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

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Introduction: Recombinant human endostatin is a novel inhibitor of tumor angiogenesis that acts specifically on neovascular endothelial cells. Studies have shown that endostar plus vinorelbine-cisplatin chemotherapy could improve objective response rates (ORR) and overall survival (OS) of advanced non-small cell lung cancer (NSCLC) patients. This study is to explore the clinical efficacy of endostar plus paclitaxel-carboplatin (TC) in advanced NSCLC patients.

Methods: A phase II, multicenter, randomized, double-blind, placebo-controlled study was carried out. Patients were randomly assigned to the treatment (TC + endostar) or the control group (TC + placebo). The efficacy was evaluated at the end of each cycle. Follow-up continued until disease progression or death.

Results: A total of 126 patients were enrolled, of whom 122 were evaluable, with 61 in each group. ORR was 39.3% in the treatment group versus 23.0% in the control group ($p = 0.078$), and the disease control rate was 90.2% versus 67.2% ($p = 0.004$), respectively. The median progression-free survival (PFS) was 7.1 versus 6.3 months ($p = 0.522$) in the treatment and control groups, the 24-week rate of PFS was 78% versus 59% ($p = 0.017$), and the median OS was 17.6 versus 15.8 months ($p = 0.696$), respectively. There were no significant differences, either in the incidence of adverse events or serious adverse events, between the two groups.

Conclusions: In previously untreated, advanced NSCLC patients, treatment with TC plus endostar seemed to improve ORR. However, the differences in PFS or OS between the two groups were not statistically significant. Treatment with TC plus endostar exhibited a good safety profile.

Key Words: Recombinant human endostatin, Endostar, Paclitaxel, Carboplatin, NSCLC.

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Lung cancer is one of the most malignant tumors, representing a significant threat to human health. In China, about 500,000 new patients are diagnosed each year, with the number expected to be 1 million in 2025.[1] The majority of non-small cell lung cancer (NSCLC) patients are at unresectable stage IIIB or IV disease when diagnosed. For these patients, chemotherapy is the primary therapeutic option. However, the response rate of chemotherapy for advanced NSCLC is only 30% and has reached a plateau.[2] Thus, there is an urgent need to find a new strategy for NSCLC therapy.

In recent years, the clinical application of antiangiogenic therapy has brought promise for the treatment of NSCLC and has become an important addition in the treatment of tumor invasion and metastasis. It has been proposed that tumor growth is dependent on neoangiogenesis, and this has been confirmed by basic and clinical research.[3] In 1997, a peptide was isolated from mouse hemangioendothelioma, with a molecular weight of about 20 kD.[4] By amino acid sequencing, this peptide was confirmed to be a C-terminal fragment of type XVIII collagen; it had antiangiogenic effects and was named endostatin. The same researchers then treated mice bearing Lewis lung cancer with murine endostatin and found that the size of primary tumors was decreased to less than 1 mm^3 and that the tumor cells entered quiescence.[5]

The direct target of endostatin was new capillary endothelial cells around the tumor. Furthermore and impor-

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tantly, it did not exhibit toxic effects in normal cells. More recent preclinical studies have indicated that endostatin is one of the most effective angiogenesis inhibitors currently known.[6,7] Endostatin specifically acts on neovascular endothelial cells, inhibits cell migration, and induce cell apoptosis, thus playing a major antiangiogenic role by acting on tumor-associated neovascular endothelial cells. In addition, endostatin seems to play a multitarget antiangiogenic role by regulating expression of vascular endothelial growth factor and activity of proteolytic enzymes, indirectly leading to the quiescence or reduction of tumors. Recombinant human endostatin (rh-endostatin) has been produced by the Entremed Company using a yeast expression system. Phase I and II clinical trials were conducted in September 1999 and October 2002, respectively.[8]

In 2005, China State Food and Drug Administration licensed endostar plus vinorelbine-cisplatin (NP) to treat advanced NSCLC as a first-line therapy. The decision was mainly based on a phase III study,[9] which was a randomized, double-blind, multicenter trial comparing treatment with NP plus endostar and NP alone, first line, in advanced NSCLC patients. The objective response rates (ORR) in the NP plus endostar group ($N = 322$) and the NP alone group ($N = 164$) were 35.4% and 19.5% ($p < 0.01$), the median time to progression 6.3 and 3.6 months ($p < 0.001$), the median survival time 14.8 and 9.9 months ($p < 0.001$), and the 1-year survival rate 62.7% and 31.5% ($p < 0.001$), respectively. The incidence and severity of adverse events were comparable between the two groups. These results indicated that endostar exhibited synergistic effects with NP. Endostar not only increased the response rate but also significantly improved the overall survival (OS) without increasing the adverse effects.

Paclitaxel-carboplatin (TC) is the first-line treatment for NSCLC approved by the US Food and Drug Administration. We assumed that this TC chemotherapy plus endostar could also improve the clinical efficacy in advanced NSCLC patients. Therefore, we conducted an exploratory, randomized, double-blind, placebo-controlled, multicenter trial to compare the clinical efficacy of endostar plus TC and TC alone in advanced NSCLC patients (ClinicalTrials.gov Identifier: NCT00708812).

MATERIALS AND METHODS

Study Design

This study was an exploratory, randomized, double-blind, placebo-controlled, multicenter phase II trial. The primary end point was progression-free survival (PFS); the secondary end points included ORR, OS, and safety.

Patients eligible for this study needed to meet the following inclusion criteria: histologically or cytologically confirmed, previously untreated stage IIIB or IV NSCLC; Eastern Cooperative Oncology Group performance status of 0 to 2; and measurable lung lesions (according to RECIST criteria[10]). Exclusion criteria were as follows: symptomatic brain metastases; bone metastases and related complications or cognitive disabilities; bleeding diathesis or coagulopathy; major organ dysfunction or other serious complications; pregnant or lactating women; and patients who participated in other clinical trials within 4 weeks before the study.

After signing informed consent, patients received a cycle of TC chemotherapy. The 126 patients who were evaluated as having stable disease or better, and met the other inclusion criteria, were randomly assigned to the treatment group (TC + endostar) or the control group (TC + placebo). Patients subsequently received another three cycles of treatment in both groups. Efficacy was evaluated at the end of each cycle, and had to be confirmed if it was a stable disease (SD) or better. Follow-up continued after the end of treatment and was conducted every 2 months until disease progression or death. Safety was evaluated based on adverse events, vital signs, or laboratory changes. Toxicity and adverse events were classified according to Common Toxicity Criteria (CTC, version 2) of the National Cancer Institute.

Blinding and Quality Control

This was a double-blind study. Random codes were generated via a randomized method by an independent biostatistician. Based on these random codes, agents were numbered by the staff who was not involved in this trial. Patients were enrolled in a competitive program, and agents were distributed in sequence. Two-step unblinding was used.

During the trial, clinical monitors visited the hospitals periodically to ensure that all regulations were being followed. Data management was performed by the Department of Epidemiology and Health Statistics, Nanjing Medical University. To ensure the accuracy of data entry, the data were independently input twice and then proofread.

Informed Consent and Ethics

The clinical trial was strictly in compliance with the ethical guidelines for human medical research in the Declaration of Helsinki. The research program was in line with the standards of Good Clinical Practice proposed by the State Food and Drug Administration. The clinical trial was approved by the Medical Ethics Committees of the head unit, Shanghai Chest Hospital, and all other participating units (Ethics Approval No.: 2007-11 and 2007-24).

Before joining the trial, all patients were informed of the details by the researchers and given sufficient time to consider their options. They voluntarily agreed to participate in the trial and signed the informed consent form.

Treatment Schemes

Endostar (injection of recombinant human endostatin) was a product of Shandong Simcere-Medgenn Bio-Pharmaceuticals (National Medicine Permit No.: S20050088). Placebo was also produced by this company. Paclitaxel and carboplatin were obtained from the Bristol-Myers Squibb Company.

Paclitaxel (175 mg/m^2) and carboplatin (AUC = 5), were administered (intravenously) on the first day of each 21-day cycle. Patients also received endostar (7.5 mg/m^2/d) or placebo on the 8 to 21 days of every cycle. Endostar was dissolved in 250 ml normal saline and administered by intravenous infusion for at least 3 hours.

After the first course of PC alone, to determine eligibility, patients in both groups received treatment for three cycles, with one cycle being 21 days. If intolerable adverse events, serious protocol violations, or disease progression were observed, the treatment was terminated.

Statistical Analysis

Continuous variables were summarized by the mean, SD, median, minimum, and maximum. Categorical variables were summarized by frequencies and percentages. Efficacy analysis was performed on the intent-to-treat (ITT) population. The ORR and the disease control rate (DCR) were calculated for each group, and the groups were compared using Fisher's exact test. Event-time distributions were estimated by the Kaplan-Meier method. The Cox model with time-dependent variables was used to estimate hazard ratios for tumor progression at different study periods.[11] Descriptive analysis was used to summarize the safety data. Adverse events were compared using Fisher's exact test. All reported p values were two sided, and values <0.05 was considered to be statistically different. Confidence intervals (CIs) are at the 95% level.

RESULTS

Between July 18, 2007, and August 8, 2008, 126 patients with previously untreated, advanced NSCLC were enrolled in this study and randomly assigned to the treatment group ($n = 63$) or the control group ($n = 63$). One patient in each group did not start treatment, and one patient in each group was excluded for being allergic to paclitaxel. According to the ITT principle, there were 122 cases included in the efficacy analysis, 61 in each group. Baseline characteristics of patients in the two groups are summarized in Table 1. The two groups were well balanced, except for a difference in distribution according to sex (men accounted for 80.3% of patients in the treatment group and 62.3% of those in the control group; $p = 0.045$, with Fisher's exact test).

There were 124 cases in the safety analysis set, 62 cases in each group. By September 14, 2010, one patient in the treatment group and three patients in the control group were lost to follow-up, giving a total lost to follow-up rate of 3.3% (Figure 1).

Efficacy

In the ITT population, ORR in the treatment group was moderately higher than that in the control group (39.3% versus 23.0%, $p = 0.078$). The DCR in the treatment group was also significantly higher than that in the control group (90.2% versus 67.2%, $p = 0.004$). The median PFS was 7.1 months (95% CI: 6.6–7.7) in the treatment group and 6.3 months (95% CI: 5.6–6.9) in the control group, with no significant difference ($p = 0.522$, hazard ratio = 0.883, 95% CI: 0.604–1.292). The 24-week rates of PFS in the treatment group and control group were 78% and 59%, respectively ($p = 0.017$). By September 14, 2010, a total of 90 deaths (71%) were observed, 48 cases (76.2%) in the treatment group and 42 cases (66.7%) in the control group. The 1-year survival rates in the treatment group and the control group were 61.7% and 55.1% ($p = 0.462$), and the 2-year survival rates were 31.4% and 36.1% ($p = 0.589$), respectively. The median OS in the treatment group and control group was 17.6 months (95% CI: 13.4–21.7) and 15.8 months (95% CI: 9.4–22.9) ($p = 0.696$), respectively (Table 2 and Figure 2).

TABLE 1. Baseline Characteristics of the Patients

Characteristic	Endostar + Paclitaxel/ Carboplatin ($N = 61$)	Placebo + Paclitaxel/ Carboplatin ($N = 61$)
Sex, *n* (%)		
Male	49 (80.3)	38 (62.3)
Female	12 (19.7)	23 (37.7)
Age (yr)		
Median	57	58
Range	38–78	28–75
Disease stage at entry, *n* (%)		
IIIB	18 (29.5)	25 (41.0)
IV	43 (70.5)	36 (59.0)
Histology, *n* (%)		
Squamous carcinoma	23 (37.7)	14 (23.0)
Adenocarcinoma	37 (60.7)	41 (67.2)
Other	1 (1.6)	6 (9.8)
ECOG performance status, *n* (%)		
0	9 (14.8)	4 (6.6)
1	48 (78.7)	55 (90.2)
2	4 (6.6)	2 (3.3)
Smoking index, *n* (%)		
≤400	34 (55.7)	42 (68.9)
>400	27 (44.3)	19 (31.1)

ECOG, Eastern Cooperative Oncology Group.

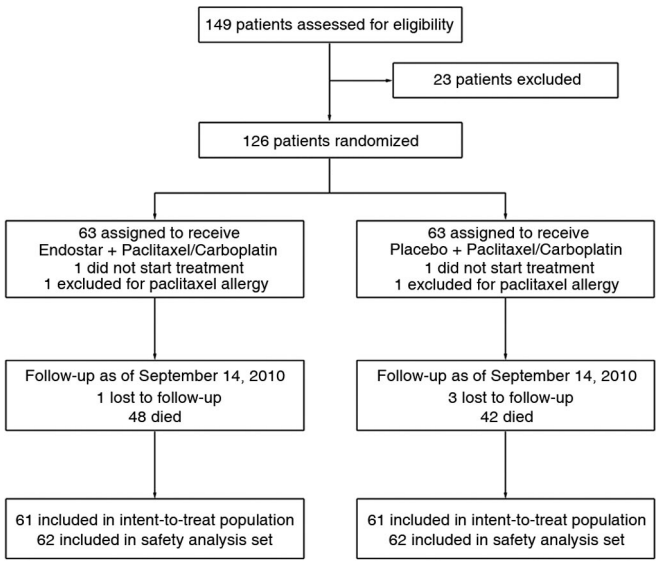

FIGURE 1. Enrollment, randomization, and follow-up of patients in the study.

Safety

In the safety analysis set population, the incidence rate of drug-related adverse events was 51.6% in the treatment

TABLE 2. The Efficacy of Paclitaxel-Carboplatin Alone or with Endostar for Advanced Non-small Cell Lung Cancer

	TC + Endostar (Treatment Group) (N = 61)	TC + Placebo (Control Group) (N = 61)	p
ORR	24 (39.3%)	14 (23.0%)	0.078
DCR	55 (90.2%)	41 (67.2%)	0.004
PFS (95% CI), mo	7.1 (6.6–7.7)	6.3 (5.6–6.9)	0.522
OS (95% CI), mo	17.6 (13.4–21.7)	15.8 (9.4–22.9)	0.696

TC, paclitaxel-carboplatin; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; CI, confidence interval.

group and 50.0% in the control group. The incidence rate of drug-related CTC grade 3 or 4 adverse events was 24.2% in the treatment group and 35.5% in the control group. The incidence rate of serious adverse events was 3.2% in the treatment group and 8.1% in the control group. There were no significant differences between the two groups. Common adverse events observed in the two groups are summarized in Table 3.

The incidence rates of arrhythmia and myocardial ischemia were 8.1% and 4.8% in the treatment group and 4.8% and 3.2% in the control group, respectively. Arrhythmia and myocardial ischemia were grade 1 or 2, with no significant difference between the two groups.

There was no significant difference between the two groups in the change of vital signs before and after the treatment. After treatment, mild electrocardiogram changes were observed in seven cases in the treatment group and three cases in the control group.

DISCUSSION

TC is a standard first-line treatment for NSCLC.[12] Our study addressed to the question of whether endostar in combination with TC chemotherapy could benefit patients with advanced NSCLC. The primary end point of PFS showed a negative result (p = 0.522), and the OS difference was not statistically significant. However, endostar combined with TC did improve ORR, DCR, and the 24-week rates of PFS. In addition, treatment with TC plus endostar did not increase toxicity, especially those typically observed in other antian-

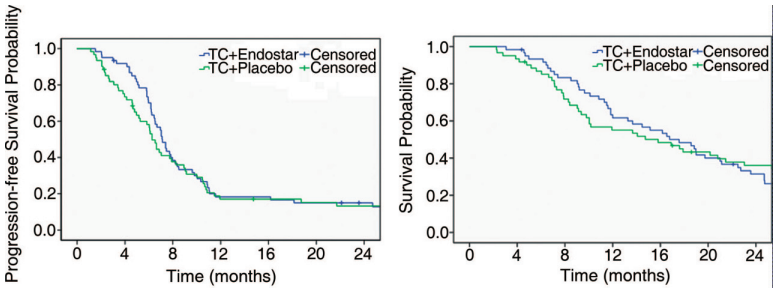

FIGURE 2. Progression-free survival and overall survival.

TABLE 3. Adverse Events

Adverse Events	Endostar + Paclitaxel/ Carboplatin (N = 62)		Placebo + Paclitaxel/ Carboplatin (N = 62)	
	All Adverse Events	CTC Grade 3 or 4	All Adverse Events	CTC Grade 3 or 4
Hematological toxicity				
Granulocytopenia	43 (69.4)	25 (40.3)	46 (74.2)	30 (48.4)
Hemoglobin reduction	49 (79.0)	0 (0.0)	54 (87.1)	2 (3.2)
Leukopenia	54 (87.1)	17 (27.4)	56 (90.3)	25 (40.3)
Lymphopenia	9 (14.5)	4 (6.5)	14 (22.6)	10 (16.1)
Thrombocytopenia	19 (30.6)	1 (1.6)	20 (32.3)	2 (3.2)
Nonhematological toxicity				
Alopecia	35 (56.5)		39 (62.9)	
Arrhythmia	5 (8.1)	0 (0.0)	3 (4.8)	0 (0.0)
Infection	3 (4.8)	0 (0.0)	5 (8.1)	2 (3.2)
Myocardial ischemia	3 (4.8)	0 (0.0)	2 (3.2)	0 (0.0)
Nausea	12 (19.4)	1 (1.6)	13 (21.0)	0 (0.0)
Sensory nervous system disorder	13 (21.0)	1 (1.6)	16 (25.8)	0 (0.0)
Skin disorder	5 (8.1)	0 (0.0)	4 (6.5)	0 (0.0)
Transaminase elevation	16 (25.8)	1 (1.6)	14 (22.6)	0 (0.0)
Vomiting	9 (14.5)	1 (1.6)	4 (6.5)	0 (0.0)

Values are given as number of patients (%).
CTC, Common Toxicity Criteria.

giogenesis therapies, such as hemorrhage and cardiovascular toxicity. It also did not significantly increase the risk of hemorrhage in patients with squamous carcinoma.

In the E4599 and AVAiL studies, the antiangiogenesis agent, bevacizumab plus chemotherapy, not only increased ORR but also improved PFS.[13,14] However, in our phase II study, PFS curves of the two groups approached each other in the later part of the study. The reason might be that endostar treatment was stopped after three cycles, whereas in the E4599 study, patients in the TC plus bevacizumab group continued to receive bevacizumab monotherapy every 3 weeks until evidence of disease progression or unacceptable toxic effects developed. In the AVAiL study, 94% of eligible patients received bevacizumab maintenance therapy, with a median time of bevacizumab usage of six cycles. This observation may indicate the importance of maintaining endostar therapy. The OS differences between our two groups were also not significant, although the second-line treatment may have had some effects on the result. When patients were allowed to take other therapies, 15 patients (24.6%) in the treatment group received other chemotherapies, with none receiving epidermal growth factor receptor tyrosine kinase inhibitor treatment. In the control group, 12 patients (19.7%) received other chemotherapies, with 6 (9.8%) receiving epidermal growth factor receptor tyrosine kinase inhibitor treatment.

One cycle of TC chemotherapy was applied to screen the patients in our study because lung cancer patients do not seem to benefit from antiangiogenesis as monotherapy, such as bevacizumab or endostar alone. The response rate of endostar alone in advanced NSCLC patients was only 3%.[15] Therefore, endostar seems to enhance the efficacy of chemotherapy. However, there is no evidence that it reverses the chemotherapy resistance. From our previous experience, effective chemotherapy was a prerequisite for the efficacy of this combination therapy. Effective chemotherapy may decrease tumor load, reduce tumor activity, and decrease the secretion of angiogenic cytokines in tumors.[16,17] Moreover, antiangiogenesis therapy is believed to block tumor angiogenesis and cut off the supply system of tumor growth, thus increasing the efficacy of chemotherapy and perhaps extending the duration of its effectiveness. The combination of chemotherapy and antiangiogenesis therapy has been proven effective to treat cancers in recent years. However, there are still many unsolved problems. For instance, which patients are the most suitable for such combination therapy and which biomarkers could predict efficacy? In this study, we tried to use chemotherapy effectiveness as a screening criterion, with only those patients evaluated as SD or better after one cycle of chemotherapy alone, who were randomly assigned to the treatment or the control group. The sample size was too small to apply stratified randomization; hence, there was a difference in distribution according to sex between the two groups. Nevertheless, the other baseline characteristics of the patients were well balanced.

Special attention was given to those toxic effects typically observed in antiangiogenesis treatment. In the treatment group, five patients (8.1%) were reported to have arrhythmia and three patients (4.8%) developed myocardial ischemia. In the control group, three patients (4.8%) had arrhythmia and two patients (3.2%) myocardial ischemia. All were CTC grade 1 or 2 and did not influence further treatment. Although there were no significant differences between the two groups, incidences of arrhythmia and myocardial ischemia were slightly higher in the treatment group, something that should be followed in future studies. This study did not exclude patients with squamous cell carcinoma. Twenty-three patients (37.7%) in the treatment group and 14 patients (23.0%) in the control group had squamous histology. Of interest, no life-threatening lung hemorrhage was observed, which was different from bevacizumab studies. The cause and mechanism of this observation are unknown. One patient in the treatment group had cerebral thrombosis after the first cycle of endostar treatment and was withdrawn from study. In the control group, two patients developed pulmonary embolism and one had phlebothrombosis; all three cases were withdrawn from study. Hypertension and proteinuria were not observed in the treatment group. The incidence and severity of adverse events were comparable between the two groups. Therefore, endostar, in combination with TC chemotherapy, was not shown to increase toxicity.

In conclusion, endostar, in combination with TC chemotherapy, was shown to slightly increase ORR but could not significantly improve PFS and OS. Compared with other antiangiogenesis treatment, endostar exhibited an excellent safety profile. However, cardiac toxicity remains a concern. Antiangiogenesis therapy is a promising method that has become a part of the standard treatment for NSCLC.[18] However, as a new strategy, it still has many issues to be resolved by further studies.

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REFERENCES

1. Qin XJ, Shi HZ. Major causes of death during the past 25 years in China. *Chin Med J (Engl)* 2007;120:2317–2320.
2. Soon YY, Stockler MR, Askie LM, et al. Duration of chemotherapy for advanced non-small-cell lung cancer: a systematic review and meta-analysis of randomized trials. *J Clin Oncol* 2009;27:3277–3283.
3. Ergun S, Tilki D, Oliveira-Ferrer L, et al. Significance of vascular stabilization for tumor growth and metastasis. *Cancer Lett* 2006;238: 180–187.
4. Folkman J. Endogenous inhibitors of angiogenesis. *Harvey Lect* 1996; 92:65–82.
5. O'Reilly MS, Boehm T, Shing Y, et al. Endostatin: an endogenous inhibitor of angiogenesis and tumor growth. *Cell* 1997;88:277–285.
6. Zhuang HQ, Yuan ZY. Process in the mechanisms of endostatin combined with radiotherapy. *Cancer Lett* 2009;282:9–13.
7. Folkman J. Antiangiogenesis in cancer therapy—endostatin and its mechanisms of action. *Exp Cell Res* 2006;312:594–607.

8. Grosios K. Endostatin (EntreMed). *IDrugs* 2000;3:799–810.
9. Wang J, Sun Y, Liu Y. Results of randomised, multicentre, double-blind phase III trial of rh-endostantin (YH-16) in treatment of advanced non-small cell lung cancer patients. *Chin J Lung Cancer* 2005;8:283–290.
10. Therasse P, Arbuck SG. New guidelines to evaluate the response to treatment in solid tumors. *Breast Cancer* 2005;12.
11. Bolard P, Quantin C, Esteve J, et al. Modelling time-dependent hazard ratios in relative survival: application to colon cancer. *J Clin Epidemiol* 2001;54:986–996.
12. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92–98.
13. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006;355: 2542–2550.
14. Martin R, Joachim P, Petr Z, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAiL. *J Clin Oncol* 2009; 8:1227–1234.
15. Yang L, Wang JW, Sun Y, et al. Randomized phase II trial on escalated doses of Rh-endostatin (YH-16) for advanced non-small cell lung cancer. *Chin J Oncology* 2006;28:138–141.
16. Zhong H, Han B, Tourkova IL, et al. Low-dose paclitaxel prior to intratumoral dendritic cell vaccine modulates intratumoral cytokine network and lung cancer growth. *Clin Cancer Res* 2007;13:5455–5462.
17. Browder T, Butterfield CE, Kraling BM, et al. Antiangiogenic scheduling of chemotherapy improves efficacy against experimental drug-resistant cancer. *Cancer Res* 2000;60:1878–1886.
18. Gutierrez M, Giaccone G. Antiangiogenic therapy in nonsmall cell lung cancer. *Curr Opin Oncol* 2008;20:176–182.

