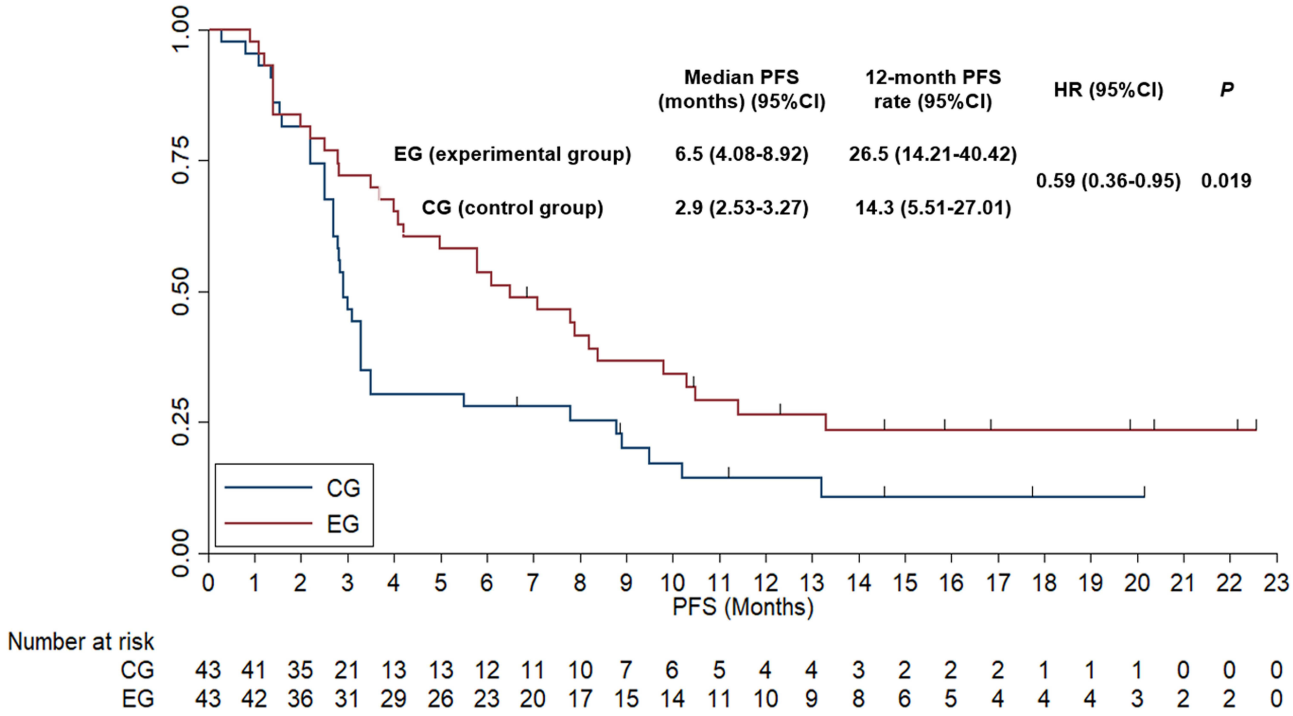

Figure 4 Comparison of progression free survival (PFS) between experimental group (EG) and control group (CG).

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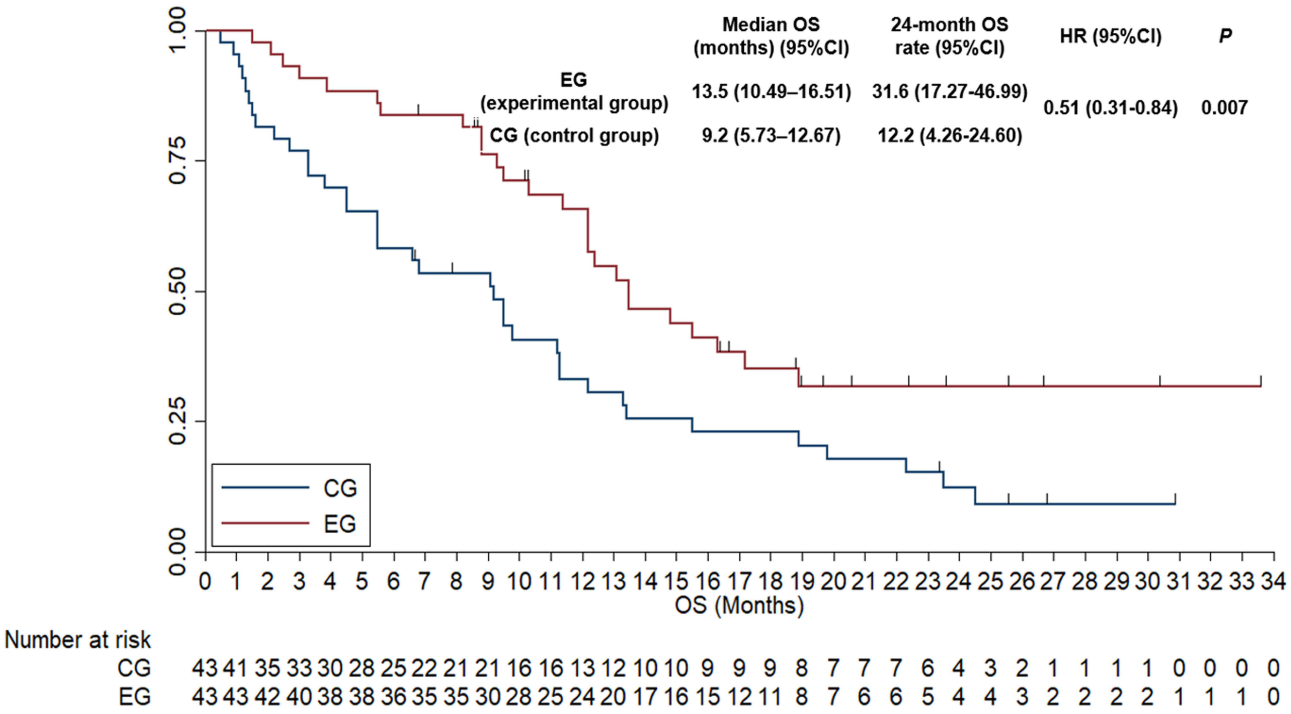

Figure 5 Comparison of overall survival (OS) between experimental group (EG) and control group (CG).

After an adequate follow-up period, 26 (60.5%) and 37 (86.0%) of death events were observed in EG and CG, respectively, providing sufficient data maturity to explore OS trends. The OS curves were illustrated in Figure 5. The median OS for patients in the EG was 13.5 months (95% CI: 10.49–16.51), compared to 9.2 months (95% CI: 5.73–12.67) in the CG, and the 24-month OS rate was 31.6% (95% CI: 17.27–46.99%) and 12.2% (95% CI: 4.26–24.60%), respectively, which also showed a statistically significant difference [χ^2 = 7.37, HR=0.51 (95% CI: 0.31–0.84), *P*=0.007].

Comparison of Safety Profile Between the EG and CG

Safety profile data during the treatment process were retrospectively collected for both the EG and CG, which were summarized in Table 2. In the EG, a total of 40 patients experienced adverse reactions of various grades with an

Table 2 Safety Profile Among Patients with Advanced NSCLC Between Experimental Group and Control Group During Treatment

Safety Profile	Experimental Group (N=43)		Control Group (N=43)	
	All Grade (N, %)	Grade ≥3 (N, %)	All Grade (N, %)	Grade ≥3 (N, %)
Any grade	40 (93.0)	22 (51.2)	36 (83.7)	19 (44.2)
Fatigue	18 (41.9)	8 (18.6)	13 (30.2)	5 (11.6)
Hematological toxicity	17 (39.5)	11 (25.6)	14 (32.6)	10 (23.3)
Gastrointestinal reactions	13 (30.2)	2 (4.7)	11 (25.6)	2 (4.7)
Hypertension	17 (39.5)	9 (20.9)	2 (4.7)	0 (0.0)
Hair loss	14 (32.6)	3 (7.0)	11 (25.6)	3 (7.0)
Abnormal liver function	15 (34.9)	4 (9.3)	10 (23.3)	3 (7.0)
Hand-foot syndrome	11 (25.6)	2 (4.7)	0 (0.0)	0 (0.0)
Oral mucositis	8 (18.6)	0 (0.0)	7 (16.3)	1 (2.3)
Hemoptysis	5 (11.6)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	4 (9.3)	0 (0.0)	5 (11.6)	0 (0.0)

incidence rate of 93.0%, and the incidence of grade ≥3 adverse reactions was 51.2%. In the CG, a total of 36 patients experienced adverse reactions with an incidence rate of 83.7%, and the rate of grade ≥3 adverse reactions was 44.2%. The most common adverse reactions in the EG were fatigue (41.9%), hematological toxicity (39.5%), gastrointestinal reactions (30.2%), hypertension (39.5%), hair loss (32.6%), and abnormal liver function (34.9%). In the CG, the most common adverse events were hematologic toxicity (32.6%), fatigue (30.2%), gastrointestinal reactions (25.6%), hair loss (25.6%) and abnormal liver function (23.3%). Both treatment regimens had a manageable safety profile, and no new or unexpected toxicities were detected.

Discussion

Advanced non-small cell lung cancer (NSCLC) remains one of the most difficult cancers to treat with a significant unmet need for efficacious therapeutic strategies.[17] Over the past decade, ICIs targeting PD-1/PD-L1 have revolutionized the treatment landscape for advanced NSCLC. These therapies have significantly improved outcomes for patients, particularly those with high PD-L1 expression.[18] However, despite these promising advancements, immunotherapy failure remains one of the most critical challenges in the management of advanced NSCLC currently.

Our study focused on a cohort of patients who had previously received immunotherapy and failed to respond. This study demonstrated that anlotinib plus docetaxel significantly improved clinical outcomes in patients with previously immunotherapy-treated advanced NSCLC compared to docetaxel monotherapy. The combination therapy achieved a longer median PFS of 6.5 months (vs 2.9 months with docetaxel alone, HR=0.59) and a superior median OS of 13.5 months (vs 9.2 months, HR=0.51), alongside a higher DCR (79.1% vs 51.2%, P=0.007). These results were particularly noteworthy given the historically worse outcomes in this population, where second-line therapies often yielded a median OS of less than 10 months,[19] providing a promising option for patients who failed immunotherapy previously.

The median age of the 86 enrolled patients in our study was 59 years. Majority of the patients had previously experienced progression after first-line treatment (72.1%). Given that docetaxel was the standard second line regimen and anlotinib was the standard third-line regimen in China, the therapeutic regimens in EG and CG of our study were ethical and reasonable.[20] Baseline characteristics of the patients in our study were similar with those of patients included in the prospective clinical research conducted by professor Wu Lin's et al.[13] However, it should be noted that in our study all the patients were previously received immunotherapy, whereas only 38% of the patients in professor Wu Lin's study had received prior immunotherapy. This discrepancy might be that their study began enrolling patients in 2018, while most of the patients in our study were enrolled after 2019. With the gradual inclusion of immunotherapy in China's National Medical Insurance after their approval in 2018, clinical application of immunotherapy became more widespread since 2019, which also reflected the shift in clinical treatment landscape of advanced NSCLC.[21]

The combination treatment in this study achieved a DCR of 79.1%, which was significantly higher than the 51.2% observed in the docetaxel monotherapy group. Moreover, the ORR was 30.2% in EG, approximately doubled that of CG (13.9%). Although the ORR was not significantly different, the higher DCR in EG was clinically meaningful, suggesting that anlotinib plus docetaxel provided a more robust and sustained response in terms of disease control. Additionally, docetaxel monotherapy achieved an ORR of 13.9% and a DCR of 51.2%, which was similar with the previous CheckMate-017 and CheckMate-057 (around 12%) trial,[22] demonstrating that the efficacy of docetaxel monotherapy as a second-line treatment for advanced NSCLC remained modest and stable in recent years and failed to exhibit significant improvement amidst changes in the treatment landscape. It also reflected that monotherapy chemotherapy currently failed to meet the clinical treatment needs currently.[23]

The most important finding of this study was that with the addition of anlotinib, the ORR in the EG increased by 16.3%, the median PFS was extended by 3.6 months, and the median OS was extended by 4.3 months. Furthermore, a significant statistical difference was observed in OS, which differed from previous studies by Professor Wu Lin et al.[13] This discrepancy might be that in Professor Wu Lin's study, more than 50% of patients in the docetaxel monotherapy group received subsequent treatment, whereas in our study, 30–40% of patients in the EG and CG received subsequent treatments, which might contribute to the extension of PFS with the combination of anlotinib and docetaxel translating into OS benefit. Additionally, it was important to note that while our study exclusively included patients previously treated with immunotherapy (100%), Wu Lin's study contained a mixed population with only 37.5% of patients having

prior immunotherapy exposure in anlotinib plus docetaxel group. Interestingly, when evaluating the immunotherapy-experienced subgroup in Wu Lin's study, the efficacy of anlotinib plus docetaxel remained consistent with our findings (ORR=33.3%, median PFS=4.4 months, median OS=12.0 months). This suggested that the combination regimen demonstrated effectiveness in the post-immunotherapy setting. However, differences in patient demographics and prior treatment exposures should still be considered when interpreting cross-study efficacy comparisons, as they might introduce potential bias. The observed PFS and OS benefits aligned with the growing body of evidence supporting the synergistic effects of anti-angiogenic agents and chemotherapy in NSCLC. Noteworthily, while the HR for OS (HR=0.51, 95% CI: 0.31–0.84) and PFS (HR=0.59, 95% CI: 0.36–0.95) demonstrated statistical significance, the relatively wide confidence intervals suggested variability due to the small sample size. Although our study was not powered for definitive OS conclusions, the observed survival trends aligned with findings in similar patient populations. The REVEL trial previously demonstrated that ramucirumab combined with docetaxel achieved an ORR of 23%, median PFS of 4.5 months, and median OS of 10.5 months in advanced NSCLC patients who progressed following platinum-based chemotherapy. In comparison, anlotinib combined with docetaxel in our study showed a relatively higher ORR of 30.2%, longer median PFS of 6.5 months, and an extended median OS of 13.5 months. Although these outcomes indicated potential clinical advantages of the anlotinib-docetaxel combination, direct cross-study comparisons must be interpreted cautiously, given the inherent differences between patient populations (post-chemotherapy versus post-immunotherapy) and methodological differences (prospective randomized versus retrospective analyses). Nonetheless, these preliminary results supported further investigation of anlotinib plus docetaxel as a promising treatment regimen versus ramucirumab plus docetaxel in post-immunotherapy settings through prospective randomized trials subsequently.[24] However, it should be noted that our study extended these findings to the immunotherapy treated setting, where the addition of anlotinib not only prolonged survival but also enhanced ORR and DCR. This suggested that anlotinib might address key resistance mechanisms in immunotherapy-exhausted tumors, which was consistent with another exploratory study initiated by Brueckl et al.[25] They also retrospectively enrolled 67 patients with previously ICI treated advanced NSCLC who received at least one cycle of third-line ramucirumab plus docetaxel and found that the this combination yielded an ORR of 36%, a median PFS of 6.8 months and a median OS of 11.0 months. It seemed that anti-angiogenic drugs combined with chemotherapy might be more efficacious among previously ICI treated subjects. A similar observation had also previously been demonstrated in a small retrospective analysis by Harada et al.[26] This work reported an ORR of 38.9%, a median PFS of 5.7 months with a sequence of ICI followed by ramucirumab plus docetaxel in contrast to ORR of 19.0% and median PFS of 2.3 months with ramucirumab plus docetaxel in previous ICI-treated patients. However, it seemed that combination of canakinumab (an interleukin-1 beta inhibitor) to docetaxel failed to provide additional benefit for patients with previously immunotherapy-treated advanced NSCLC in a Phase III clinical trial.[27] Collectively, these findings highlighted that anti-angiogenic drugs (anlotinib) might enhance the enduring effects of immunotherapy, a direction necessitating further validation for conclusive results through larger, prospective studies.

Recently, several mechanisms have been identified as contributing to ICI resistance in NSCLC, including the tumor microenvironment (TME) and the expression of alternative immune checkpoints such as TIM-3, LAG-3, and CTLA-4.[28] Additionally, the immunosuppressive nature of the TME, including recruitment of regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs), might contribute to immune evasion.[29] The underlying mechanism behind the success of anlotinib in combination with chemotherapy lies in its ability to target multiple pro-tumor pathways, including angiogenesis, VEGFR, FGFR, PDGFR and c-KIT, which reduces hypoxia and improves drug delivery. This is critical in immune-refractory tumors, where aberrant angiogenesis often contributes to treatment resistance. By inhibiting these pathways, anlotinib not only suppresses tumor progression but also enhances the efficacy of chemotherapy agents like docetaxel.[30] Additionally, the latest research indicates that anlotinib also regulates tumor microenvironment reprogramming.[31] Recent findings demonstrate that anlotinib not only improves vascular matrix reprogramming but also alleviates extracellular matrix stiffening, thus enhancing drug delivery and distribution through a non-vascular pathway.[32] This directly promotes the distribution of docetaxel in tumors, thereby exerting a synergistic effect when combined with docetaxel. These mechanisms collectively address the dual challenges of immune exhaustion and chemoresistance, providing a rationale for the observed clinical benefits.[33] Therefore, the combination of anlotinib and docetaxel demonstrates significant therapeutic implications as second-line treatment or more for previously

immunotherapy-treated advanced NSCLC in clinical practice, and the conclusion of this study is still needed to be further confirmed by a large sample size, prospective clinical trial subsequently.

Safety profile indicated that the incidence of adverse reactions in EG was 93.0% with 51.2% of patients experiencing grade ≥3 adverse reactions. In CG, the incidence of adverse reactions was 83.7%, and the incidence of grade ≥3 adverse reactions was 44.2%. These findings were generally consistent with previous research by professor Wu Lin et al.[13] However, the incidence of grade ≥3 adverse reactions in our study seemed to be higher (51.2%) than that observed in professor Wu Lin's study (30.0%). This discrepancy might be the fact that considerable patients (27.9%) in our study had previously received second-line treatment, whereas all patients in Professor Wu Lin's study had only received first-line treatment, which might contribute to the higher incidence of grade ≥3 adverse reactions in our study. Another potential explanation for this difference was the variation in patient populations, as all patients (100%) in our study were prior immunotherapy exposure, whereas only 38% of patients in Wu Lin's study had received immunotherapy. As the previous study found that prior treatment exposure, particularly immunotherapy, might contribute to cumulative toxicity, increasing the likelihood of adverse events with subsequent therapy.[34] These two aspects might be account for the higher incidence of grade ≥3 adverse reactions in our study. Regarding common adverse reactions, the combination of anlotinib and docetaxel appeared to increase the incidence of typical docetaxel-related adverse reactions, including fatigue, hematologic toxicity, gastrointestinal toxicity, alopecia and liver function abnormalities. This was in line with the previous study on bevacizumab combined with docetaxel, where the incidence of grade ≥3 adverse reactions also exceeded 40%. Moreover, the addition of bevacizumab contributed to an increased incidence of docetaxel-related adverse reactions.[35] Furthermore, in this study, hypertension (39.5%), hand-foot syndrome (25.6%) and hemoptysis (11.6%) appeared to be more closely resulted from anlotinib, which was consistent with those reported in earlier anlotinib monotherapy trials, such as ALTER0303 and an anlotinib monotherapy retrospective study, where the incidence of hypertension was 33.1–64.6% and hand-foot syndrome was 29.7–43.2%.[10,36] These findings suggested that the toxicity profile of anlotinib in our study aligned with prior reports and was not significantly exacerbated by combination therapy. Collectively, no new or unexpected toxicities were observed, and the safety profile was in line with previous studies evaluating combination therapy. This suggested that anlotinib combined with docetaxel might be considered as a feasible and tolerable therapeutic option for patients with previously immunotherapy-treated advanced NSCLC clinically.

While this study provided valuable insights, several limitations should be acknowledged. Firstly, this study was retrospective in nature, which limited the ability to draw definitive conclusions and raised concerns about potential biases in patient selection and treatment allocation. Secondly, the small sample size might impact the robustness of definitive OS conclusions. As a result, subgroup analysis and multiple comparisons were not conducted in this study analysis. As a retrospective study, this analysis was inherently subject to selection bias and unmeasured confounders. However, to mitigate these limitations, we applied strict inclusion/exclusion criteria, systematically compared baseline characteristics between groups, and performed statistical adjustments using Cox proportional hazards models and stepwise multivariable regression analysis to account for significant prognostic factors. Despite these measures, prospective randomized controlled trials were warranted to further validate our findings. Thirdly, the follow-up duration was relatively inadequate, and long-term survival data was needed to assess the durability of the observed benefits. Finally, another key limitation of this study was the lack of biomarker-driven subgroup analysis. Given that PD-L1 expression levels, tumor mutational burden (TMB) and angiogenesis-related indicators might influence treatment responses, future study should incorporate biomarker analysis to identify patient subgroups that derived the greatest benefit from anlotinib plus docetaxel treatment, particularly in the context of overcoming immunotherapy resistance.

Conclusion

In conclusion, anlotinib combined with docetaxel is a promising treatment regimen for patients with previously immunotherapy-treated advanced NSCLC, significantly improving PFS, OS and DCR compared to docetaxel monotherapy. The results support the administration of this combination therapy as the second-line or more line settings preliminarily, providing a potential new approach for treating this difficult-to-manage patient population. Given the manageable safety profile and the clinical benefits observed, further studies are warranted to validate these findings in larger cohorts and to explore biomarkers that can predict the response to this combination.

Ethics and Consent Statement

Despite the informed consent was waived by the Ethics Committee of the First Affiliated Hospital of Heilongjiang University of Chinese Medicine, we confirmed that the data of the patients included in this study was anonymized or maintained with confidentiality.

Disclosure

The authors declare that there are no conflicts of interest.

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