


ORIGINAL ARTICLE

Efficacy and safety of rh-endostatin (Endostar) combined with pemetrexed/cisplatin followed by rh-endostatin plus pemetrexed maintenance in non-small cell lung cancer: A retrospective comparison with standard chemotherapy

Shengyu Zhou¹, Lijie Zuo², Xiaohui He¹, Jinping Pi², Jun Jin² & Yuankai Shi¹ 

¹ Department of Medical Oncology, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, National Cancer Center/ National Clinical Research Center for Cancer/ Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

² Department of Medical Oncology, Beijing Sanhuan Cancer Hospital, Beijing, China

Keywords

Anti-angiogenesis; maintenance; non-small cell lung cancer; rh-endostatin.

Correspondence

Yuankai Shi, Department of Medical Oncology, Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College; Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, No.17 Panjiayuan Nanli, Chaoyang District, Beijing 100021, China.
Tel: +86 10 8778 8293
Fax: +86 10 8777 8740
Email: syuankai@cicams.ac.cn

Received: 4 May 2018;

Accepted: 4 July 2018.

doi: 10.1111/1759-7714.12827

Thoracic Cancer **9** (2018) 1354–1360

Abstract

Background: Recombinant human endostatin (rh-endostatin) plus standard chemotherapy in advanced non-small cell lung cancer (NSCLC) patients has shown improved efficacy; however, it is unclear whether it is effective and safe when added to pemetrexed/cisplatin and used as maintenance therapy.

Methods: We retrospectively evaluated the data of untreated NSCLC patients administered rh-endostatin plus pemetrexed/cisplatin or pemetrexed/cisplatin. The primary endpoint was progression-free survival (PFS).

Results: Fifty-six and 39 patients received rh-endostatin plus pemetrexed/cisplatin and pemetrexed/cisplatin, and 34 and 29 underwent maintenance treatment, respectively. The median PFS was 10 months (95% confidence interval [CI] 5.85–14.15) in the rh-endostatin and 8.2 months (4.04–12.36) in the chemotherapy group, but the difference was not statistically significant ($P = 0.13$). In patients administered maintenance treatment, rh-endostatin plus pemetrexed was associated with prolonged PFS compared to single-agent pemetrexed when PFS was calculated from first dosing (13.7 [9.41–17.99] vs. 8.2 [4.16–12.24]; $P = 0.032$); however, PFS did not differ between the groups (hazard ratio 0.618; 95% CI 0.368–1.038; $P = 0.069$) after adjusting for clinical factors. No difference was observed in the objective response rate between the groups (48.2% vs. 38.5%; $P = 0.346$), with the exception of men (62.1% vs. 33.3%; $P = 0.032$) or in the incidence of drug-related or grade 3–4 adverse events.

Conclusion: In previously untreated, advanced-stage NSCLC patients, first-line treatment with pemetrexed/cisplatin plus rh-endostatin did not prolong PFS or overall survival when compared to pemetrexed/cisplatin, but a trend of improved PFS was observed in patients administered maintenance rh-endostatin plus pemetrexed.

Introduction

Lung cancer remains a global health burden as the most common cancer and the leading cause of cancer-related death, with an estimated 224 390 new cases diagnosed and 158 080 deaths per year in the United States, and an estimated 733 300 new cases diagnosed and 610 200 deaths per year in China.^{1,2} Non-small cell lung cancers (NSCLCs)

comprise approximately 75–80% of lung cancers, which mainly consist of adenocarcinoma and squamous cell carcinoma. A platinum-based, doublet chemotherapy regimen has been established as standard treatment. Recently, the introduction of pemetrexed has been found to be more effective than gemcitabine as a component of first-line treatment for patients with non-squamous carcinoma, particularly adenocarcinoma (median 12.6 vs. 10.9 months).^{3,4}

Angiogenesis plays a key role in the development of cancer.^{5–7} Several agents that target vascular endothelial growth factor receptor (VEGFR) have been approved for the treatment of NSCLC. In a first-line setting, the addition of bevacizumab to chemotherapy significantly improved the clinical outcome with overall survival (OS) of 12.3 months in a Western population and 24.3 months in a Chinese population.^{8,9} However, increased toxicity was observed during bevacizumab treatment and class-related adverse events including hypertension, proteinuria, febrile neutropenia and life-threatening pulmonary hemorrhage, particularly in squamous NSCLC.^{8–10} The approval of ramucirumab and nintedanib has provided new options for NSCLC patients who progressed on initial treatment, with improved OS and tolerable toxicity when combined with standard second-line chemotherapy.^{11–13} More recently, anlotinib, a novel multitarget tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor 2 (VEGFR2), platelet-derived growth factor receptor- β (PDGFR β), and fibroblast growth factor receptor-1 (FGFR1), has provided significant progression-free survival (PFS) and OS benefits as third-line treatment.¹⁴

Endostatin is a C-terminal fragment type of XVIII collagen that directly targets new capillary endothelial cells around a tumor. Using a yeast expression system, recombinant human endostatin (rh-endostatin, Endostar) has been developed. Rh-endostatin displays an increased tumor response when added to chemotherapy in NSCLC patients,¹⁵ with cardiac adverse events such as dose limited toxicity, and other mild drug-related adverse events including fever, rash, dizziness, headache, diarrhea, fatigue, palpitation, and chest discomfort.¹⁶ A randomized, double-blind, phase 3 study further confirmed these results, finding that rh-endostatin plus vinorelbine/cisplatin was associated with significantly prolonged time to progression (6.3 vs. 3.6 months; $P = 0.0000$).¹⁷ Based on the results of such studies, rh-endostatin was approved by the Chinese Food and Drug Administration in 2006 for the treatment of advanced NSCLC. However, no study has evaluated the efficacy and safety of rh-endostatin when added to pemetrexed/cisplatin, and its role as maintenance therapy. Herein, we present a retrospective comparison of efficacy and safety between rh-endostatin plus pemetrexed/cisplatin and pemetrexed/cisplatin in our department at a single center.

Methods

Patients

Retrospective analysis of data collected between November 2013 and January 2017 from a lung cancer database at the

Cancer Hospital and Institute, Chinese Academy of Medical Sciences (CAMS, Beijing, China) was conducted. The eligibility criteria were as follows: pathologically or cytologically confirmed non-squamous lung cancer; stage IIIB or IV disease (defined by American Joint Committee on Cancer Tumor Node Metastasis [TNM] staging system version 7.0); no previous systemic anticancer treatment; Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1; at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1); and adequate bone marrow, hepatic, and renal functions. The primary endpoint was PFS, while secondary endpoints were objective response rate (ORR), disease control rate (DCR), OS, and safety.

This study was conducted in compliance with the Declaration of Helsinki and applicable local regulations. The hospital institutional review board approved the study protocol and written informed consent was obtained from each participant.

Treatment

Patients were administered pemetrexed 500 mg/m² and cisplatin 75 mg/m² on day 1 by intravenous infusion (chemotherapy group) plus rh-endostatin 7.5 mg/m² on days 1–14 (rh-endostatin group), every three weeks. Patients who experienced a tumor response or achieved stable disease (SD) after four to six cycles of treatment continued to receive maintenance rh-endostatin plus pemetrexed or single-agent pemetrexed until unacceptable adverse events or disease progression. Dose reduction or interruption of study drugs was allowed according to label recommendations. Clinical data was recorded at baseline, including age, gender, PS, biomarker analysis, disease stage, pathological subtype, and smoking status. Imaging evaluation by computed tomography (CT) scan was conducted every six to eight weeks according to clinical practice. Safety was monitored during the study period.

Treatment evaluation

All patients underwent a CT scan at the start of chemotherapy and then every six to eight weeks to evaluate the tumor response using RECIST v1.1. Safety assessments included physical examination, documentation of adverse events, electrocardiogram, and laboratory tests. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Tumor response was assessed every six to eight weeks using RECIST v1.1. The response-evaluable population was defined as patients who received at least two cycles of treatment regimens with a measurable lesion.

Table 1 Patient characteristics

Characteristic	Chemotherapy + Endostar (<i>n</i> = 56)	Chemotherapy (<i>n</i> = 39)	<i>P</i>
Age (year, mean ± SD)	54.07 ± 9.48	57.41 ± 11.09	0.119
Gender			
Female	27 (48.2)	12 (30.8)	0.089
Male	29 (51.8)	27 (69.2)	
Disease stage			
IIIb	7 (12.5)	2 (5.1)	0.395
IV	49 (87.5)	37 (94.9)	
ECOG PS score			
0–1	56 (100.0)	38 (97.4)	0.411
2	0 (0.0)	1 (2.6)	
Smoking status			
Yes	20 (35.7)	20 (51.3)	0.131
No	36 (64.3)	19 (48.7)	
Presence of distinct metastasis			
Yes	55 (98.2)	39 (100.0)	1.000
No	1 (1.8)	0 (0.0)	
Biomarker status			
Unknown	20 (35.7)	19 (48.7)	0.402
Wild	17 (30.4)	10 (25.6)	
<i>EGFR</i> 19 Del	7 (12.5)	1 (2.6)	
<i>EGFR</i> 21 L858R	8 (14.3)	4 (10.3)	
Other <i>EGFR</i> mutation	1 (1)	1 (2.6)	
<i>ALK</i> rearrangement	3 (5.4)	4 (10.3)	

Del, deletion; ECOG PS, Eastern Cooperative Oncology Group performance score; SD, standard deviation.

Statistical analysis

The two groups were compared regarding basic clinical characteristics; efficacy outcomes in terms of PFS, ORR, DCR, and OS; and safety. PFS was measured as the interval between the date of first dosing and the date of disease progression or intolerable toxicity. ORR was defined as the percentage of patients who had a tumor response (complete response [CR] and/or partial response [PR]). DCR was defined as the percentage of patients who had CR and/or PR and SD. OS was measured as the interval between the date of first dosing and the date of death or last follow-up. Survival analysis was conducted using the Kaplan–Meier method, and the differences according to treatment were compared using the log-rank test. A Cox regression model was used for PFS and OS multivariate analyses to test the effect of independent variables such as gender, histology, disease stage, smoking status, and duration of treatment. Statistical analyses were performed using SPSS version 20 (IBM Corp., Armonk, NY, USA). A *P* value < 0.05 was considered significant.

Results

Patient characteristics

From November 2013 to January 2017, 95 patients met the inclusion criteria and were included in the analysis. A total of 39 patients received pemetrexed/cisplatin and 56 received pemetrexed/cisplatin plus rh-endostatin. No significant

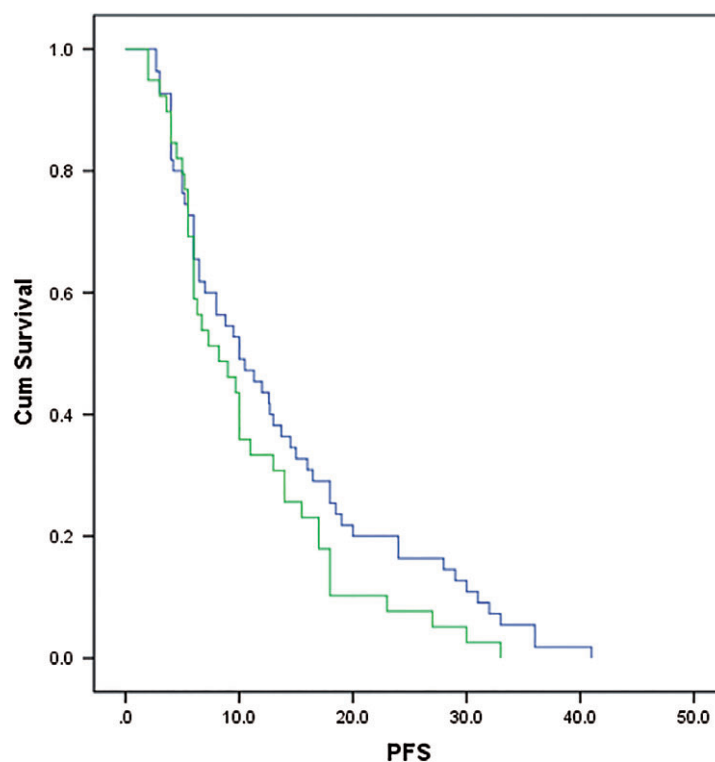
differences were observed in treatment cycles between the groups (Table S1).

Baseline characteristics and demographics were similar between the groups (Table 1). The mean ages were 54.07 and 57.41 years in the rh-endostatin and chemotherapy groups, respectively. There were more male patients in the chemotherapy group than in the rh-endostatin group (69.2% vs. 51.8%), but the difference was not statistically significant. All patients had lung adenocarcinoma, with the majority of patients in both arms with stage IV disease and good performance (PS score 0–1). A total of 51.3% patients in the chemotherapy group and 35.7% in the rh-endostatin group were smokers. Test results of biomarkers in 56 patients showed *EGFR* mutations or *ALK* rearrangement. Biomarker status was also similar between the groups (Table 1).

Efficacy

All patients experienced disease progression (*n* = 90) or died (*n* = 5). Figure 1 shows the Kaplan–Meier curve for overall PFS; the median PFS was 10 months (95% confidence interval [CI] 5.85–14.15) in the rh-endostatin group and 8.2 months (4.04–12.36) in the chemotherapy group, but the difference was not statistically significant (*P* = 0.13) (Fig 1, Table 2). After adjusting for clinical factors (age, gender, disease stage, and smoking status), PFS did not differ in the overall study population between the rh-endostatin and chemotherapy groups (hazard ratio

Figure 1 Kaplan–Meier curves for progression-free survival (PFS). (—) Rh-endostatin plus chemotherapy with or without maintenance therapy and (—) chemotherapy with or without maintenance therapy.



[HR] 0.788, 95% CI 0.510–1.216; $P = 0.282$). The influence of the addition of maintenance on PFS is summarized in Table S2. No statistically significant difference in PFS was found between the groups in subgroup analysis, including gender, disease stage, or smoking status (Table S3). We also explored PFS in patients with identified tumor driven mutations, which was 7 months (95%CI 4.43–9.57), 9.5 months (4.24–14.76), and 17 months (15.72–18.28) for patients with *EGFR* 19 Del, *EGFR* 21 L858R, and *ALK* rearrangement, respectively.

All patients had measurable lesions. The ORR and DCR were 48.2% and 98.2% in the rh-endostatin group, and

38.5% and 100% in the chemotherapy group, respectively, without statistical difference ($P = 0.346$ and $P = 1.000$ for ORR and DCR, respectively) (Table 2). Similar response rates in women, non-smokers, patients with stage IIIB or IV disease, and those with ECOG PS 0-1 were observed between the groups (Table S2). Of note, men and smokers showed a higher response rate in the rh-endostatin than in the chemotherapy group (Table S4).

At data cut-off (30 September 2017), more than half (53.7%) of the patients were still alive. The median OS was 36 months (95% CI 27.25–44.75) in the rh-endostatin group and 29 months (95% CI 25.1–32.9) in the chemotherapy group, without significant difference ($P = 0.775$) (Fig 2, Table 2). The influence of the addition of maintenance on OS is summarized in Table S2.

Table 2 Efficacy of pemetrexed/cisplatin alone or with rh-endostatin for advanced non-small cell lung cancer

Efficacy parameters	Pemetrexed/ cisplatin ($n = 39$)	Rh-endostatin + pemetrexed/ cisplatin ($n = 56$)	P
PFS (95% CI), months	8.2 (4.04–12.36)	10 (5.85–14.15)	0.13
OS (95% CI), months	36 (27.25–44.75)	29 (25.1–32.9)	0.775
CR	0	0	—
PR	27	15	—
SD	28	24	—
ORR	48.2%	38.5%	0.346
DCR	98.2%	100%	1.000

CI, confidence interval; CR, complete response; DCR, disease control rate; PFS, progression-free survival; PR, partial response; ORR, overall response rate; OS, overall survival.

Safety

The overall incidence of drug-related adverse events is listed in Table 3. There was no difference between the groups with respect to the frequency of overall drug-related adverse events (rh-endostatin 96.45 vs. chemotherapy 100%; $P = 0.511$) or grade 3 or 4 drug-related adverse events (rh-endostatin 19.6% vs. chemotherapy 23.1%; $P = 0.686$). Hematological toxicity, elevated transaminase, and gastric toxicity were the most common drug-related adverse events, and hematological toxicity was the major grade 3–4 drug-related adverse event in both groups.

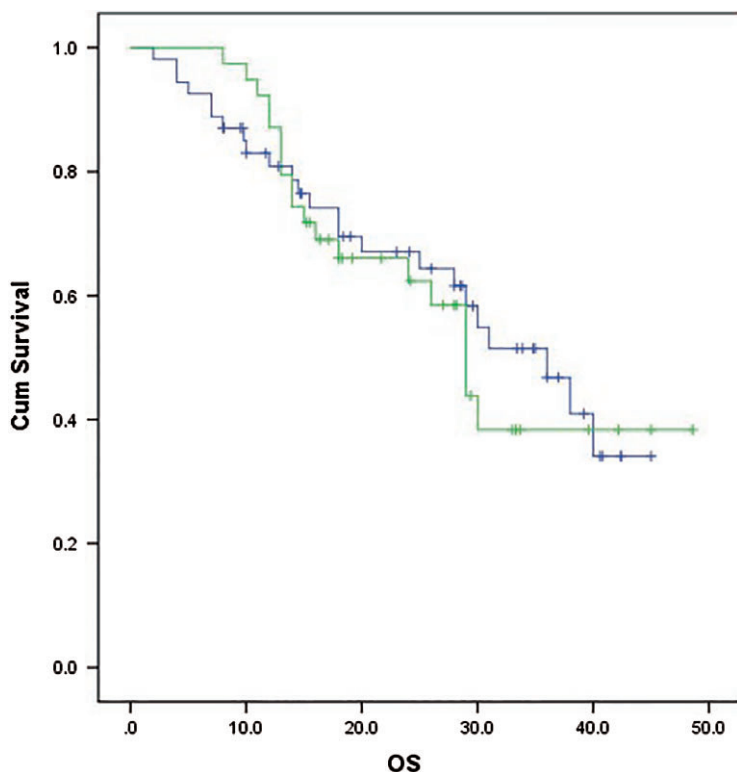


Figure 2 Kaplan–Meier curves for overall survival (OS). (—) Rh-endostatin plus chemotherapy with or without maintenance therapy, (—) chemotherapy with or without maintenance therapy, (—) Rh-endostatin plus chemotherapy with or without maintenance therapy-censored, and (—) chemotherapy with or without maintenance therapy-censored.

Discussion

Rh-endostatin is a novel recombinant human endostatin expressed and purified in *Escherichia coli*. It was approved in 2006 as a component combined with vinorelbine/cisplatin for the treatment of NSCLC. Previous studies have evaluated the efficacy and safety of the combination of rh-endostatin and platinum-based doublet chemotherapy;

however, limited data is available on the combination of rh-endostatin and pemetrexed-based first-line and maintenance therapy.^{17–20}

Despite the lack of significant differences, our results showed a trend of prolonged PFS and OS in the overall population, regardless of the addition of maintenance. Rh-endostatin plus pemetrexed/cisplatin followed by rh-endostatin plus pemetrexed maintenance significantly

Table 3 Drug-related adverse events (n/%)

Adverse event	All			Grade 3–4		
	Endostar + pemetrexed/ cisplatin (n = 56)	Pemetrexed/ cisplatin (n = 39)	P	Endostar + pemetrexed/ cisplatin (n = 56)	Pemetrexed/ cisplatin (n = 39)	P
Any	54 (96.4)	39 (100.0)	0.511	11 (19.6)	9 (23.1)	0.686
Hematological toxicity						
Myelosuppression	48 (85.7)	37 (94.9)	0.275	9 (16.1)	6 (15.4)	1.000
Thrombocytopenia	8 (14.3)	3 (7.7)	0.508	2 (3.6)	0 (0.0)	0.511
Hemoglobin reduction	24 (42.9)	20 (51.3)	0.418	1 (1.8)	2 (5.1)	0.749
Non-hematological toxicity						
Increased transaminase	13 (23.2)	9 (23.1)	0.988	—	—	—
Cardiotoxicity	1 (1.8)	1 (2.6)	1.000	1 (1.8)	0 (0.0)	1.000
Renal dysfunction	2 (3.6)	4 (10.3)	0.374	—	—	—
Pigmentation	1 (1.8)	0 (0.0)	1.000	—	—	—
Rash	0 (0.0)	1 (2.6)	0.411	—	—	—
Nausea	50 (89.3)	30 (76.9)	0.104	2 (3.6)	2 (5.1)	1.000
Vomiting	48 (85.7)	29 (74.4)	0.165	2 (3.6)	2 (5.1)	1.000
Fatigue	3 (5.4)	1 (2.6)	0.883	—	—	—
Neurotoxicity	0 (0.0)	1 (2.6)	0.411	—	—	—

improved the PFS in treatment-naïve patients with lung adenocarcinoma; however, after adjusting for clinical factors including age, gender, disease stage, and smoking status, the difference was not statistically significant. Moreover, the addition of rh-endostatin to pemetrexed/cisplatin was well tolerated without increased toxicity.

Several randomized studies have been performed to compare efficacy and safety between rh-endostatin plus platinum-based doublet chemotherapy and chemotherapy alone. The addition of rh-endostatin was associated with prolonged time-to-progression when compared to chemotherapy alone (5.7–6.6 vs. 3.2–3.7 months) for the treatment of NSCLC patients, regardless of histological subtypes or the presence of previous treatment.^{17–19} On the contrary, no PFS benefit was shown in a multicenter phase 2 study in which 126 previously untreated advanced-stage NSCLC patients were enrolled and randomized to receive rh-endostatin plus paclitaxel/carboplatin or paclitaxel/carboplatin.²⁰ Despite a numerical prolongation of survival, there was no statistically significant difference in PFS (7.1 vs. 6.3 months, respectively; $P = 0.522$) or OS (17.6 vs. 15.8 months, respectively; $P = 0.696$) between the groups. However, the study designs of the abovementioned studies did not allow us to ascertain any benefit of the combination of rh-endostatin and pemetrexed-based first-line chemotherapy and the continued administration of rh-endostatin after the end of chemotherapy. Pemetrexed-based first-line and maintenance chemotherapy is a relatively modern standard regimen for treatment-naïve, advanced-stage NSCLC patients, especially for those with the non-squamous subtype, with a median PFS of 6.9–7.7 months.^{21,22} In the current study, the median PFS for patients receiving only first-line treatment was five months in each group, thus the addition of rh-endostatin to pemetrexed/cisplatin did not improve PFS ($P = 0.81$) during the induction period. For patients receiving maintenance treatment, rh-endostatin plus pemetrexed significantly improved PFS. Although our results were not statistically significant different because of the small patient sample, it should be noted that patients in the rh-endostatin group tended to be younger, female, at stage IIIB disease, and non-smokers, which could have favorably affected efficacy results. Further analysis using a Cox regression model found borderline PFS benefits in patients treated with maintenance rh-endostatin plus pemetrexed.

Despite the lack of significant difference, the Kaplan–Meier plots show a divergent trend in OS in patients receiving maintenance therapy. It is possible that no OS differences were observed in this study because the data were premature and we had a limited sample size. In this study, the efficacy of rh-endostatin, including survival benefit and tumor response did not differ in subgroups such as gender, disease stage, and smoking status, with the exception of tumor response in men. The lack of an association between

clinical characteristics and efficacy is probably related to the limited number of patients in each subgroup.

Regarding safety, the adverse event profile of rh-endostatin in this study was consistent with previous studies, without unexpected safety concerns.^{15–20} Adding rh-endostatin to pemetrexed/cisplatin did not increase the incidence of drug-related or grade 3/4 adverse events, suggesting that toxicity is related to chemotherapy. No class-related side effects of antiangiogenic therapy, such as hemorrhage, hypertension, or venous thromboembolism were observed.²³ The main drug-related adverse events of rh-endostatin plus pemetrexed/cisplatin comprise hematological, gastrointestinal, and reversible increases in liver enzymes, which compare with the incidence of adverse events of other antiangiogenic therapies²³ and are consistent with that reported for rh-endostatin in other clinical studies^{15–20}

Our study has some limitations. The small number of subjects limited statistical validity. The retrospective nature of the study introduced selection bias, which resulted in an unbalanced population. Finally, the short follow-up period meant that only half of the OS events were observed. These limitations should be considered when interpreting the results of this study.

In summary, to the best of our knowledge, this is the first study to evaluate the benefit of the continued administration of rh-endostatin after induction chemotherapy. The combination of rh-endostatin and pemetrexed/cisplatin was not associated with a significant improvement in PFS or OS in patients with treatment-naïve advanced-stage lung adenocarcinoma, regardless of the addition of maintenance. There are several possible explanations for these negative results, including the retrospective nature of the study and limited sample size. The unbalanced treatment exposure between the groups should also be noted, as fewer patients received maintenance treatment in the rh-endostatin + pemetrexed/cisplatin group. Prospective randomized study is warranted to further investigate the clinical benefits of rh-endostatin.

Acknowledgment

The authors would like to acknowledge support from the China International Medical Foundation (CIMF-F-H001-283).

Disclosure

No authors report any conflict of interest.

References

- 1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin* 2017; **67**: 7–30.

- 2 Chen W, Zheng R, Baade PD *et al.* Cancer statistics in China, 2015. *CA Cancer J Clin* 2016; **66**: 115–32.
- 3 Scagliotti GV, Parikh P, von Pawel J *et al.* Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 2008; **26**: 3543–51.
- 4 Syrigos KN, Vansteenkiste J, Parikh P *et al.* Prognostic and predictive factors in a randomized phase III trial comparing cisplatin-pemetrexed versus cisplatin-gemcitabine in advanced non-small-cell lung cancer. *Ann Oncol* 2010; **21**: 556–61.
- 5 Folkman J. Role of angiogenesis in tumor growth and metastasis. *Semin Oncol* 2002; **29**(6 Suppl 16): 15–8.
- 6 Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell* 2000; **100**: 57–70.
- 7 Skobe M, Rockwell P, Goldstein N, Vosseler S, Fusenig NE. Halting angiogenesis suppresses carcinoma cell invasion. *Nat Med* 1997; **3**: 1222–7.
- 8 Sandler A, Gray R, Perry MC *et al.* Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. (Published erratum appears in *N Engl J Med* 2007; 356: 318.). *N Engl J Med* 2006; **355**: 2542–50.
- 9 Zhou C, Wu YL, Chen G *et al.* BEYOND: A randomized, double-blind, placebo-controlled, multicenter, phase III study of first-line carboplatin/paclitaxel plus bevacizumab or placebo in Chinese patients with advanced or recurrent nonsquamous non-small-cell lung cancer. *J Clin Oncol* 2015; **33**: 2197–204.
- 10 Johnson DH, Fehrenbacher L, Novotny WF *et al.* Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 2004; **22**: 2184–91.
- 11 Garon EB, Ciuleanu TE, Arrieta O *et al.* Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): A multicentre, double-blind, randomised phase 3 trial. *Lancet* 2014; **384**: 665–73.
- 12 Reck M, Kaiser R, Mellemaard A *et al.* Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): A phase 3, double-blind, randomised controlled trial. *Lancet Oncol* 2014; **15**: 143–55.
- 13 Hanna NH, Kaiser R, Sullivan RN *et al.* Nintedanib plus pemetrexed versus placebo plus pemetrexed in patients with relapsed or refractory, advanced non-small cell lung cancer (LUME-Lung 2): A randomized, double-blind, phase III trial. *Lung Cancer* 2016; **102**: 65–73.
- 14 Han B, Li K, Zhao Y *et al.* Anlotinib as a third-line therapy in patients with refractory advanced non-small-cell lung cancer: A multicentre, randomised phase II trial (ALTER0302). *Br J Cancer* 2018; **118**: 654–61.
- 15 Yang L, Wang JW, Cui CX *et al.* [Rh-endostatin (YH-16) in combination with vinorelbine and cisplatin for advanced non-small cell lung cancer: A multicenter phase II trial.]. *Chin J New Drugs* 2005; **14**: 204–7 (In Chinese).
- 16 Yang L, Wang JW, Tang ZM. [A phase I clinical trial for recombinant human endostatin.]. *Chin J New Drugs* 2004; **13**: 548–53 (In Chinese).
- 17 Wang J, Sun Y, Liu Y *et al.* [Results of randomized, multicenter, double-blind phase III trial of rh-endostatin (YH-16) in treatment of advanced non-small cell lung cancer patients.]. *Zhongguo Fei Ai Za Zhi* 2005; **8**: 283–90 (In Chinese).
- 18 Sun Y, Wang JW, Liu YY *et al.* Long-term results of a randomized, double-blind, and placebo-controlled phase III trial: Endostar (rh-endostatin) versus placebo in combination with vinorelbine and cisplatin in advanced non-small cell lung cancer. *Thorac Cancer* 2013; **4**: 440–8.
- 19 Shi GY, Su YH. [The clinical observation of Endostar injection combined with GP regimen in advanced non-small cell lung cancer.]. *J Med Forum* 2009; **30**: 53–4. (In Chinese).
- 20 Han BH, Xiu QY, Wang HM *et al.* A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy of paclitaxel-carboplatin alone or with endostar for advanced non-small cell lung cancer. *J Thorac Oncol* 2011; **6**: 1104–9.
- 21 Ciuleanu T, Brodowicz T, Zielinski C *et al.* Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: A randomised, double-blind, phase 3 study. *Lancet* 2009; **374**: 1432–40.
- 22 Paz-Ares L, de Marinis F, Dediu M *et al.* Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): A double-blind, phase 3, randomised controlled trial. *Lancet Oncol* 2012; **13**: 247–55.
- 23 Gadgeel SM. Safety profile and tolerability of antiangiogenic agents in non-small-cell lung cancer. *Clin Lung Cancer* 2012; **13**: 96–106.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1. Treatment cycles of the two groups

Table S2. Efficacy of pemetrexed/cisplatin alone or with rh-endostatin for advanced non-small cell lung cancer according to the presence of maintenance therapy

Table S3. Subgroup analysis of progression-free survival by clinical characteristics

Table S4. Subgroup analysis of response rate by clinical characteristics