


ORIGINAL ARTICLE

Evaluation of calculating carboplatin dosage in carboplatin-pemetrexed therapy as the first-line therapy for Chinese patients with advanced lung adenocarcinoma

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Keywords

Advanced; area under the curve; carboplatin-pemetrexed; lung adenocarcinoma.

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Abstract

Objective: This study aims to explore the application of actual carboplatin in carboplatin plus pemetrexed regimen as first-line treatment for advanced lung adenocarcinoma, and to determine the recommended dose of carboplatin for Chinese populations.

Methods: From January 2014 to April 2016, 151 advanced lung adenocarcinoma patients who received carboplatin and pemetrexed (500 mg/m²) were included. The area under the curve (AUC) of carboplatin was back-calculated from actual dosages using the Calvert formula. According to the median of calculated AUC, patients were divided into AUC ≥4 and <4 groups.

Results: The median of AUC was 4 (1.8–5.5). A total of 79 patients had an AUC ≥4 and 72 patients had an AUC <4. The mean relative dose intensities of pemetrexed were 100.4% for the AUC ≥4 group, and 101.4% for <4 group. Baseline characteristic variables were balanced between the two groups, except for Eastern Cooperative Oncology Group Performance score ($P = 0.044$). The overall response rate (ORR) and disease control rate (DCR) were 33.8% and 90.1%, respectively, 35.4% and 86.1% for the AUC ≥4 group, and 31.9% and 94.4% for the AUC <4 group. No significant difference was observed in ORR ($P = 0.650$) and DCR ($P = 0.086$) between the two groups.

Conclusion: Compared with an AUC of 5 or 6, the actual clinical application of AUC was generally insufficient for Chinese populations; fortunately, therapeutic efficacy remained equal. We found that AUC <4 was as adequate as AUC ≥4 in pemetrexed plus carboplatin regimen as first-line treatment for them.

Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancers, and approximately 70% of patients with NSCLC are diagnosed at the locally advanced stage (stage IIIB) or metastatic (stage IV) disease.¹ Lung adenocarcinoma is the predominate subtype of NSCLC. Meta-analysis indicated that cisplatin-based chemotherapy improved overall survival and quality of life for patients with advanced NSCLC, compared with best supportive care alone.² Therefore, cisplatin-based doublet combinations are reference regimens for advanced NSCLC. In a phase III study carried out among untreated patients with NSCLC, there were non-inferior efficacy and better tolerability for

cisplatin-pemetrexed than for cisplatin-gemcitabine in first-line treatment of lung adenocarcinoma and large cell carcinoma.³ Although, in some studies in advanced NSCLC patients, epidermal growth factor receptor (EGFR)/anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKI) offered significant benefits over platinum-based chemotherapy for those with corresponding genetic alterations, platinum-based chemotherapy remains the standard first-line treatment for those with EGFR/ALK mutation-negative.^{4–6}

Carboplatin, a second-generation platinum-containing drug, has been widely used as a substitute for cisplatin regimens in clinical settings, as it has been shown to be less toxic, convenient, and capable of being administered on an

outpatient basis.⁷ In previous studies in non-squamous NSCLC, combination therapy of carboplatin and pemetrexed as a first-line treatment has an excellent safety profile and a convenient administration schedule.^{8,9} A retrospective study in non-Hodgkin lymphoma patients, DeVIC ± R therapy (combination therapy of dexamethasone, etoposide, ifosfamide, and carboplatin with or without rituximab) yielded a significantly higher overall response rate (ORR) for the area under the curve (AUC) ≥ 4 than for AUC < 4 , and the frequency of grade ≥ 3 decreased platelet and neutrophil counts occurred at higher rates for AUC ≥ 4 .¹⁰ However, in another study of small cell lung cancer patients, no significant difference in ORR (ORR 69.2% vs. 71.4%) and overall survival (median 10.0 vs. 12.0 months) were observed between the AUC ≤ 5 and > 5 groups for carboplatin plus etoposide treatment.¹¹ Whether the difference in AUC of carboplatin was correlated with the efficacy has not yet been determined, and there are few studies to evaluate it in first-line treatment for advanced lung adenocarcinoma patients. Therefore, we conducted the study to explore the application of carboplatin in carboplatin–pemetrexed treatment, and to determine the recommended dose of carboplatin for Chinese patients with untreated advanced lung adenocarcinoma.

Methods

Eligibility

Patients with cytologically- or histologically-confirmed lung adenocarcinoma, classified as stage IV by the seventh edition of the American Joint Committee on Cancer manual, were eligible if they had measurable lesions, Eastern Cooperative Oncology Group Performance score (ECOG PS) ≤ 2 , and received the carboplatin–pemetrexed (500 mg/m²) regimen as the initial treatment between January 2014 and April 2016 at the Ethics Committee of the Cancer Hospital of the Chinese Academy of Medical Sciences (Beijing, China). Patients were not eligible if they have previously received EGFR/ALK-TKI, anti-programmed death 1 antibodies (nivolumab or pembrolizumab), other chemotherapy regimens, or had no efficacy confirmed after carboplatin–pemetrexed therapy.

Study design

AUC was back-calculated using the Calvert formula on the basis of initial carboplatin dosages administered to patients receiving carboplatin–pemetrexed therapy.¹² According to the optimal AUC cut-off point using the median of the calculated AUC, patients were divided into two

groups, to compare treatment efficacy and safety. Pemetrexed was given at a dose of 500 mg/m² by 10-minute intravenous infusion followed by intravenous infusion of carboplatin over at least 30 minute (AUC < 4 or ≥ 4) on day 1. Combination chemotherapy was repeated every 3 weeks for a maximum of six cycles. After the completion of four to six cycles, patients with controlled disease were allowed to continue maintenance therapy with pemetrexed, until progressive disease (PD). During the treatment, all patients received folic acid and vitamin B₁₂. Patients were scheduled to receive at least two cycles, and therapeutic efficacy was evaluated after every two cycles. Evaluation of treatment efficacy when symptom aggravation occurred or when patients stopped the treatment for intolerable toxicity after one cycle was allowed.

Efficacy and safety

The efficacy end-points were complete remission (CR), partial response (PR), stable disease (SD), PD, confirmed complete and partial responses (ORR = CR + PR), and disease control rate (DCR = CR + PR + SD) according to the Response Evaluation Criteria in Solid Tumors 1.1 criteria,¹³ measured by computed tomography scans, magnetic resonance imaging, bone scanning, or positron emission tomography/computed tomography scans. Progression-free survival (PFS) was defined as the duration of time from the start of treatment to the date of confirmation of PD or the date of death from any cause. Any adverse medical events that occurred during the initiation of investigational treatment and one month after completion of investigational treatment were recorded as adverse events (AEs), regardless of whether the AEs were associated with the treatment. The evaluation of AEs was based on the National Cancer Institute-Common Toxicity Criteria 3.0 version.

Statistical analysis

The patients' characteristics and responses were analyzed using descriptive methods. The numbers and incidences of AEs were summarized using descriptive statistics, absolute frequencies, and percentages in the tables. Continuous variables were compared using *t*-tests, and categorical variables were compared using χ^2 -tests. PFS was calculated with the Kaplan–Meier product limit method. The logistic regression model was used to identify risk factors independently associated with response. All statistical analyses were carried out using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA), and a *P*-value < 0.05 was considered significant.

Results

Patient and group assignment

A total of 151 patients were enrolled in this study during the survey period. All of them had been confirmed with stage IV lung adenocarcinoma. The median and mean of AUC were 4 (1.8–5.5) and 3.92 (3.92 ± 0.720), respectively. And among the 151 patients, there were just 14 cases (9.3%) with AUC ≥5, and none had an AUC ≥6. A value of 4 was set as the AUC cut-off point to divide the patients into two groups, according to median of the AUC. The baseline characteristics are shown in Table 1. A total of 79 patients had an AUC ≥4, and 72 patients had an AUC <4. A total of 12 patients (7.9%) had carboplatin dose reduction (7 patients with AUC ≥4 and 5 patients with AUC <4). Five patients experienced treatment delay (3 patients with AUC ≥4 and 2 patients with AUC <4). The median age was 60 years for the AUC ≥4 group (range 27–76 years), and 58 years for the AUC <4 group (range 37–76 years), respectively. Among these patients, 13 patients (8.6%) were aged older than 70 years (5 patients with AUC ≥4 and 8 patients with AUC <4).

Overall, 53 patients were men (67.1%) in the AUC ≥4 group, and 36 patients were men (50.0%) in the AUC <4 group. A total of 21 (29.2%) patients had ECOG PS 0 in the AUC <4 group, and 36 (45.6%) patients had ECOG PS 0 in the AUC ≥4 group. A total of 23 (31.9%) patients received more than six treatment cycles in the AUC ≥4 group, and 18 (22.8%) patients received more than six treatment cycles in the AUC <4 group. The mean relative dose intensities of pemetrexed were 100.4% for the AUC ≥4 group, and 101.4% for the <4 group. A total of 21 (10 patients in the AUC ≥4 and 11 patients in the AUC <4) altered the treatment into targeted therapy due to AEs or personal reasons. Furthermore, 46 patients (20 patients in the AUC ≥4 and 26 patients in the AUC <4) continued pemetrexed monotherapy maintenance treatment. Women were more likely to have an ECOG PS ≥1 and to receive treatment more than six cycles in the AUC <4 group, but the men showed a higher frequency of having ECOG PS 0 and less than four treatment cycles in the AUC ≥4 group. However, baseline characteristic variables were balanced with no statistical difference between the two groups, except for PS ($P = 0.044$). The AUC <4 group had higher PS.

Table 1 Baseline characteristics of all patients

Characteristics	Total (n = 151)	AUC		P
		<4 (n = 72)	≥4 (n = 79)	
Age, years (%)				0.956
<65	95 (62.9)	48 (66.7)	47 (59.5)	
≥65	56 (37.1)	24 (33.3)	32 (40.5)	
Sex (%)				0.242
Male	89 (58.9)	36 (50.0)	53 (67.1)	
Female	62 (41.1)	36 (50.0)	26 (32.9)	
ECOG performance status (%)				0.044
0	57 (37.7)	21 (29.2)	36 (45.6)	
1	80 (53.0)	41 (56.9)	39 (49.4)	
2	14 (9.3)	10 (13.9)	4 (5.0)	
Smoking (%)				0.291
No	75 (49.7)	39 (54.2)	36 (45.6)	
Yes	76 (50.3)	33 (45.8)	43 (54.4)	
Charlson Comorbidity Index (%)				0.137
0	111 (73.5)	50 (69.4)	61 (77.2)	
1	35 (23.2)	21 (29.2)	14 (17.7)	
≥2	5 (3.3)	1 (1.4)	4 (5.1)	
Dosage of pemetrexed (mg/m ²) (%)	504.26 ± 34.93	502 ± 34.8	507 ± 35.1	0.0380
No. of treatment cycles (%)				0.228
<4	26 (17.2)	8 (11.1)	18 (22.8)	
4–6	63 (41.7)	30 (41.7)	33 (41.8)	
>6	41 (27.1)	23 (31.9)	18 (22.8)	
Followed by TKI	21 (14.0)	11 (15.3)	10 (12.7)	
Pemetrexed maintenance (%)				0.150
No	105 (69.5)	46 (63.9)	59 (64.7)	
Yes	46 (30.5)	26 (36.1)	20 (25.3)	

AUC, area under the blood concentration–time curve; ECOG, Eastern Cooperative Oncology Group; TKI, tyrosine kinase inhibitors

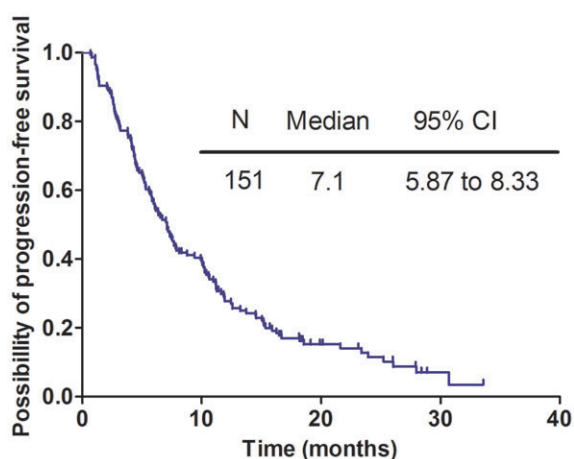


Figure 1 Kaplan–Meier curves for progression-free survival for the entire population. N, number of all patients; CI, confidence interval.

Therapeutic efficacy

The median follow-up was 14 months (range 1.4–18.5 months). The median PFS was 7.1 months (95% CI 5.87–8.33 months) (Fig 1). For patients with pemetrexed maintenance therapy, the median PFS was 7.7 months (95% CI 4.88–10.50 months) (Fig 2). All patients were evaluated for drug efficacy (Table 3). The ORR of all patients was 33.8% and DCR of 90.1% (0 CR, 51 PR, and 85 SD), respectively (Table 3). The ORR and DCR were 35.4% and 86.1% (0 CR, 28 PR, and 40 SD) for patients in the AUC ≥ 4 group, and 31.9% and 94.4% (0 CR, 23 PR, and 45 SD) in the AUC < 4 group (Table 2). There was no statistically significant difference in ORR ($P = 0.650$) and DCR ($P = 0.086$) between the two groups (Table 2).

Safety and tolerability

All patients who received the treatment were eligible for safety analysis. In the present study, there were no treatment-related deaths. All-grade major treatment-related AEs are shown in Table 4. The grade 3–4 hematological adverse toxicities were neutropenia (15.9%), leukopenia

Table 3 Adverse events of all patients

Adverse events	Total (n = 151)	AUC		P
		<4.0 (n = 72)	≥ 4.0 (n = 79)	
Leukopenia (%)				
All grade	84 (55.6)	45 (62.5)	39 (49.4)	0.105
Grade ≥ 3	16 (10.5)	10 (13.9)	6 (7.6)	0.219
Anemia (%)				
All grade	47 (31.1)	21 (29.2)	26 (32.9)	0.370
Grade ≥ 3	1 (0.6)	1 (1.4)	0	0.293
Neutropenia (%)				
All grade	80 (53.0)	40 (55.6)	40 (50.6)	0.620
Grade ≥ 3	24 (15.9)	15 (20.8)	9 (11.4)	0.113
Thrombocytopenia (%)				
All grade	15 (9.9)	7 (9.7)	8 (10.1)	0.934
Grade ≥ 3	1 (0.6)	1 (1.4)	0	0.293
Nausea and vomiting (%)				
All grade	101 (66.9)	51 (70.8)	50 (63.3)	0.325
Grade ≥ 3	1 (0.6)	1 (1.4)	0	0.293
Fatigue (%)				
All grade	28 (18.5)	13 (18.1)	15 (19.0)	0.854
Grade ≥ 3	2 (1.3)	2 (2.8)	0	0.218
ALT/AST elevation (%)				
All grade	45 (29.8)	20 (27.8)	25 (31.6)	0.645
Grade ≥ 3	2 (1.3)	1 (1.4)	1 (1.3)	0.947
Rash (%)				
All grade	3 (2.0)	1 (1.4)	2 (2.5)	—
Grade ≥ 3	0	0	0	—
Fever (%)				
All grade	2 (1.3)	0	2 (2.5)	—
Grade ≥ 3	2 (1.3)	0	2 (2.5)	—
Alopecia (%)				
All grade	2 (1.3)	1 (1.4)	1 (1.3)	—
Grade ≥ 3	0	0	0	—
Peripheral neuropathy (%)				
All grade	1 (0.6)	0	1 (1.3)	—
Grade ≥ 3	0	0	0	—
Myalgia/arthralgia (%)				
All grade	1 (0.6)	0	1 (1.3)	—
Grade ≥ 3	0	0	0	—

ALT, alanine transaminase; AST, aspartate transaminase; AUC, area under the blood concentration–time curve.

Table 2 Treatment outcome according to area under the curve

Overall best response	Total (n = 151)	AUC		P
		<4.0 (n = 72)	≥ 4.0 (n = 79)	
CR (%)	0	0	0	
PR (%)	51 (33.8)	23 (31.9)	28 (35.4)	
SD (%)	85 (56.3)	45 (62.5)	40 (50.6)	
PD (%)	13 (9.9)	4 (5.6)	11 (14.0)	
ORR (%)	51 (33.8)	23 (31.9)	28 (35.4)	0.650
DCR (%)	136 (90.1)	68 (94.4)	68 (86.1)	0.086

AUC, area under the blood concentration–time curve; CR complete response; DCR, disease control rate (DCR = CR + PR + SD); ORR, overall response rate (ORR = CR + PR); PD, progressive disease; PR, partial response; SD, stable disease.

(10.5%), anemia (0.6%), and thrombocytopenia (0.6%). The grade 3–4 non-hematological AEs were fever (1.4%), alanine transaminase/aspartate transaminase elevation (1.3%), fatigue (1.3%), and nausea and vomiting (0.6%) (Table 3). No significant difference in all-grade or grade ≥ 3 AEs was observed in both the AUC ≥ 4 and < 4 groups (Table 3).

Risk factors for ORR

The logistic regression model was used to identify risk factors independently associated with ORR (Table 4). All variables including age, sex, ECOG PS, smoking history, Charlson Comorbidity Index, dosage of pemetrexed, and AUC of carboplatin were performed. Unfortunately, both univariate and multivariate analyses indicated that no factor was significantly associated with ORR ($P > 0.05$).

Discussion

A combination therapy of platinum compounds (cisplatin or carboplatin) and pemetrexed had been shown to be effective and well-tolerated for advanced non-squamous NSCLC.^{3,14,15} A previous study showed that carboplatin is predominantly excreted by the kidneys, with approximately 70% eliminated in the urine.¹² Multiple studies^{16,17} demonstrated that the utility of extrapolating the Calvert formula in calculating the dosage of carboplatin was better than the calculation method according to the body surface area, as it takes into account individual differences in renal

function.³ In the previous study, different carboplatin doses (AUC 5 or 6) were used of the pemetrexed (500 mg/m²) and carboplatin combination regimen as the first-line treatment for Japanese patients with advanced non-squamous NSCLC, and the results showed that ORR were 66.7% and 57.1% for the AUC 5 ($n = 6$) and 6 ($n = 14$) groups, respectively.¹⁸ Another study of a Japanese population of pemetrexed (500 mg/m²) and carboplatin treatment for elderly (aged ≥ 75 years) untreated patients ($n = 17$) with advanced non-squamous NSCLC showed that ORR were 33.3%, 57.1%, and 42.9% for the AUC 4, 5, and 6 groups, respectively.¹⁹ However, the above studies failed to evaluate the efficacy between different AUC of carboplatin (Fig 2).

Based on the data of 151 patients with stage IV lung adenocarcinoma between 2014 and 2016, we determined 4 as the AUC cut-off limit according to the median of the AUC. This population-based analysis displayed a total ORR of 33.8%, and 35.4% and 31.9% for the AUC ≥ 4 and < 4 group. Furthermore, no difference was observed in ORR ($P = 0.650$) between the two groups.

In previous phase II studies from Western populations, a combination therapy with pemetrexed (500 mg/m²) and carboplatin (AUC 6) showed an ORR of 24.0–31.6%.^{9,20} Another randomized phase III trial yielded an ORR of 34.0% for carboplatin (AUC 5) and pemetrexed (500 mg/m²) therapy as the first-line setting for Western patients with advanced non-squamous NSCLC.¹⁵ Therefore, the recommended dose was determined to be carboplatin at an AUC of 5 or 6 in combination with pemetrexed (500 mg/m²) in a clinical setting. In the present study, the mean

Table 4 Factors influencing therapeutic efficacy resulting in overall response rate for advanced adenocarcinoma non-small cell lung cancer after carboplatin–pemetrexed treatment by logistic regression models analysis

Characteristics	Univariate analysis			Multivariate analysis				
	<i>P</i>	OR	95% CI	<i>P</i>	OR	95% CI		
Age								
≥ 65 vs. < 65	0.684	1.159	0.569	2.361	0.814	1.097	0.508	2.370
Sex								
Female vs. male	0.991	1.004	0.510	1.977	0.886	1.087	0.348	3.398
ECOG performance status								
1 vs. 0	0.557	2.719	0.599	2.533	0.516	1.277	0.611	2.668
2 vs. 0	0.222	8.682	0.239	3.139	0.838	0.871	0.233	3.258
Smoking								
Yes vs. no	0.818	0.924	0.471	1.814	0.644	0.849	0.425	1.697
Charlson Comorbidity Index								
1 vs. 0	0.607	1.231	0.557	2.719	0.444	1.387	0.601	3.202
2 vs. 0	0.725	1.389	0.222	8.682	0.779	1.320	0.190	9.156
Dosage of pemetrexed (mg/m ²)								
≥ 500 vs. < 500	0.164	0.618	0.313	1.218	0.164	0.618	0.313	1.218
AUC								
3.5– < 4.5 vs. < 3.5	0.259	1.596	0.709	3.591	0.257	1.604	0.709	3.628
≥ 4.5 vs. < 3.5	0.966	0.978	0.352	2.715	0.977	0.985	0.353	2.751

AUC, area under the blood concentration–time curve; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; OR, odds ratio; ORR, overall response rate.

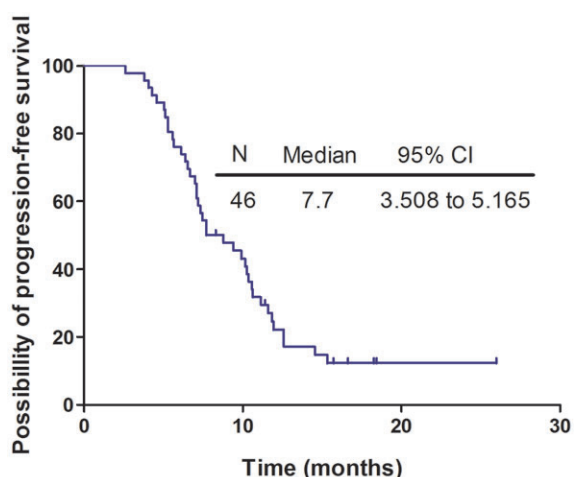


Figure 2 Kaplan–Meier curves for progression-free survival for patients with pemetrexed maintenance therapy. N, number of all patients; CI, confidence interval.

relative dose intensities of pemetrexed were 100.8% ($504.26 \pm 34.93 \text{ mg/m}^2$); however, the mean and median of the AUC were 3.92 (3.92 ± 0.720) and 4, respectively. Compared with previous studies, the carboplatin dosage was insufficient among Chinese populations, according to the Calvert formula.^{9,15} Fortunately, the therapeutic efficacy of overall patients was similar to the previous data. Furthermore, we carried out multivariate logistic regression analyses to identify factors associated with the therapeutic efficacy, which influenced CR and PR. Consistent with the results above, a higher AUC of carboplatin could not be recognized as an independent factor associated with ORR in both univariate and multivariate analyses. The results suggested that pemetrexed plus carboplatin treatment showed convincing therapeutic efficacy, regardless of initial AUC of carboplatin ≥ 4 or < 4 , according to the Calvert formula. One possible reason for the results was that 4 might not be the optimal AUC cut-off value for carboplatin, which led to a negative result in the efficacy between the two groups. Another explanation was that carboplatin dose was not the decisive factor influencing the efficacy in the pemetrexed plus carboplatin regimen, although previous randomized phase III trials showed that pemetrexed plus carboplatin treatment was superior to single-agent pemetrexed in first-line treatment for advanced NSCLC.^{9,15} The third possible reason was ethnic difference. The results of both a Japanese report¹⁸ and the present study showed that AUC < 5 was efficacious in pemetrexed–carboplatin treatment, despite the absence of comparison with Western populations.

What is noteworthy is that there were just 14 cases (9.3%) with AUC ≥ 5 , and none had an AUC ≥ 6 . In addition, women were more likely to have ECOG PS ≥ 1 in

the AUC < 4 group, but men showed a higher frequency of having ECOG PS 0 in the AUC ≥ 4 group. The results suggested that the AUC of carboplatin in the present study was lower than that of 6, and it seemed to have a higher AUC for patients who were male or had better ECOG PS, and lower AUC for those who were female or had poorer ECOG PS, according to physicians' individual choice.

Previous studies reported that pemetrexed–carboplatin (AUC 5 or 6) combination therapy followed by pemetrexed maintenance therapy for those with controlled disease was generally tolerable, and could improve the survival for patients with advanced NSCLC.^{18,19} In the present study, DCR were 94.4% and 86.1% for the AUC ≥ 4 and AUC < 4 groups, respectively. These data showed that $> 80\%$ of patients in the real world had the opportunity to receive maintenance therapy. We also found that there were higher frequencies of receiving more than six cycles of treatment in the patients with AUC < 4 , whereas there were fewer treatment cycles in those with AUC ≥ 4 . The reason might be that more patients received maintenance therapy with pemetrexed in those with AUC < 4 . However, there were just 36.1% of the AUC ≥ 4 group and 25.3% of the AUC < 4 group that received pemetrexed maintenance in the present study. This is because some of those patients changed their treatment to receive EGFR/ALK-TKI due to adverse events or personal reasons. Other reasons were that some of the patients were reluctant to continue maintenance treatment, or PD had occurred before starting maintenance treatment. Patients with pemetrexed maintenance therapy in the present study had a PFS of 7.7 months (95% CI 4.88–10.50 months), consistent with a previous study (median PFS 6.9 months, 95% CI 6.2–7.5 months).²¹

Some studies revealed that the frequency of thrombocytopenia and leukopenia has been reported to increase when the AUC of carboplatin increased.^{22–24} Whereas another study of B-cell non-Hodgkin's lymphoma revealed that grade ≥ 3 neutropenia was similar between the AUC ≥ 4 and < 4 groups.²⁵ In a study that examined the recommended dose of pemetrexed (500 mg/m^2) and carboplatin regimen for treatment of untreated advanced NSCLC (AUC 5 [$n = 6$] and AUC 6 [$n = 14$]), the major toxicities equal to or greater than grade 3 were neutropenia (83.3%), anemia (66.7%), thrombocytopenia (66.7%), and leukopenia (16.7%) for the AUC 5 group, and neutropenia (71.4%), anemia (50.0%), thrombocytopenia (42.9%), and leukopenia (14.3%) for the AUC 6 group.¹⁸ Another similar study in older adults (aged ≥ 75 years) showed that dose-limiting toxicities were not observed in AUC 4 or 5, whereas three patients in AUC 6 observed dose-limiting toxicities (including grade 4 thrombocytopenia and grade 3 febrile neutropenia).¹⁹ In the present

study, the main grade 3–4 adverse toxicities were neutropenia (15.9%) and leukopenia (10.5%). The frequency of grade 3–4 neutropenia and leukopenia were 11.4% and 7.6% in the AUC ≥ 4 group, and 20.8% and 13.9% in the AUC < 4 group, with no statistically significant difference in both neutropenia ($P = 0.113$) and leukopenia ($P = 0.219$) observed between the two groups. Despite the absence of a direct comparison, we found that AUC < 5 might mean a lower incidence of adverse toxicities. A possible reason was that a combination therapy of carboplatin–pemetrexed was well tolerated, and our patients' AUC were commonly < 5 , hence most were without any observed AEs. Another explanation is that it was difficult to evaluate differences in AEs between the two groups because of the retrospective design of this study. Third, the sample size of the present study was small, which might lead to a negative result. We are looking forward to further studies to confirm the results.

There were many limitations to the present study. First, it was a retrospective and single-center study, and thus patients might be selected, which led to the bias of our data. In contrast, the sample size in the present study was small, therefore we might be unable to identify an optimal cut-off value of the AUC. Third, some of patients in the present study received maintenance therapy with pemetrexed, but some did not. Additionally, some patients changed their therapy to targeted treatment due to AEs or personal reasons during chemotherapy. Hence, we failed to explore the correlation between the AUC of carboplatin and survival.

In summary, this was the first dose-escalation study that examined the different AUC of carboplatin in the efficacy of carboplatin–pemetrexed combination regimen in the first-line treatment for advanced lung adenocarcinoma patients in a Chinese population. Our study suggested that although the actual clinical application of AUC for Chinese populations was generally insufficient, fortunately, therapeutic efficacy remained equal, compared with an AUC of 5 or 6. The response rate did not increase by maintaining the AUC at ≥ 4 . In addition, AUC ≤ 5 had a lower incidence of adverse toxicities compared with AUC 6. Therefore, we posited that AUC < 4 was as adequate as AUC ≥ 4 in the carboplatin–pemetrexed combination regimen for the first-line treatment in a Chinese population. Randomized controlled trials with a large sample size are required to confirm these findings.

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Disclosure

No authors report any conflict of interest.

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