Severe Pulmonary Toxicity With Concurrent Anlotinib and Chemoradiotherapy in Stage III NSCLC: The ALTER-L042 Phase 1 Clinical Trial

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ABSTRACT

Introduction: Anlotinib has brought about marked progression-free survival and overall survival benefit compared with placebos as third-line or further treatment in advanced NSCLC. Nevertheless, the safety and efficacy of concurrent anlotinib and chemoradiotherapy are still unclear.

Methods: Patients with histologically or cytologically confirmed stage III NSCLC suitable for concurrent chemoradiotherapy were enrolled in this study. The enrolled patients were treated with concurrent two cycles of anlotinib and chemoradiotherapy followed by anlotinib consolidation until disease progression or intolerance toxicity. The primary end point was the maximum tolerance dose of anlotinib, whereas the secondary end point was the overall response rate.

Results: Seven patients were enrolled in this study. Six patients completed concurrent anlotinib and chemoradiotherapy and then entered the consolidation period. Among the patients, 28.57% (two of seven patients) developed fatal treatment-related adverse events (fatal pneumonitis and fatal hemoptysis). In addition, two other patients developed grade 3 radiation pneumonitis; one was induced by a cold, and the patient received only 18 Gy per nine fractions of radiotherapy. This study was terminated early owing to the high rate of fatal adverse events and radiation pneumonitis.

Conclusions: This study presented severe pulmonary toxicity with concurrent anlotinib and chemoradiotherapy. Several previous clinical trials evaluated the safety of concurrent bevacizumab and radiotherapy or chemoradiotherapy; all were terminated owing to severe treatment-related toxicity. Results of these studies suggest that concurrent antiangiogenic and thoracic radiotherapy should be avoided until appropriate safety data are presented, at least for bevacizumab and anlotinib.

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Keywords: NSCLC; Anlotinib; Thoracic radiotherapy; Pulmonary toxicity

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Introduction

The PACIFIC study established the consolidation therapy role of immunotherapy for inoperable stage III NSCLC.\(^1\) The KEYNOTE-799 study suggested promising antitumor activity and manageable safety of pembrolizumab with concurrent chemoradiotherapy in naive locally advanced stage III NSCLC.\(^2\) Osimertinib consolidation therapy was being explored for EGFR mutation-positive stage III NSCLC.\(^3\) Considering the toxicity of concurrent bevacizumab and thoracic radiotherapy for NSCLC and SCLC, antiangiogenesis therapy is not used in stage III lung cancer.\(^4,5\)

Anlotinib is an orally administered, multitarget, antiangiogenesis tyrosine kinase inhibitor, mainly targeting vascular endothelial growth factor, fibroblast growth factor, platelet-derived growth factor receptors, and c-kit, which can inhibit both tumor angiogenesis and tumor cell proliferation.\(^6\) In a phase 3 clinical trial, ALTER-0303, anlotinib brought about substantial progression-free survival and overall survival benefit compared with placebos as third-line or further treatment in advanced NSCLC.\(^7\) Subgroup analysis of ALTER-0303 revealed that patients with previous chest radiotherapy had a substantial progression-free survival benefit compared with those without previous chest radiotherapy.\(^8\) Anlotinib also presented substantial survival benefit in SCLC, soft-tissue sarcoma, and medullary thyroid carcinoma and was approved as later line or first-line treatment for these diseases in the People’s Republic of China.\(^9,10\) Chu et al.\(^11\) also found that combined anlotinib and sintilimab achieved an excellent objective response rate and disease control rate as first-line treatment for EGFR/ALK/ROS1-negative advanced NSCLC.

Considering the outstanding performance and manageable safety of anlotinib in advanced NSCLC, especially in patients with previous chest radiotherapy, we aimed to determine whether anlotinib could offer survival benefit for stage III NSCLC, addressing the scarcity of antiangiogenesis agents for stage III NSCLC. In this study, we launched a single-institution phase 1 clinical trial to evaluate the safety of concurrent anlotinib and chemoradiotherapy followed by anlotinib consolidation treatment. Unfortunately, this clinical trial was terminated early owing to severe pulmonary toxicity.

Materials and Methods

Patients

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol was reviewed and approved by the institutional review board and ethics committee of Shandong Cancer Hospital and Institute. All patients provided informed consent before enrolment. The inclusion criteria were as follows: (1) age 18 to 75 years, regardless of sex; (2) newly histologically or cytologically diagnosed unresectable or refused surgery stage III NSCLC; (3) Eastern Cooperative Oncology Group performance status score of 0 to 1; and (4) forced expiratory volume in the first second greater than or equal to 1.45 liter/s. The main exclusion criteria were the following: (1) SCLC (including mixed small cell and nonsmall cell cancers); (2) lung squamous cell carcinoma with empty cavities; (3) patients with active hemorrhage or at risk of hemorrhage; (4) previous systemic antitumor therapy; (4) interstitial pneumonia, active pulmonary tuberculosis, and other pulmonary infection; and (5) some other cases unsuitable for this trial as assessed by the investigators. Detailed inclusion and exclusion criteria were listed in ClinicalTrials.gov (NCT04958993).

Trial Design

All enrolled patients were treated with two concurrent cycles of anlotinib and chemoradiotherapy followed by anlotinib consolidation until disease progression or intolerance toxicity; preinduction chemotherapy was allowed. The total radiotherapy dose was 54 to 66 Gy, with a single dose of 1.8 to 2.0 Gy. The radiation dose for organ at risk, such as the lung, heart, and spinal cord was limited by the attending doctor, with no additional radiation-dose limitation. The chemotherapy regimen was selected according to histologic type (platinum and docetaxel for squamous cell carcinoma; platinum and pemetrexed for adenocarcinoma), with no additional limitation in chemotheraphy dose. Anlotinib dose was escalated from 8 mg and 10 mg to 12 mg according to standard 3 + 3 design, once a day for 2 weeks and stopped for 1 week. The dose-limiting toxicity was grade 3 nonhematological toxicity or grade 4 hematological toxicity according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Tumor response was assessed by the investigators according to the Response Evaluation Criteria in Solid Tumors Version 1.1 every 6 weeks. Treatment-related adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 criteria. The maximum tolerance dose period was defined as 21 days after the first cycle of anlotinib was administered to the patients, including events in the first anlotinib cycle, which were verified in the second cycle. Radiation pneumonitis (RP) was assessed in 4 to 6 weeks after complete concurrent anlotinib and chemoradiotherapy and was also monitored for 1 year. All patients were monitored for 21 days.
after the last anlotinib dose to detect any new adverse events.

**Objectives**

The primary end point was the maximum tolerance dose of anlotinib, whereas the second end point was the objective response rate, which is defined as the percentage of subjects with evidence of a confirmed complete response (CR) or partial response as per the Response Evaluation Criteria in Solid Tumors Version 1.1 before progression or any further therapy.

**Results**

Seven patients with stage III NSCLC were enrolled in this clinical trial between November 2020 and November 2021; the patients’ clinical characteristics are presented in Table 1. The median age was 59 years, with most of them being male and presenting with adenocarcinoma. Six patients completed concurrent anlotinib and chemoradiotherapy and then entered the consolidation period. Patient 2 experienced chest distress and cough after the first cycle of anlotinib and chemotherapy, but no evidence for pneumonitis was observed by means of chest computed tomography. The second cycle of concurrent anlotinib and chemotherapy was terminated by the attending physician to complete radiotherapy safely, and the patient withdrew from this study. The median total lung V20 of all patients was 20.84% (0%–31.16%).

Unfortunately, severe toxicity, especially pulmonary toxicity, was associated with this treatment. All grade greater than or equal to 2 treatment-related adverse events are presented in Table 2. Of seven patients, four developed a grade greater than or equal to 3 treatment-related adverse events. Furthermore, two patients developed fatal treatment-related adverse events. Patient 3 (male) presented with stage IIIc lung adenocarcinoma and underwent concurrent anlotinib and chemoradiotherapy followed by anlotinib consolidation therapy without induction chemotherapy. CR was observed during anlotinib consolidation. Nevertheless, 1.5 months after CR, the patient suffered sudden fatal hemothysis and apnea at home, which was considered a result of rapid tumor remission and antiangiogenic effects. Patient 4 (male) presented with stage IIIc lung adenocarcinoma and underwent concurrent anlotinib and chemoradiotherapy followed by anlotinib consolidation after four cycles of induction chemotherapy. The patient developed grade 3 pneumonitis after initial anlotinib consolidation. Glucocorticoid and antibiotic treatment failed to treat pneumonitis, and the patient died a month after concurrent therapy. In addition, patient 1 developed grade 2 RP during anlotinib consolidation; patients 2 and 7 developed grade 3 RP, and patient 7’s RP was induced by a cold after radiotherapy of only 18 Gy per nine fractions. Patient 3 (male) presented with IIIc lung squamous cancer; two cycles of induction treatment with docetaxel and platinum were followed by concurrent anlotinib and chemoradiotherapy. Nevertheless, after a radiotherapy dose of 18 Gy per nine fractions, the patient suddenly developed chest distress, cough, and fever (38.2°C); grade 3 RP was confirmed by a chest computed tomography. After a comprehensive review of this case, we concluded that the cold was partly responsible for the RP. At that stage, only patients 5 and 6 were still undergoing anlotinib consolidation treatment. Nevertheless, the clinical trial was terminated early by the investigator due to severe pulmonary toxicity observed. The treatment information and related pulmonary toxicity timeline are presented in Figure 1.

**Discussion**

In January 2010, Spigel et al. reported a high incidence of severe tracheoesophageal fistulae during concurrent bevacizumab and chemoradiotherapy for patients with NSCLC and SCLC in two clinical trials. In March 2012, Lind et al. reported a phase 1 clinical trial
with concurrent bevacizumab and thoracic radiotherapy, wherein four of six patients developed a grade greater than or equal to 2 RP. In April 2019, Wang et al.\textsuperscript{13} found that when treating ultracentral lung tumor with stereotactic body radiation therapy, patients with a history of antiangiogenesis agent use within 90 days had a marked higher probability of fatal pulmonary hemorrhage compared with the other patients. In 2012, Socinski et al.\textsuperscript{14} attempted concurrent bevacizumab and chemoradiotherapy for 45 patients with stage III NSCLC. Only 28 patients completed induced and concurrent bevacizumab and chemoradiotherapy; 29\% patients developed grade greater than or equal to 3 esophagitis and one patient developed grade 3 tracheoesophageal fistulae.

Although the severe pulmonary toxicity of concurrent thoracic radiotherapy and bevacizumab was reported in previous studies, we still argue that antiangiogenesis therapy should not be abandoned for stage III NSCLC. Anlotinib is an oral-administered, multitarget, antiangiogenic tyrosine kinase inhibitor that presented manageable safety in later-line therapy for advanced NSCLC and SCLC. We initiated this study in our institution to assess the safety of concurrent anlotinib and chemoradiotherapy in stage III NSCLC. Seven patients were treated with concurrent anlotinib and chemoradiotherapy followed by anlotinib consolidation, but unacceptable treatment-related pulmonary toxicity was observed. Two patients developed fatal treatment-related adverse event and another two patients developed grade 3 RP, presenting an extremely high rate of pulmonary toxicity, which could be fatal.

Despite the small sample size in these studies, the results consistently suggest severe toxicity with concurrent antiangiogenic agents and thoracic radiotherapy. As the most important local treatment means, radiotherapy has been combined with chemotherapy and immunotherapy and target therapy in NSCLC.\textsuperscript{15,16} Despite the consecutive failed attempts to combine antiangiogenic and thoracic radiotherapy for NSCLC, we still consider that the combination of antiangiogenesis and thoracic radiotherapy should not be completely disregarded for treating NSCLC. Nevertheless, the best application of this combination remains to be determined. In future, adequate caution must be exercised when conducting similar clinical studies on concurrent antiangiogenesis agents and radiotherapy. Such therapy should be avoided until appropriate safety data are presented, at least for bevacizumab and anlotinib.

### Table 2. The Grade 2 or Worse Treatment-Related Adverse Events of These Patients

| Treatment-Related Adverse Events | P1 | P2 | P3 | P4 | P4 | P6 | P7 |
|----------------------------------|----|----|----|----|----|----|----|
| Hemoptysis                       | 5  |    |    |    |    |    |    |
| Radiation pneumonitis            | 2  | 3  | 5  | 2  | 2  |    | 3  |
| Radiation esophagitis            | 2  | 2  | 2  | 2  | 2  | 2  | 2  |
| Leukocytopenia                   | 2  | 2  | 2  | 2  | 2  | 2  | 2  |
| Lymphocytopenia                  | 3  | 3  | 3  | 3  | 3  | 3  | 3  |
| Thrombocytopenia                 |    |    |    |    |    |    |    |
| Fatigue                          |    |    |    |    |    |    |    |
| Hypertension                     | 2  | 2  |    |    |    |    |    |
| Weight loss                      |    |    |    |    |    |    |    |
| Hand-foot syndrome               | 2  |    |    |    |    |    |    |

P, patient.

Figure 1. The timeline of treatment information and treatment-related adverse event. p, patient.
CRediT Authorship Contribution Statement

Hui Zhu: Conceptualization, Writing—review and editing.
Wenxiao Jia: Data curation, Methodology, Writing—original draft.
Xuquan Jing: Investigation, Writing—original draft.
Wei Huang: Project administration, Formal analysis.
Linlin Wang: Methodology, Project administration.
Jinming Yu: Conceptualization, Supervision, Writing—review and editing, Funding acquisition.

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