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Original article

Phase II trial of recombinant human endostatin in combination with concurrent chemoradiotherapy in patients with stage III non-small-cell lung cancer

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ABSTRACT

Purpose: The objective of this study was to evaluate the efficacy and safety of Endostar combined with concurrent chemoradiotherapy (CCRT) in patients with stage III non-small-cell lung cancer (NSCLC).
Methods: Patients with unresectable stage III NSCLC were treated with Endostar (7.5 mg/m^2/d) for 7 days at weeks 1, 3, 5, and 7, while two cycles of docetaxel (65 mg/m^2) and cisplatin (65 mg/m^2) were administered on days 8 and 36, with concurrent thoracic radiation to a dose of 60–66 Gy. Primary end points were short-term efficacy and treatment-related toxicity.
Results: Fifty patients were enrolled into the study, and 48 were assessable. Of the 48 patients, 83% had stage IIIB and 65% had N3 disease. Median follow-up was 25.0 months. Overall response rate was 77%. The estimated median progression-free survival (PFS) was 9.9 months, and the estimated median overall survival (OS) was 24.0 months. The 1-, 2-, and 3-year local control rates were 75%, 67%, and 51%, PFS rates were 48%, 27%, and 16%, and OS rates were 81%, 50%, and 30%, respectively. All toxicities were tolerable with proper treatment.
Conclusions: The combination of Endostar with CCRT for locally advanced NSCLC patients was feasible and showed promising survival and local control rates.
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Currently, concurrent chemoradiotherapy (CCRT) is considered to be the standard treatment for locally advanced non-resectable non-small-cell lung cancer (NSCLC), which was supported by multiple successful clinical studies [1–3] that combined various chemotherapeutic drugs and radiation dosages [4–7]. However, the clinical outcome is very unsatisfying, with a 5-year survival rate of only approximately 20% (15–40%) [8,9]. A more effective combined-modality therapy strategy is necessary for further improvement in the treatment of locally advanced NSCLC. With the knowledge of the molecular pathology of NSCLC improving, new strategies of multimodal therapeutic approaches have been under investigation to manage NSCLC. Several biological agents have been introduced to combine with chemoradiotherapy, including EGFR pathway inhibitors, cyclo-oxygenase inhibitors, as well as angiogenesis inhibitors [10,11]. While EGFR is an attractive target, studies with cetuximab combined with chemoradiotherapy in treatment of advanced NSCLC have mixed results [12]. Interestingly, a recent analysis indicates that the expression levels of EGFR are not associated with OS or time to progression [13], underlying the importance of exploring alternative biological pathways in NSCLC treatment.

Endostatin, a C-terminal fragment naturally derived from type XVIII collagen, is an endogenous inhibitor of angiogenesis [14]. Recombinant human endostatin (Endostar) was reported to be efficient in blocking angiogenesis and suppressing primary tumor and metastatic growth [15]. Endostar has been proven to be able to normalize tumor vasculature, alleviate hypoxia and increase sensitivity of tumors to radiation in mouse tumor models as well as in patients [16–20]. Reports showed that combination of Endostar

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with chemotherapy could successfully improve the response rate (RR) and lengthen median survival time (MST) in advanced NSCLC patients [21,22]. Therefore, in 2005 Endostar was approved by the Chinese SFDA for use in combination with chemotherapy in NSCLC patients [23]. Furthermore, Endostar in combination with radiotherapy has also shown better short-term therapeutic effects in the treatment of NSCLC [17]. It is reasonable to hypothesize that the combined therapy of Endostar with CCRT for locally advanced NSCLC would generate a beneficial result for patients.

We designed a prospective phase II clinical study applying Endostar with CCRT for patients with locally advanced NSCLC for evaluation of safety and efficacy.

Materials and methods

The study was approved by the Ethics Committee of Sun Yat-Sen University Cancer Center and all participating institutions, and written informed consent was obtained from each patient. This study was registered with ClinicalTrials.gov, number NCT01218594.

Eligibility

Inclusion criteria were patients $\geqslant$18 years of age with untreated pathologically confirmed inoperable stage IIIA or IIIB NSCLC, weight loss <10% in the past 6 months, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1, forced vital capacity in 1 s (FEV1) >0.8 L, measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST), absolute neutrophil count (ANC) $\geqslant$1500/μL, hemoglobin $\geqslant$10 mg/dL, platelets $\geqslant$100,000/μL, serum creatinine $\leqslant$1.25 times the upper limit of normal (ULN), calculated creatinine clearance $\geqslant$60 mL/min, bilirubin 1.5 $\times$ ULN, and AST and ALT <2.5 $\times$ ULN.

Exclusion criteria were patients having a history of other malignant diseases, any contraindications for chemoradiotherapy, malignant pleural and/or pericardial effusions, pre-existing bleeding diathesis or coagulopathy, pregnancy or nursing, prior chemotherapy or chest irradiation therapy for NSCLC, or any therapy targeted at the epidermal growth factor receptor pathway.

Baseline evaluation included a complete medical history and physical examination of PS, recent weight loss, and laboratory analysis within 1 week before study enrollment. Patients were examined by computed tomography (CT) scan of the chest and abdomen, radionuclide bone scan (or positron emission tomography, PET), magnetic resonance imaging (MRI) scan of the brain, electrocardiogram (ECG), and pulmonary function tests within 4 weeks before enrollment. CT scans were performed for all subsequent treatment evaluations.

Study design

This study was designed as a prospective, multiple-center, single-arm, phase II trial. The treatment schema is shown in Supplementary data 1. An intravenous (IV) dose of Endostar (Simcere Pharmaceutical, Nanjing, China) (7.5 mg/m^2/d) was administered over 4 h each day for 7 days at weeks 1, 3, 5, and 7. Patients received two doses of docetaxel (Aventis Pharmaceutical, USA) (65 mg/m^2) and cisplatin (Hansoh Pharmaceutical, Jiangsu, China) (65 mg/m^2) on days 8 and 36, with concurrent three-dimensional (3-D) conformal radiation at 60 $\sim$ 66 Gy in 30 $\sim$ 33 fractions for 6 $\sim$ 7 weeks. Dexamethasone and 5-hydroxytryptamine agonist were recommended for premedication to minimize allergic and emetogenic responses to docetaxel and cisplatin. Body weight change, complete blood count, ECG, and routine laboratory tests including urinalysis, bleeding, and coagulation time were performed every 2 weeks. Adverse events (AE) were monitored and documented according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0.

Administration of docetaxel, cisplatin, and Endostar was held back if the neutrophil level dropped below 1000/μL or the patient experienced febrile neutropenia. Chemotherapy with docetaxel and cisplatin was held back if the platelet count dropped below 100,000/μL. Treatment resumed once these parameters were back to acceptable levels. Docetaxel and cisplatin were held back for grade 3 nonhematologic toxicities until the toxicity had resolved to grade $\leqslant$2. Endostar was discontinued in patients with grade $\geqslant$3 hemorrhage, hypersensitivity, hypertension, or proteinuria.

Radiation treatment procedure

Thoracic radiation therapy (TRT) began on day 8 and all patients received 3-D conformal radiotherapy. Patients laid themselves in a supine position on a vacuum bag and refrained from moving, and a contrast-enhanced CT simulation was performed, scanning from the second cervical vertebra to the second lumbar vertebra [24]. Patients were then treated with a linear accelerator using 8-MV photons. The targets were contoured in accordance with the International Commission on Radiation Units and Measurements (ICRU 62) guidelines. Gross tumor volume (GTV) included the primary tumor (GTV-T), positive lymph nodes (GTV-N) with lymph nodes in the mediastinum with a short diameter of 1 cm or more, or lymph nodes with positive tumor cell sampling, or clusters of small lymph nodes of short diameter <1 cm within 1 region, or having an [18F] fluoro-2-deoxy-D-glucose (18F-FDG) standard uptake value of 2.5 on PET/CT at initial staging. The clinical target volume-tumor (CTV-T) included the GTV-T with a margin of 6 mm for squamous cell carcinoma and 8 mm for nonsquamous cell carcinoma, so that 95% of microscopic tumor extension was included [25]. The CTV-N included the involved positive lymph nodal regions and ipsilateral hilum [26]. There was no additional elective nodal irradiation to cover the uninvolved lymphatics. CTVs (including CTV-T and CTV-N) were edited according to anatomy. The planning target volumes (PTV) involved CTVs with a margin of 1–1.5 cm.

Patients received a total dose of 60–66 Gy in 30–33 fractions over 6–7 weeks; 2 Gy $\times$ 20 fractions to an initial target volume including PTV, followed by 2 Gy $\times$ (10–13) fractions to a boost volume including GTV-T and GTV-N with a margin of 1–1.5 cm [27]. The entire PTV was encompassed within the 95% isodose surface and no more than 5% of the volume within this isodose surface was allowed to receive greater than 110% of the prescription dose. The protocol recommended that the volume of total lung receiving more than 20 Gy (V20) be 35% and the mean lung dose (MLD) be less than 17 Gy (calculated based on lung volume not involved with tumor). The maximum spinal cord point dose allowance was 50 Gy. Specific esophageal dose constraints were not mandated. Radiotherapy interruptions or delays were permitted for grade $\geqslant$3 pulmonary toxicity, esophagitis, mucositis, or skin toxicity; resumption of radiotherapy was allowed once toxicity had resolved to grade $\leqslant$2. Interruptions in radiotherapy longer than 2 weeks resulted in removal of the patient from protocol treatment.

Study objectives

The primary objective was to assess the treatment response rate (RR) of Endostar in combination with CCRT. Secondary objectives included assessment of the feasibility of the combined therapy as measured by safety, local control, progression-free survival (PFS), and overall survival (OS). Data were collected for evaluation of efficacy and safety until the first follow-up visit 4 weeks after completion of protocol treatment. Patients were seen in follow-up every 3 months for 2 years and then every 6 months thereafter. Physical

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