A phase III, randomized, double-blind, controlled trial of carboxyamidotriazole plus chemotherapy for the treatment of advanced non-small cell lung cancer

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Abstract

Background: Carboxyamidotriazole (CAI), a calcium channel blocker, inhibits tumor cell proliferation, metastasis, and angiogenesis. This trial aimed to determine whether CAI combined with conventional chemotherapy could prolong progression-free survival (PFS) in non-small cell lung cancer (NSCLC) patients.

Methods: Patients were assigned into groups (3:1 ratio) to receive either chemotherapy + CAI or chemotherapy alone. Cisplatin (25 mg/m^2) was administered by intravenous infusion on days 1, 2, and 3, and vinorelbine (25 mg/m^2) on days 1 and 8 of each 3-week cycle for four cycles. CAI was administered at 100 mg daily with concomitant chemotherapy; this treatment was continued after chemotherapy was ceased until serious toxicity or disease progression had occurred. PFS was the primary endpoint, and the secondary endpoints were objective response rate (ORR), disease control rate, overall survival (OS), and quality of life.

Results: In total, 495 patients were enrolled in the trial: 378 in the chemotherapy + CAI group and 117 in the chemotherapy + placebo group. PFS was significantly greater in the chemotherapy + CAI [median, 134 days; 95% confidence interval (CI) 127–139] than in the chemotherapy + placebo (median, 98 days; 95% CI: 88–125) group, with a hazard ratio of 0.690 (95% CI: 0.539–0.883; $p = 0.003$). There was no difference in the OS rates of both groups. The ORR was greater in the chemotherapy + CAI group than in the chemotherapy + placebo group (34.6% *versus* 25.0%, $p = 0.042$). Adverse events of ⩾grade 3 occurred more frequently in the CAI group [256 (68.1%) *versus* 64 (55.2%); $p = 0.014$].

Conclusion: CAI + platinum-based chemotherapy prolonged PFS and could be a useful therapeutic option to treat NSCLC.

Clinical Trial Registration: chinadrugtrials.org.cn identifier: CTR20160395

Keywords: carboxyamidotriazole, chemotherapy, cisplatin, non-small cell lung cancer, vinorelbine

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Introduction

Lung cancer is a leading cause of death, accounting for approximately 18.4% of all cancer-related fatalities worldwide[1] and for more than 600,000 deaths in China in 2015.[2] Strategies to improve therapeutic efficacy in patients with advanced non-small cell lung cancer (NSCLC) mainly involve the administration of different combinations of cytotoxic drugs. Carboxyamidotriazole (CAI) blocks non-voltage-dependent calcium channels and, consequently, affects various cell signaling pathways. CAI is known to inhibit inositol triphosphate (IP_3)

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synthesis and nitric oxide (NO) formation and prevent calcium ion (Ca^2+)-dependent endothelial cell proliferation induced by vascular endothelial growth factor-A (VEGF-A).[3,4] Thus, reduction in intracellular release of IP_3, production of NO, and Ca^2+-dependent VEGF-A production by CAI leads to inhibition of angiogenesis and aberrant tumor cell growth.

During phase I clinical and pharmacokinetic studies of CAI gelatin capsules (gelcaps), the maximum-tolerated dose (MTD) of CAI was found to be 75 mg/m^2.[5] Further, a phase I trial in Chinese patients with cancer showed that the gelcap formulation of CAI was well-tolerated with an MTD of 100 mg/day; the most common adverse events (AEs) were nausea and vomiting.

To determine the safety and efficacy of CAI in combination with cisplatin + vinorelbine, 183 patients with advanced NSCLC were enrolled in a phase II trial that involved 20 medical centers: 60 were assigned to a CAI 100 mg + chemotherapy group, 60 to a CAI 150 mg + chemotherapy group, and 63 to a placebo + chemotherapy group, with objective response rate (ORR) as the primary endpoint. The ORR was improved in the CAI 100 mg + chemotherapy group in comparison with the placebo + chemotherapy group (25.4% *versus* 14.3%, $p = 0.171$).

Therefore, we aimed to conduct a multicenter, double-blind, randomized phase III trial to confirm the safety and efficacy of CAI + chemotherapy, compared with chemotherapy alone, as a first-line treatment for patients with NSCLC.

Methods

Design of the trial

This trial (chinadrugtrials.org.cn, number CTR20160395) was conducted on NSCLC patients who were enrolled from 36 medical centers between 11 September 2011 and 31 October 2014. All patients provided their written consent before taking part in the trial approved by the Ethics Committee of every participating center (see Supplemental Material file 1 online).

Patients

Chemotherapy-naive patients definitively diagnosed with stage IV NSCLC using histological or cytological techniques were enrolled in the study. Other inclusion criteria were age of 18–75 years; Eastern Cooperative Oncology Group (ECOG) status 0 or 1; satisfactory heart, kidney, bone marrow, and liver functions; and the presence of ≥ 1 tumor lesion. The exclusion criteria were squamous cell carcinoma with hemoptysis, uncontrolled brain metastases, active infections, and pregnancy.

Chemotherapy

An intravenous infusion of cisplatin (25 mg/m^2) was administered on days 1, 2, and 3, and of vinorelbine (25 mg/m^2) was administered on days 1 and 8 of a 3-week cycle (for up to four treatment cycles). CAI (100 mg daily) or a matching placebo was given along with concomitant chemotherapy and continued after chemotherapy was ceased, until progression of advanced NSCLC or serious toxicity had occurred. The dose of vinorelbine and cisplatin should be reduced by 25% if patients experienced severe hematological AEs, including absolute neutrophil count $<0.5 \times 10^9$/L, or febrile neutropenia (absolute neutrophil count $<1.0 \times 10^9$/L), or platelets $<50 \times 10^9$/L. Prior to chemotherapy, absolute neutrophil count had to be $\geq 1.5 \times 10^9$/L and platelets $\geq 75 \times 10^9$/L. If chemotherapy was postponed for >2 weeks, the patient was discontinued from the study; patients can have a maximum of one dose modification of chemotherapy, or quit the study.

Assessments

Imaging of tumor size was used to assess the responses of tumors to treatment by following Response Evaluation Criteria in Solid Tumor guidelines (version 1.1). Assessments were carried out at 6-week intervals after randomization until disease progression (DP) or death. An independent Review Committee reviewed all tumor assessments.

Patients were followed up at 6-week intervals to evaluate the clinical outcome. The data included toxicity, drug efficacy, and survival times until patient death or the cutoff date. AEs were assessed according to the Functional Assessment of Cancer Therapy-Lung Cancer Subscale (FACT-LCS, version 3) at baseline and every 6 weeks until DP or death.

Statistical analysis

SAS version 9.2 was used for all statistical analyses. Sample sizes were calculated based on a hazard ratio (HR) of 0.65 for progression-free

survival (PFS) using a 3-to-1 randomization method; 4-month median PFS in the chemotherapy group according to published literature;[6] a presumed increase in PFS from 4 months in the placebo + chemotherapy group to 6.15 months in the CAI + chemotherapy group; a two-sided significance $p = 0.05$; and statistical power of 80%; recruitment period of 1 year; and follow-up for 1 year. In total, 496 patients had to be enrolled and followed up to realize 349 PFS events.

We assessed efficacy in the full analysis set (FAS) and the per-protocol (PPS) set. The FAS value was based on all patients who received the study drugs on one or more occasion, whereas PPS was based on patients treated with study drugs for ⩾2 cycles. We assessed safety in all patients who were treated with the study drugs on at least one occasion.

Survival times were evaluated using a stratified log-rank test. HR was evaluated using Cox regression for randomized strata and a regression model to identify potential prognostic factors. Differences in ORR and disease control rates between groups were analyzed using the Cochran–Mantel–Haenszel test. Changes in FACT-LCS questionnaire scores were evaluated with a Wilcoxon rank-sum test. Statistical tests were conducted based on a two-sided $\alpha = 0.05$ and a 95% confidence interval (CI).

Results

Figure 1 shows a scheme of the clinical trial. In total, 506 patients were assessed for eligibility, and 495 were randomly assigned to the chemotherapy + CAI ($n = 378$) and the chemotherapy + placebo ($n = 117$) groups. After

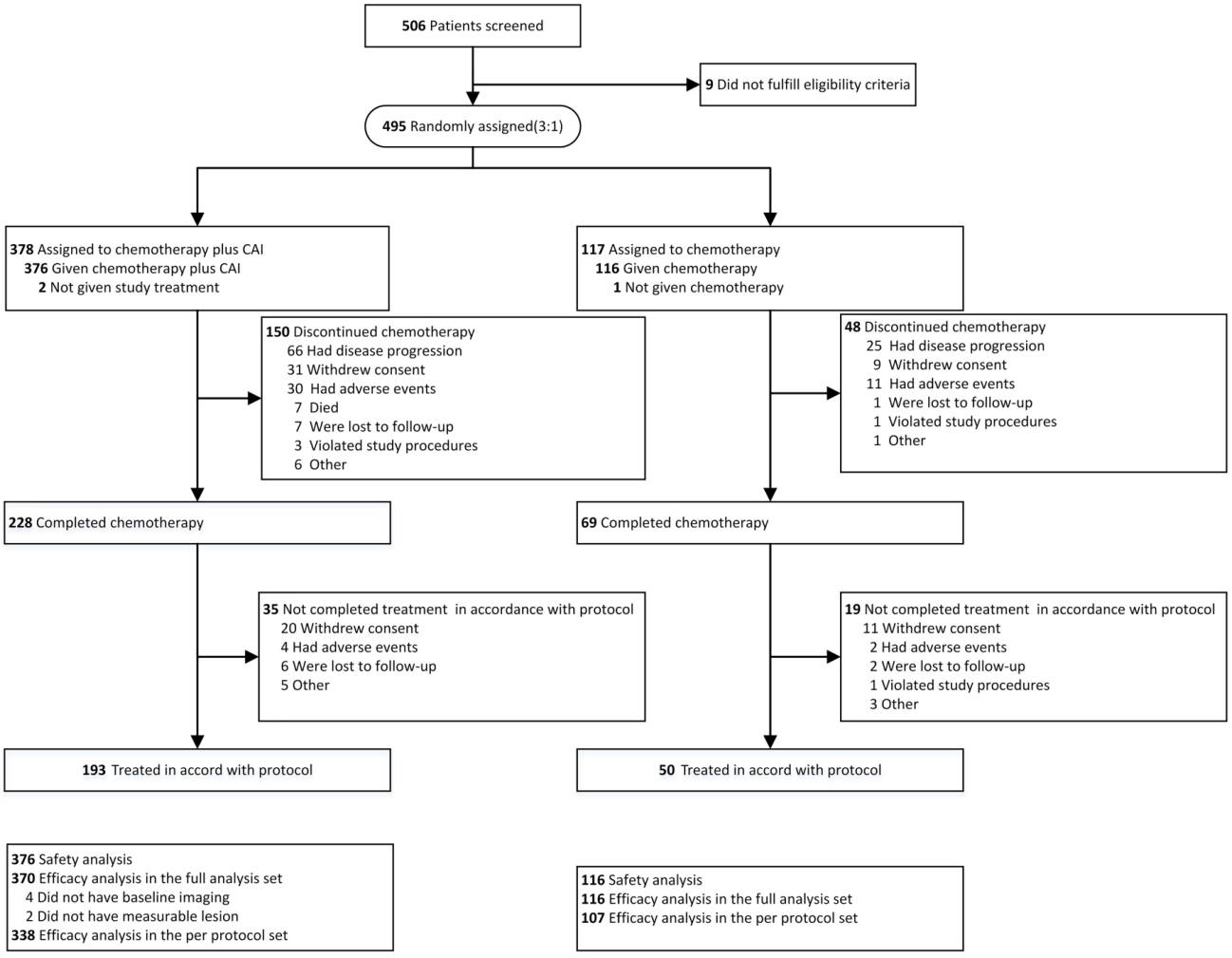

Figure 1. Study flowchart.
CAI, carboxyamidotriazole.

Table 1. Baseline characteristics of full analysis set population.

		Cisplatin and vinorelbine + CAI *n* = 370	Cisplatin and vinorelbine *n* = 116	*p*-value
Age, years	Median (range)	56 (31–71)	55 (25–75)	0.112
Sex	Male (%)	226 (61.1%)	80 (69.0%)	0.152
	Female (%)	144 (38.9%)	36 (31.0%)	
Histology	Squamous cell carcinoma (%)	83 (22.5%)	26 (22.4%)	0.844
	Adenocarcinoma (%)	266 (72.1%)	85 (73.3%)	
	Others (%)	21 (5.6%)	5 (4.3%)	
Brain metastasis	No	212 (57.9%)	65 (56.0%)	0.318
	Yes	154 (42.1%)	51 (44.0%)	
ECOG PS	0	102 (27.6%)	45 (38.8%)	0.028
	1	267 (72.2%)	70 (60.3%)	
	2	1 (0.9%)	1 (0.3%)	

Others = including adenosquamous carcinoma, large cell carcinoma, and undifferentiated carcinoma.
CAI, carboxyamidotriazole; ECOG PS, Eastern Cooperative Oncology Group performance status.

randomization, trial therapy was not administered to two patients in the chemotherapy + CAI group because of AEs and withdrawal of consent. One patient in the chemotherapy group withdrew their consent. Four patients did not have baseline imaging, and two patients did not have measurable tumor lesions in the chemotherapy + CAI group; hence, they were excluded from the FAS. Two patients with ECOG performance status 2 were enrolled due to protocol deviation. Four hundred and eighty-three patients (290 patients in the chemotherapy + CAI group and 84 in the chemotherapy group) had achieved the primary endpoint or withdrawn before the data cutoff date (15 December 2015).

Table 1 lists the well-balanced baseline characteristics (except ECOG performance status) of FAS patients across all groups.

The median PFS was 134 days (95% CI: 127–139) for the chemotherapy + CAI group, which was clearly higher than that for the chemotherapy group [98 days (95% CI: 88–125); HR, 0.690 (95% CI: 0.539–0.883); $p = 0.003$; Figure 2A]. There was no significant difference in the overall survival (OS) between the two groups [HR 1.046; (95% CI: 0.797–1.373)], median 360 days (95% CI: 298–426) in the chemotherapy + CAI group and 353 days (95% CI: 290–408) in the chemotherapy group [HR, 1.046 (95% CI: 0.797–1.373); $p = 0.744$; Figure 2B].

The results clearly reveal the beneficial effects of chemotherapy + CAI treatment on PFS. It is noteworthy that patients with adenocarcinoma had an HR of 0.631 (95% CI: 0.472–0.844) for PFS, and patients without brain metastasis had an HR of 0.647 (95% CI: 0.499–0.839) (Figure 3A). The OS benefits in favor of chemotherapy + CAI treatment were not observed across subgroups (Figure 3B). The ORR was higher in the chemotherapy + CAI group of patients than in the chemotherapy group. However, there was no significant difference in the disease control rate (DCR) between the two groups (Table 2).

Changes in the FACT-LCS scores in the first 12 weeks were not detectably altered in either group. Table 3 shows AEs that occurred in at least 5% of the patients. AEs of all grades were similar in both groups [372 (98.9%) *versus* 114 (98.3%); $p = 0.571$]. AEs of ⩾grade 3 occurred

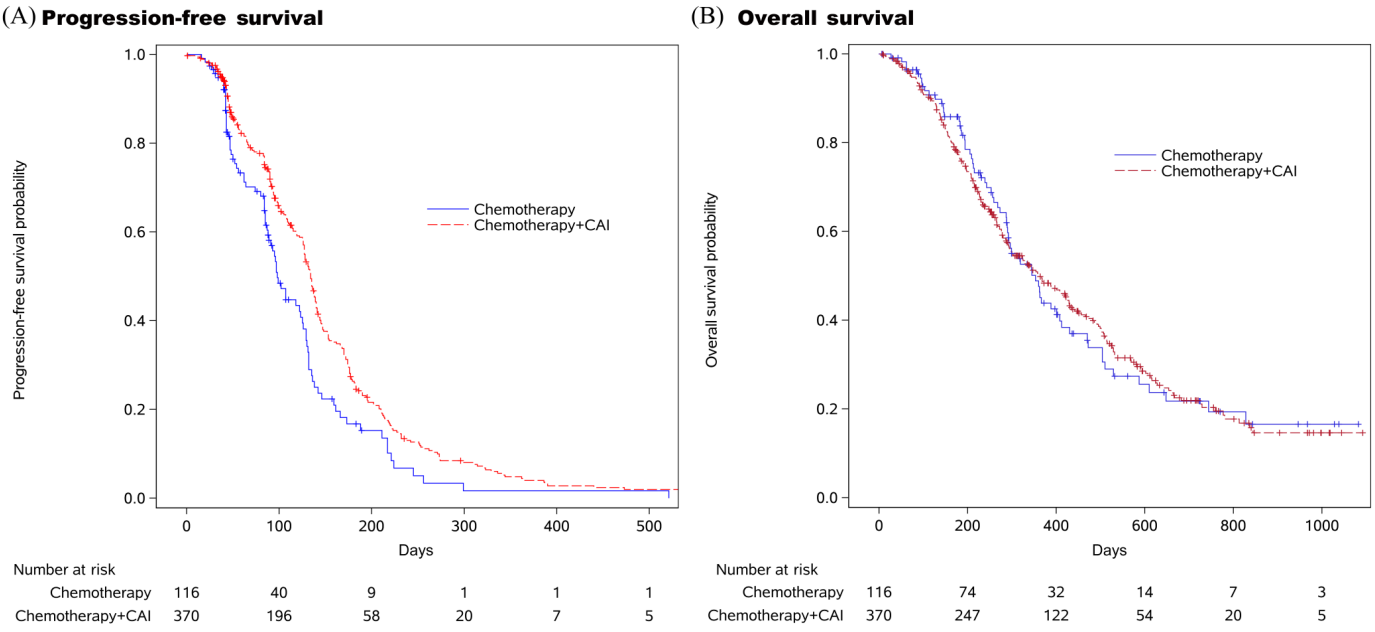

Figure 2. Kaplan–Meier estimates of progression-free survival (PFS) and overall survival (OS) in the full-analysis set. (A) The median PFS for the chemotherapy + CAI group was 134 days [95% confidence interval (CI): 127–139]; the median PFS for the chemotherapy plus placebo group was 98 days (95% CI: 88–125). The hazard ratio (HR) was 0.690 (95% CI: 0.539–0.883; $p = 0.003$). (B) The median OS for the chemotherapy + CAI group was 360 days (95% CI: 298–426); the median OS for the chemotherapy plus placebo group was 353 days (95% CI: 290–408). The HR was 1.046 (95% CI: 0797–1.373; $p = 0.744$).
CAI, carboxyamidotriazole.

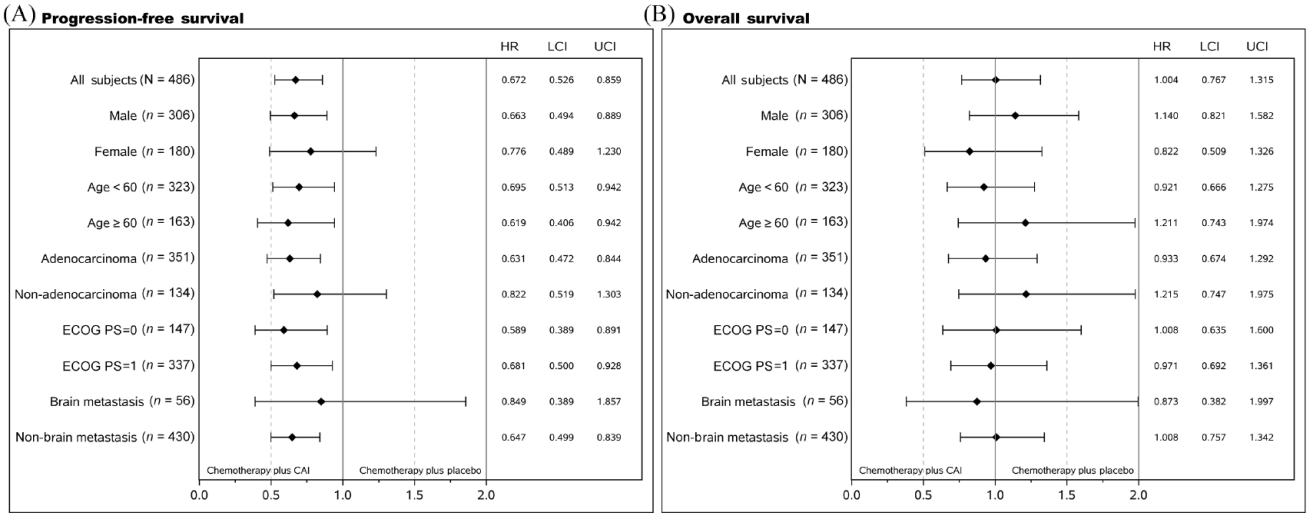

Figure 3. Subgroup analysis of progression-free survival and overall survival.
CAI, carboxyamidotriazole; ECOG, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LCI, lower confidence interval; UCI, upper confidence interval.

more commonly in the chemotherapy + CAI group than in the patients treated with the chemotherapy + placebo [256 (68.1%) *versus* 64 (55.2%); $p = 0.014$]. Leukopenia of ⩾grade 3 (43.9% *versus* 29.3%) and neutropenia ⩾grade 3 (47.3% *versus* 35.3%) were more frequently observed in patients in the chemotherapy + CAI group. The rates of chemotherapy dose-down

Table 2. Overall response percentages in chemotherapy plus CAI/placebo groups.

		Cisplatin and vinorelbine + CAI $n=370$		Cisplatin and vinorelbine $n=116$		$p1$	$p2$
		Investigator assessment	Independent review	Investigator assessment	Independent review		
ORR	FAS	34.6%	29.5%	25.0%	20.7%	0.042	0.055
	PPS	36.7%	32.2%	27.1%	22.4%	0.044	0.033
DCR	FAS	74.6%	60.3%	72.4%	59.5%	0.663	0.994
	PPS	80.2%	60.7%	77.6%	64.5%	0.461	0.672

$p1$= the p-value for investigator assessment; $p2$ = the p-value for independent review.
CAI, carboxyamidotriazole; DCR, disease control rate; FAS, full analysis set; ORR, objective response rate; PPS, per-protocol set.

were 27.1% and 17.2% in the combination group and the control group, respectively. The death rate associated with AEs in the combination group was higher than that of the control group [25 (6.6%) of 376 *versus* 2 (1.7%) of 116, $p=0.059$], although without significantly difference. The reasons of deaths in the combination group included neutropenia ($n=1$), anemia ($n=1$), intestinal obstruction ($n=1$), acute pancreatitis($n=1$), pneumonia ($n=3$), hemoptysis ($n=2$), respiratory failure ($n=7$), spinal cord injury ($n=1$), cerebral hernia ($n=1$), arterial embolism ($n=1$), septic shock ($n=2$), acute renal failure ($n=1$), multiple organ failure ($n=2$), and sudden death ($n=1$). The reasons of deaths in the control group included respiratory failure ($n=1$) and sudden death ($n=1$).

Discussion

The present clinical trial assessed the safety and efficacy of CAI + chemotherapy as the initial therapy for NSCLC; the results reveal that PFS was prolonged when CAI was included in the chemotherapy treatment regimen. The ORR was also significantly greater in the chemotherapy + CAI group of patients than in the chemotherapy group, which is consistent with the results from the phase II trial.

All subgroup analyses of PFS favored the CAI group. The ORR and DCR after therapy with cisplatin/vinorelbine were consistent with previously reported data.[7] Our findings strongly suggest that Chinese patients with advanced NSCLC will benefit from CAI treatment.

There was no significant difference in OS between the chemotherapy + CAI group and the chemotherapy group. However, as data on the post-study treatment of the two groups were not collected in this trial, we could not exclude the effect of subsequent treatment on OS.

The AEs that occurred most frequently were associated with hematological and gastrointestinal toxicity; most AEs were manageable. Compared with other randomized studies with cisplatin/vinorelbine,[7,8] hematological AEs in this trial could be attributed mostly to chemotherapy. More patients with ECOG PS 1 were enrolled in the CAI group, which may have been a cause of the higher rate of occurrence of grade ⩾3 leukopenia and neutropenia. One concern with anti-angiogenic treatment is bleeding, especially hemoptysis in lung cancer patients. In this trial, the incidence rate of hemoptysis was similar in both groups.

This trial had some limitations. First, data on driver gene alterations, for example, epidermal growth factor receptor (*EGFR*) mutations, and rearrangement of anaplastic lymphoma kinase (*ALK*), were not collected in enrolled patients, and it is possible that they may not be balanced across the two groups. This trial was designed before 2011 when *EGFR* mutations, *ALK* rearrangement, and other genetic alterations were not widely tested in China, and targeted agents were not available for some Chinese patients. Therefore, this study did not collect data on driver genetic mutation. The changes in clinical practice in the following year and the widespread use of targeted agents could have affected the OS

Table 3. Adverse events in the safety set population.

	Cisplatin and vinorelbine + CAI *n* = 376				Cisplatin and vinorelbine *n* = 116				*p*1	*p*2
AEs	**All grades, *n* (%)**	**Grades ⩾3, *n* (%)**	**Grade 4, *n* (%)**	**Grade 5, *n* (%)**	**All grades, *n* (%)**	**Grades ⩾3, *n* (%)**	**Grade 4, *n* (%)**	**Grade 5, *n* (%)**		
Any AEs	372 (98.9%)	256 (68.1%)	114 (38.3%)	25 (6.6%)	114 (98.3%)	64 (55.2%)	32 (27.6%)	2 (1.7%)	0.571	0.014
Hematological AEs										
Leukopenia	297 (79.3%)	165 (43.9%)	52 (13.8%)	1 (0.3%)	84 (72.4%)	34 (29.3%)	8 (6.9%)	0 (0.0%)	0.128	0.005
Neutropenia	241 (64.4%)	178 (47.3%)	106 (28.2%)	1 (0.3%)	68 (58.6%)	41 (35.3%)	22 (19.0%)	0 (0.0%)	0.286	0.025
Anemia	155 (41.2%)	32 (8.5%)	8 (2.1%)	1 (0.3%)	47 (40.5%)	5 (4.3%)	0 (0.0%)	0 (0.0%)	0.893	0.161
Thrombocytopenia	68 (18.1%)	7 (1.9%)	0 (0.0%)	0 (0.0%)	21 (18.1%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1.000	0.687
Non-hematological AEs										
Nausea	255 (67.8%)	16 (4.2%)	1 (0.3%)	0 (0.0%)	71 (61.2%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0.217	0.088
Anorexia	219 (58.2%)	2 (0.5%)	0 (0.0%)	0 (0.0%)	63 (54.3%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0.455	0.555
Vomiting	181 (48.1%)	16 (4.2%)	2 (0.5%)	0 (0.0%)	49 (42.2%)	2 (1.7%)	0 (0.0%)	0 (0.0%)	0.288	0.266
Fatigue	130 (34.6%)	5 (1.4%)	1 (0.3%)	0 (0.0%)	33 (28.4%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0.259	1.000
Constipation	95 (25.3%)	4 (1.1%)	0 (0.0%)	0 (0.0%)	25 (21.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.460	0.577
Fever	82 (21.8%)	3 (0.8%)	1 (0.3%)	0 (0.0%)	22 (19.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0.699	1.000
Cough	52 (13.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (11.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.533	NA
ALT elevation	26 (6.9%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	7 (6.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.835	1.000
AST elevation	22 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.085	NA
Dizziness	31 (8.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (10.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.577	NA
Headache	21 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (11.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.057	NA
Dyspnea	26 (6.9%)	5 (1.3%)	0 (0.0%)	0 (0.0%)	7 (6.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.835	0.596
Hemoptysis	24 (6.6%)	2 (0.5%)	0 (0.0%)	2 (0.5%)	6 (5.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.667	NA
Pneumonia	19 (5.1%)	8 (2.1%)	3 (0.8%)	3 (0.8%)	3 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.316	0.208

*p*1, = *p*-value for AEs of all grades between the two groups; *p*2 = *p*-value for AEs of grades ⩾3 between the two groups.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAI, carboxyamidotriazole; NA, not available.

of the patients in this trial. Driver gene alterations and the corresponding targeted therapy may have affected OS. Patients might take testing driver genetic mutations after experiencing progressive disease in this study and receive targeted therapies. It showed that targeted treatment following first-line therapy also brings significant benefits to driver genetic mutant patients.[9,10] Second, the chemotherapy regimen of cisplatin/vinorelbine used in this study is considered to be less effective and more toxic and, hence, is infrequently used. Moreover, platinum-based chemotherapy is considered to be the initial therapeutic regimen for NSCLC patients without oncogenic driver mutations.[11] Immune checkpoint inhibitors have dramatically changed therapy for NSCLC. Recently, a combination of immune checkpoint inhibitors has been approved as first-line chemotherapy.[12,13] If there would be an ideal predictive factor for immunotherapy, CAI + platinum-based chemotherapy might be an option for non-immunotherapy-responsive patients. Deciding the best choice for first-line therapy, however, warrants further investigation.

In conclusion, adding CAI to platinum-based chemotherapy prolonged PFS in the Chinese patients with NSCLC in this phase III trial. CAI + platinum-based chemotherapy could be a promising first-line treatment option to treat advanced NSCLC.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

References

1. Bray F, Ferlay J, Soerjomataram I, *et al.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68: 394–424.
2. Chen W, Zheng R, Baade PD, *et al.* Cancer statistics in China, 2015. *CA Cancer J Clin* 2016; 66: 115–132.
3. Kohn EC, Alessandro R, Spoonster J, *et al.* Angiogenesis: role of calcium-mediated signal transduction. *Proc Natl Acad Sci U S A* 1995; 92: 1307–1311.
4. Faehling M, Kroll J, Föhr KJ, *et al.* Essential role of calcium in vascular endothelial growth factor A-induced signaling: mechanism of the antiangiogenic effect of carboxyamidotriazole. *FASEB J* 2002; 16: 1805–1807.
5. Berlin J, Tutsch KD, Hutson P, *et al.* Phase I clinical and pharmacokinetic study of oral carboxyamidotriazole, a signal transduction inhibitor. *J Clin Oncol* 1997; 15: 781–789.
6. Wozniak AJ, Crowley JJ, Balcerzak SP, *et al.* Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small-cell lung cancer: a Southwest Oncology Group study. *J Clin Oncol* 1998; 16: 2459–2465.
7. Yang Y, Chang J, Huang C, *et al.* A randomised, multicentre open-label phase II study to evaluate the efficacy, tolerability and pharmacokinetics of oral vinorelbine plus cisplatin versus intravenous vinorelbine plus cisplatin in Chinese patients with chemotherapy-naive unresectable or metastatic non-small cell lung cancer. *J Thorac Dis* 2019; 11: 3347–3359.
8. Gebbia V, Galetta D, Lorusso V, *et al.* Cisplatin plus weekly vinorelbine versus cisplatin plus vinorelbine on days 1 and 8 in advanced non-small cell lung cancer: a prospective randomized phase III trial of the G.O.I.M. (Gruppo Oncologico Italia Meridionale). *Lung Cancer* 2008; 61: 369–377.
9. Shaw AT, Kim D-W, Nakagawa K, *et al.* Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med* 2013; 368: 2385–2394.
10. Zhou C, Wu YL, Chen G, *et al.* Final overall survival results from a randomised, phase

III study of erlotinib versus chemotherapy as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer (OPTIMAL, CTONG-0802). *Ann Oncol* 2015; 26: 1877–1883.

11. Dietrich MF and Gerber DE. Chemotherapy for advanced non-small cell lung cancer. *Cancer Treat Res* 2016; 170: 119–149.
12. Socinski MA, Jotte RM, Cappuzzo F, *et al.* Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med* 2018; 378: 2288–2301.
13. Reck M. Pembrolizumab as first-line therapy for metastatic non-small-cell lung cancer. *Immunotherapy* 2018; 10: 93–105.