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ORIGINAL ARTICLE

Phase II study of cisplatin/etoposide and endostar for extensive-stage small-cell lung cancer

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Abstract
Purpose To investigate the efficacy and safety of endostar, a novel recombinant human endostatin, plus cisplatin, and etoposide in patients with extensive-stage small-cell lung cancer (ED-SCLC).
Patients and methods Chemotherapy-naïve patients with histologically confirmed, measurable ED-SCLC were enrolled. Treatment consisted of cisplatin (25 mg/m^2) administered intravenously (IV) on days 1–3; etoposide (120 mg/m^2) administered intravenously (IV) on days 1–3; endostar (15 mg) administered intravenously (IV) on days 1–14 every 21 days for up to four cycles. The primary objective was to assess the progression-free survival (FPS). Secondary objectives were to assess the objective response rate, median overall survival (OS), and treatment-related toxicity.
Results Thirty-three patients were enrolled, the median age of the patients was 53 years (range, 29–74), twenty-three patients (69.7%) were men and 10 patients were women. Eastern Cooperative Oncology Group performance status scores were 0, 1,and 2 in 30.3, 60.6, and 9.1% of the patients, respectively. The overall response rate was 69.7%, one patient (3%) had a complete response, and 22 patients (66.7%) had partial responses. Five patients (15.1%) had stable disease; the median PFS was 5.0 months (95% CI, 4.2–5.6 months), and the 6-month PFS was 33.3%. The median OS was 11.5 months (95% CI, 9.6–13.4 months), and the 1-year OS was 38.1% (95% CI, 26–50.1%). Sixteen patients (48.5%) had at least one grade 3/4 adverse events; the most common grade 3/4 hematologic toxicity included neutropenia in 57.6%, thrombocytopenia in 12.1% of patients. The most common grade 3/4 non-hematologic toxicities included fatigue in 15.2%, nausea/vomiting in 9.1%, diarrhea in 6.1%, anorexia in 6.1%, mucositis in 6.1% of patients.
Conclusion The addition of rh-endostain to cisplatin and etoposide in patients with ED-SCLC results in slightly improved PFS and OS relative to historical controls who received this chemotherapy regimen alone. This regimen appears to be well tolerated; the promising results suggest the further randomized phase III trial to define endostar's impact on SCLC treatment.

Keywords Small-cell lung cancer · Endostar · Cisplatin · Etoposide · Chemotherapy

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Introduction

Small-cell lung cancer (SCLC) is a highly aggressive disease that accounts for 16% of lung cancer [1]. Patients are categorized as having limited-stage disease, defined as disease that is confined to the ipsilateral hemithorax that can be encompassed within a tolerable radiation port, or

extensive-stage disease (ED), defined as the presence of overt metastatic disease by imaging or physical examination [2]. Two-thirds of patients are diagnosed with ED at presentation [3]. Despite the development of novel drugs, the therapeutic approach to SCLC has been stagnant for more than 2 decades. Standard treatment for ED-SCLC remains cisplatin and etoposide (PE), a regimen that yields a median survival of approximately 10 months and a 5-year survival rate of 1–2% [4]. Newer treatment approaches are needed.

Angiogenesis is a fundamental event in tumor growth and metastatic discrimination. The angiogenesis inhibitors for the treatment of cancer as a new approach are based on the Forkman's theory in 1971 [5]. Endostatin, the 20 kD internal fragment of the carboxyterminus of collagen XVIII, was first identified in the conditioned media of hemangioendothelioma cells as an antiangiogenic molecule in 1997 by Folkman et al. [6] and was discovered as a potent inhibitor of angiogenesis. Animal studies demonstrated that endostatin strongly inhibited the growth of a variety of murine and xenotransplanted human tumors by suppressing the neovascularization [7, 8]. On the cellular level, Endostatin was shown to inhibit endothelial cell proliferation and migration [9, 10] and to induce endothelial cell apoptosis [11] and cell cycle arrest [12]. Endostatin thought to be an ideal anticancer weapon and was quickly pushed into clinical trials [13, 14].

Endostar, a novel recombinant human endostatin which expressed and purified in *E. coli*, The addition of endostar to standard chemotherapy with vinorelbine and cisplatin in patients with advanced non-small-cell lung cancer (NSCLC) resulted in a significant increase in overall survival (OS) compared with chemotherapy alone [15] and was approved by the SFDA for the treatment of non-small-cell lung cancer in 2005.

On the basis of this knowledge, we initiated a phase II trial in which endostar was combined with EP in patients with ED-SCLC to evaluate the efficacy and safety.

Patients and methods

Eligibility

Patients with previously untreated, histologically or cytologically confirmed ED-SCLC were eligible. Additional eligibility requirements included age 18 years or older; measurable disease; an ECOG performance status (PS) of 0–2; life expectancy of greater than 12 weeks; adequate hematologic, hepatic, and renal functions. All patients gave written informed consent prior to registration.

Exclusion criteria were prior chemotherapy, unmeasurable disease, pregnancy, and breastfeeding; CNS metastases; active infection and unhealing wounds; hepatic and renal functions deficiency; serious cardio-cerebrovascular disease such as coronary heart disease, unstable angina pectoris, myocardial infarction, cardiac arrhythmias, cerebral infarction, and hemorrhage or psychiatric illness that would have affected compliance.

The study was approved by the ethics committee of Zhongnan Hospital of Wuhan University and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All persons gave their informed consent prior to their inclusion in the study.

Study design

The primary objective of this phase II study was to assess the progression-free survival (FPS). Secondary objectives were to assess the objective response rate, median overall survival (OS), and treatment-related toxicity. FPS was defined as the time from the date of study entry to progression; OS was measured from the date of study entry until the date of death. If there was intolerable toxicity or discontinuation of treatment secondary to toxicity, the patient was considered assessable, but was classified as a treatment failure. If other cancer therapy was initiated before progressive disease occurred, the patient was censored on the date on which the other therapy began. If a patient was lost to follow-up, the patient was censored on the date of last contact.

Treatment plan

Cisplatin 25 mg/m^2 was administered intravenously over 30–60 min on days 1–3, etoposide 120 mg/m^2 was administered intravenously over 60 min on days 1–3; Endostar 15 mg was administered over 90 min by IV infusion on days 1–14. Repeated every 3 weeks for up to four cycles. Patients were treated for at least four cycles unless disease progression or unacceptable toxicity was observed.

Dose modifications were based on adverse events on day 1 of each cycle, and doses were not increased once modified. Etoposide and cisplatin doses were reduced in 25% decrease in subsequent cycles for grade 4 neutropenia, febrile neutropenia, or grade 4 thrombocytopenia. The dose of cisplatin was reduced by 25% of the planned dose in patients with grade-2 renal toxicity.

Assessments

The baseline evaluation included a complete medical history and physical examinations, assessment of ECOG PS, blood counts, serum chemistry, chest and abdominopelvic computed tomography (CT) scan. Follow-up history, physical examinations, and toxicity assessment were

performed before each cycle of treatment. Complete blood counts, blood chemistry were obtained before the beginning of each cycle. All adverse events were graded according to the National Cancer Institute Common Toxicity Criteria, version 3.0. The evaluation with imaging was done after cycles 2 and 4 of chemotherapy. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) [16] and was assessed by chest and abdominopelvic CT.

Statistical analyses

A one-stage design using the binominal probability was used to determine the sample size. Assuming that a response rate of 50% would indicate potential usefulness, whereas a rate of 15% would be the lower limit of interest. With $\alpha = 0.05$ and $\beta = 0.2$, the estimated accrual number was 30 patients. Allowing for a 10% loss to follow-up rate, a total of 33 patients were planned to enroll. Efficacy outcomes were based on intent-to-treat analyses. Survival curves were constructed using the Kaplan–Meier method, and survival were compared using the Log-Rank test.

Results

Patients characteristics

Thirty-three patients were enrolled; the baseline characteristics are listed in Table 1. The median age of the patients was 53 years (range, 29–74), twenty-three patients (69.7%) were men and 10 patients were women. Eastern Cooperative Oncology Group performance status scores were 0, 1, and 2 in 30.3, 60.6, and 9.1% of the patients, respectively. Metastatic sites included liver (57.6%), extrathoracic lymph nodes (27.3%), bone (45.5%), adrenal glands (18.2%), and retroperitoneal (3%).

All patients received at least one cycle of treatment, twenty-nine (87.9%) patients completed four cycles of treatment (median three cycles). Fourteen patients required a dose reduction according to the dose modification rules as outlined earlier.

The median follow-up at the time of analysis was 12.5 months (95% CI 11.6–13.1 months).

Table 1 Patients characteristics

Characteristics	*n*	%
Age		
Median	53	
Range	29–74	
Sex		
Male	23	69.7
Female	10	30.3
Performance status		
0	10	30.3
1	20	60.6
2	3	9.1
Metastasic site		
Bone	15	45.5
Liver	19	57.6
Extrathoracic lymph nodes	9	27.3
Adrenal	6	18.2
Retroperitoneal	1	3

Efficacy results

Thirty-one patients are included in the response analysis, two patients were not assessable for response because of treatment-related toxicity (Table 2). The overall response rate was 69.7%, one patient (3%) had a complete response and 22 patients (66.7%) had partial responses. Five patients (15.1%) had stable disease. Unconfirmed complete responses were seen in 2 patients (6.1%).

The median PFS was 5.0 months (95% CI, 4.2–5.6 months), and the 6-month PFS was 33.3% (Fig. 1). The median OS was 11.5 months (95% CI, 9.6–13.4 months; Fig. 2), and the 1-year OS was 38.1% (95% CI, 26–50.1%).

Safety and toxicity

All 33 patients were assessable for toxicity at least for the first cycle. As shown in Table 3.

The most frequent non-hematologic adverse events of any grade were fatigue (89%), anorexia (56%), vomiting (39%), stomatitis (39%); The most frequent hematologic adverse events of any grade were neutropaenia (61%), leukopaenia (50%), and anemia (33%).

Sixteen patients (48.5%) had at least one grade 3 or 4 adverse events (Table 3).

The most common grade 3/4 hematologic toxicity included neutropenia in 57.6%, thrombocytopenia in 12.1%, and anemia in 3% of the patients. Three patients

Table 2 Response rates

Response	Patients ($N = 33$)	
	No.	%
Complete	1	3
Partial	22	66.7
Stable disease	5	15.1
Progression disease	3	9.1
No assessable	2	6.1

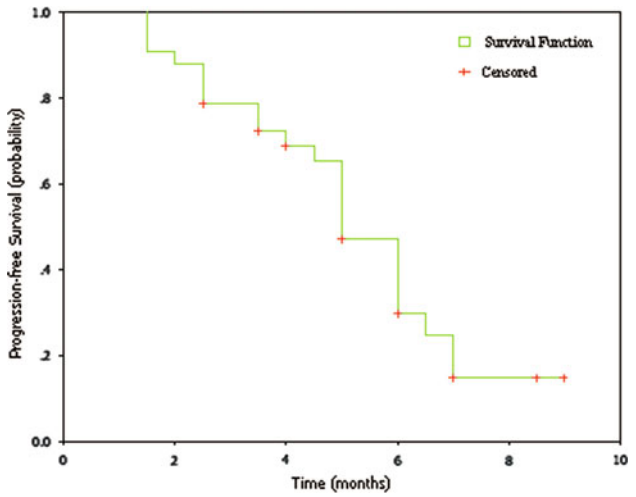

Fig. 1 Kaplan–Meier curve for progression-free survival (PFS). The median PFS was 5.0 months (95% CI, 4.2–5.6 months)

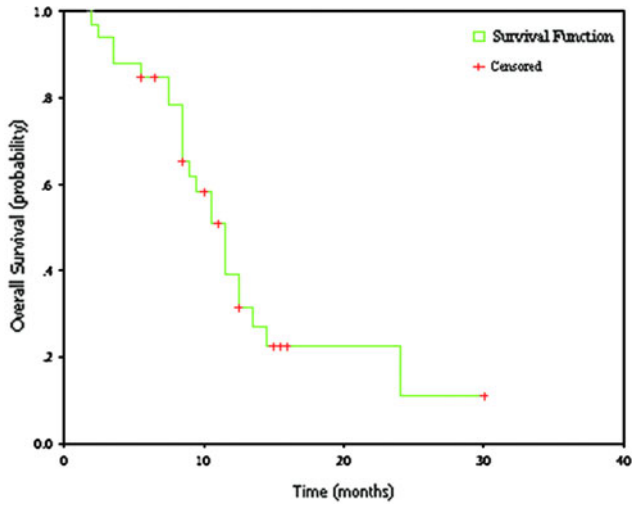

Fig. 2 Kaplan–Meier curve for overall survival (OS). The median OS was 11.5 months (95% CI, 9.6–13.4 months)

Table 3 Grade 3–4 toxicity

Toxicity	Grade 3		Grade 4	
	No.	%	No.	%
Neutropenia	15	45.5	4	12.1
Thrombocytopenia	3	9.1	1	3
Anemia	1	3		0
Leukopenia	7	21.2	3	9.1
Febrile fever	3	9.1	1	3
Anorexia	2	6.1	0	
Nausea/vomiting	3	9.1	0	
Fatigue	5	15.2	0	
Constipation	1	3	0	
Mucostitis	2	6.1	0	
Diarrhea	2	6.1	0	

(9.1%) developed febrile fever. The most common grade 3/4 non-hematologic toxicities included fatigue in 15.2%, nausea/vomiting in 9.1%, diarrhea in 6.1%, anorexia in 6.1%, mucositis in 6.1%, and constipation in 3% of patients.

Cardiovascular events thought to be related to the endostar were 6.1% and generally mild and included a grade 1 sinus bradycardia, a grade 1 nodal/junctional arrhythmia, and a grade 2 sinus tachycardia. No patients experienced grade 3/4 cardiovascular events.

Discussion

Angiogenesis plays a role in the metastatic process of the SCLC. Lucchi et al. [17] retrospectively investigated a homogenous cohort of 87 patients with SCLC and found that SCLC has a higher vascularization than NSCLC as results from the higher number of microvessels; the microvessel count (MVC) and the VEGF protein expression significantly affected the prognosis in SCLC. SCLC may be an ideal field to test new antiangiogenic drugs associated to chemotherapy.

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody. Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis [18]. Bevacizumab is the first of a new class of antineoplastic drugs that inhibit the formation of new blood vessels and was approved by the FDA for use in colorectal cancer [19], lung cancer [20], and breast cancer [21] in combination with standard first-line chemotherapy. Based on the advances above, recently, three other trials have combined bevacizumab with chemotherapy in patients with ED-SCLC. CALGB (Cancer and Leukemia Group B) 30306 study [22] enrolled 72 patients and treated with bevacizumab (15 mg/kg on day 1), cisplatin (30 mg/m^2 on days 1 and 8), and irinotecan (85 mg/m^2 on days 1 and 8) every 21 days for up to six cycles. The authors reported a higher response rate and PFS of 75% and 7.1 months, respectively, and an OS of 11.7 months. Higher incidence of nausea/vomiting, diarrhea was observed in this study. In a phase II trial by Spigel et al. [23], 51 patients with ED-SCLC were enrolled and administered carboplatin (AUC 4 on day 1), irinotecan (60 mg/m^2 on days 1, 8, and 15), and bevacizumab (10 mg/kg every 2 weeks). Results shown objective response rate 84% (95% CI 71–93%): 1 complete and 42 partial responses. Two patients (4%) had stable disease, and two patients had progressive disease. Median TTP was 9.13 months (95% CI 7.36–9.46 months). Median overall survival was 12.1 months (95% CI

9.6–13.5 months); 1- and 2-year overall survivals were 51 and 14%, respectively. These outcomes compared favorably with others studies with chemotherapy alone. ECOG (Eastern Cooperative Oncology Group) E3501 [24] enrolled 63 patients and treated with bevacizumab 15 mg/kg plus cisplatin 60 mg/m^2 and etoposide 120 mg/m^2, which was followed by bevacizumab alone until death or disease progression occurred. The 6-month PFS was 30.2%, the median PFS was 4.7 months, and OS was 10.9 months. The response rate was 63.5%. The most common adverse event was neutropenia (57.8%). Only one patient had grade 3 pulmonary hemorrhage. The addition of bevacizumab to cisplatin and etoposide in patients with ED-SCLC results in improved PFS and OS relative to historical controls who received this chemotherapy regimen alone. This regimen appears to be well tolerated and has minimal increase in toxicities compared with chemotherapy alone.

Endostar is a novel recombinant human endostatin which expressed and purified in *E. coli*. The preclinical model study showed that endostar suppressed the VEGF-stimulated proliferation, migration, and tube formation of human umbilical vein endothelial cells (HUVECs) in vitro. Endostar blocked microvessel sprouting from rat aortic rings in vitro. Moreover, it could inhibit the formation of new capillaries from pre-existing vessels in the chicken chorioallantoic membrane (CAM) assay and affect the growth of vessels in tumor. Further study found the anti-angiogenic effects of endostar were correlated with the VEGF-triggered signaling. Endostar suppressed the VEGF-induced tyrosine phosphorylation of KDR/Flk-1(VEGFR-2) as well as the overall VEGFR-2 expression and the activation of ERK, p38 MAPK, and AKT in HUVEC [25]. In clinical study, the addition of endostar to standard chemotherapy with vinorelbine and cisplatin in patients with advanced non-small-cell lung cancer (NSCLC) resulted in a significant increase in overall survival (OS) compared with chemotherapy alone and is no increase in adverse events and was approved by the SFDA for the treatment of non-small-cell lung cancer in 2005.

This is the first study to investigate the efficacy and safety of endostar plus cisplatin and etoposide in patients with extensive-stage disease, small-cell lung cancer (ED-SCLC). In our study, the addition of endostar to EP regimen in patients with ED-SCLC results in a similar response and slightly improved PFS and OS relative to historical controls who received this chemotherapy alone. Toxicity was generally manageable in this study and this regimen did not increase toxicities compared with chemotherapy alone.

In summary, this study suggests there may be improved efficacy slightly and well tolerated when endostar is given concurrently with etoposide and carboplatin. However, this trial is only an exploratory phase II study with small number of patients, these results is not sufficient to define endostar's impact on SCLC treatment. The role of endostar in the treatment of SCLC remains unknown. Based on the promising results our study shown, the further randomized phase III trial is needed to investigate the potential added value of endostar in the first-line treatment of ES-SCLC.

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