Chemotherapy: Open Access
ISSN: 2167-7700

Wang, et al., Chemo Open Access 2016, 5:1
DOI: 10.4172/2167-7700.1000186

Brief Report Open Access

A Study Design: Concurrent EGFR-TKI and Thoracic Radiotherapy as First-line Treatment of Stage IV NSCLC Patients with EGFR Active Mutations (CERTAIN Study)

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Received date: December 26, 2015; **Accepted date:** February 10, 2016; **Published date:** February 15, 2016

Abstract

Lung cancer is a common malignant tumor with high morbidity and mortality worldwide; more than 70 percent of patients are diagnosed with advanced disease. Nowadays, chemotherapy with concurrent thoracic radiotherapy (TRT) has been proven effective in stage IV NSCLC. Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), such as gefitinib and erlotinib, is the standard first-line treatment for stage IV non-small cell lung cancer (NSCLC) patients harboring EGFR active mutations. Previous *in vitro* studies showed that EGFR-TKI could sensitize tumor cells to radiation, and some researches indicated that EGFR mutations appear to be favorable predictive and prognostic factors in NSCLC patients treated with radiotherapy. A retrospective study has indicated that the combination of EGFR-TKI with TRT as the first-line treatment for advanced NSCLC was effective. However, the efficacy of this novel combination treatment strategy needs to be further confirmed in a prospective study. This is an open-labeled, single-arm, phase II clinical trial aiming to evaluate the efficacy and safety of EGFR-TKI combined with thoracic radiotherapy as first-line treatment of stage IV NSCLC patients with positive EGFR mutations. We plan to enroll 47 patients not receiving therapy for primary and metastatic disease previously and with cytologically or pathologically confirmed stage IV NSCLC harboring EGFR active mutations. Each patient will receive erlotinib 150 mg per day orally with concurrent TRT (54~60 Gy/27~30 F/5.5~6 w, within 2 weeks from the beginning of enrollment) until disease progression or intolerable toxicities. The study has been initiated since January 2015 and will be finished in December 2017 expectedly.

Keywords: NSCLC; EGFR-TKI; Thoracic radiotherapy; Targeted molecular therapy

Introduction

Lung cancer, a common malignant tumor with high incidence and mortality rates (1.8 million and 1.6 million, respectively), is the leading cause of cancer deaths among men and the second leading cause of cancer deaths among women around the world [1]. In all cases, patients with non-small cell lung cancer (NSCLC) account for 80 percent approximately and more than 70 percent of them are diagnosed with advanced-stage disease with a poor prognosis [2]. Traditional chemotherapy concurrent with thoracic radiotherapy is the standard strategy for unresectable advanced NSCLC patients; however, the 5-year survival rate is lower than 20 percent, which is disappointing [3].

In the last decade, the discovery of epidermal growth factor receptor (EGFR) mutations in NSCLC patients has launched the era of individualized therapy, and great progress has been made in the treatment administration in advanced NSCLC [4]. EGFR tyrosine kinase inhibitor (EGFR-TKI), such as gefitinib, erlotinib and afatinib, is selective small-molecule agents targeting EGFR [5]. Several international randomized clinical trials, including IPASS, First-SIGNAL, W3405, NEJ002, OPTIMAL, EURTAC, LUX-LUNG3 and LUX-LUNG6, demonstrated that EGFR-TKI is significantly more effective in prolonging progression-free survival (PFS) and increasing disease control rate (DCR) than standard chemotherapy in advanced NSCLC patients harboring EGFR-positive mutations as the first-line treatment [6-13]. Unfortunately, in spite of remarkable response to EGFR-TKI in these selected population, it is inevitable to develop acquired resistance to EGFR-TKI within 9.2-13.1 months for almost all patients initially benefiting from EGFR-TKI, which eventually leads to progressive disease [14,15]. Nowadays, cytotoxic chemotherapy is the only standard treatment option for patients resistant to EGFR-TKI [16]. Therefore, oral EGFR-TKI alone may not be sufficient in advanced disease.

A previous study found that local therapy including radiation, radiofrequency ablation and metastasectomy followed by continued treatment with EGFR-TKI was well tolerated and was associated with prolonged PFS and OS in patients with EGFR-mutant advanced lung cancers who developed acquired resistance to EGFR-TKI [17]. For local advanced NSCLC, radiotherapy plays an important role in improving local control and alleviating tumor-related symptom [18]. Nowadays, chemotherapy concurrent with thoracic radiotherapy has been proven effective in stage IV NSCLC [19]. And thoracic radiotherapy can also prolong PFS and OS in extensive stage SCLC patients [20]. Thus we speculate that combining radiotherapy with EGFR-TKI may be a feasible approach to improving treatment outcome of advanced NSCLC. And the synergistic effect between EGFR-TKI and radiation has also been found. EGFR can be activated in response to radiation, and repeated exposure to radiation can also increase the expression of EGFR [21]. Tanaka [22] found that *in vitro*

NSCLC cells were radiosensitized by gefitinib via suppressing cellular DNA repair capacity. Moreover, EGFR-TKI radiosensitizes tumor cells by cell cycle arrest, apoptosis and accelerating repopulation [21]. Some researchers also indicate that EGFR mutations appear to be a favorable predictive and prognostic factor in NSCLC patients treated with radiotherapy [23]. A retrospective study showed that the combination of first-line EGFR-TKI with early multi-target radiotherapy was effective for treating patients with advanced non-squamous cell, non-small cell lung cancer (NsqCLC), who can respond to upfront TKI treatment, with 16 months of PFS and 84% of overall survival rate (ORR) respectively [24]. In addition, a phase II study showed that stereotactic body radiation therapy (SBRT) combined with erlotinib resulted in high PFS and OS as a second or subsequent line treatment in unselected patients with limited but progressive NSCLC [25]. Even though the rationale of EGFR-TKI combined with ionizing radiation is well established, up to now, the optimal combinational approach of EGFR-TKI and radiotherapy is poorly understood and there is lack of prospective clinical data to evaluate the value of this therapy modality. The question that whether it is necessary to add thoracic therapy to the first-line TKI treatment remains to be answered.

Our prospective study is to investigate the efficacy and safety of EGFR-TKI concurrent with thoracic radiotherapy as the first-line treatment in stage IV NSCLC with EGFR active mutations.

Patients

Eligible criteria

Patients will be enrolled according to the following criteria. The main inclusion criteria include: an age from 18 to 75 years old with Eastern Cooperative Oncology Group (ECOG) performance status 0~2; cytologically or pathologically confirmed stage IV NSCLC with EGFR active mutations; estimated survival time of more than 3 months; adequate liver, renal and hematological functions; without a therapy history of primary and metastatic disease; asymptomatic bone metastases without treatment, M1a or M1b for metastases, and the number of the distant lesions ≤10. The radiotherapy plan should be based on fusion images of 4D-CT MIP sketch tumors and lymph nodes, and the lung dose should be limited as V20 ≤ 25%, V30 ≤ 18%, MLD ≤ 14Gy, and V5 ≤ 60%.

The exclusion criteria are brain metastases; bone metastases needing local treatment; uncontrolled pleural effusion; serious functional damage to important organs; active period of acute or chronic infectious diseases; pregnants or breast-feeding females; allergic to erlotinib; unstable systemic disease; participation in other clinical trial; a history of another malignancy in the last 5 years with the exception of the malignancy cured by surgery alone and a continuous disease-free interval of 5 years or cured basal cell carcinoma of the skin or cured in situ carcinoma of the uterine cervix.

Sample size

According to ENSURE study (NCT01342965), 1-year PFS rate of patients receiving erlotinib alone is about 43% [26]. Estimated 1-year PFS rate is 60% for patients treated with erlotinib and concurrent TRT. Because of 10% total dropout rate and 10% non-event rate, adjusting one-sided $\alpha = 0.1$, $\beta = 0.2$, a sample size of 47 is needed by Freedman rules.

Study design

This is an open-labeled, single-arm, phase II clinical trial aiming to evaluate the efficacy and safety of EGFR-TKI combined with thoracic radiotherapy as the first-line treatment of stage IV NSCLC patients with positive EGFR mutations. Before recruitment of patients, the study has been registered at ClinicalTrials.gov (NCT 02353741). This study has been approved by ethics committee of the Third Military Medical University (LSD 2015024).

Fourty-seven patients will be enrolled according to the plan. After the enrollment, each patient will receive erlotinib 150 mg per day orally with concurrent TRT (5460 Gy/27~30 F/5.5~6 w, within 2 weeks from first-dose EGFR-TKI) until disease progression or intolerable toxicities. Every patient should come back to the hospital for disease evaluation every 2 months and the follow up will last for 12 months at least (Figure 1).

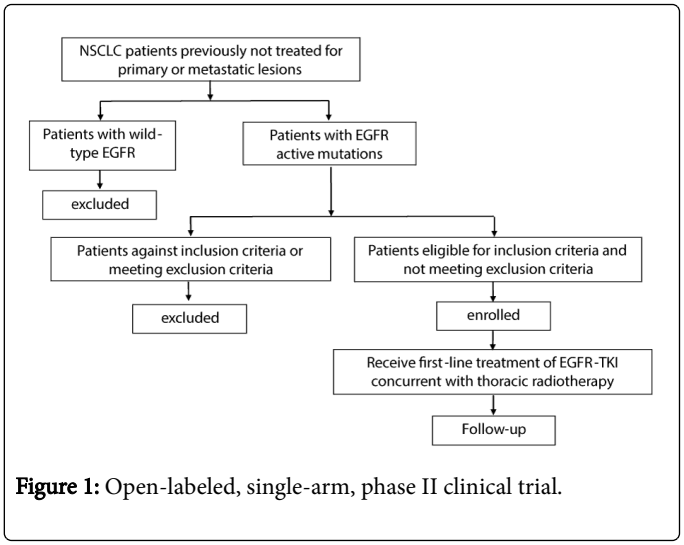

Figure 1: Open-labeled, single-arm, phase II clinical trial.

The study has been started in January 2015 and will be finished in December 2017 expectedly.

Data

For patients participating in this trial, medical data will be collected during the treatment and analyzed at the end of the study. The Response Evaluation Criteria in Solid Tumors (RECIST v1.1) will be used for assessing tumor response [27]. The Functional Assessment of Cancer Therapy-Lung (FACT-L) and Common Terminology Criteria of Adverse Events (CTCAE) will be done to assess the health-related quality of life (HRQoL) and adverse events respectively [28,29]. PFS is defined as the interval from the first day of treatment to investigator-assessed progression or death. OS is calculated from the beginning of therapy to patients' death. Disease control rate (DCR) is defined as the proportion of patients reaching overall or partial response or stable disease. Pattern of failure is defined as the number of patients who fail to respond to the combined therapy. Blood serum for analysis of immune indexes will be collected every 2 months during TKI treatment.

Statistical Analysis

The primary endpoint is 1-year PFS rate of enrolled patients. Secondary endpoints are OS, DCR, ORR, QOL, pattern of failure and

adverse events. The time to event data (OS, PFS, etc.) will be summarized with Kaplan-Meier analysis in ITT population. The Cox regression model will be used to estimate the relative hazards ratio (HR) of PFS and OS. For ORR and DCR, Chi-squared test will be applied. T test will be available in the analysis of tumor immune indexes. All the statistical analysis will be performed by Brightech International, LLC. (Chengdu, China).

Expectations and Limitations

In theory, the combined modality therapy of EGFR-TKI and ionizing radiation may exert a synergistic effect and be a new strategy to improve the treatment outcome, thus serving as an alternative to present TKI monotherapy for EGFR gene selected patients. This single-arm, phase II trial (abbreviated as CERTAIN) is the first study in which advanced NSCLC patients harboring EGFR active mutations are going to be treated with EGFR-TKI concurrent with thoracic radiotherapy as the first-line treatment. Before performing this trial, we have collected and analyzed medical data of five patients attending our hospital who were diagnosed with stage IV EGFR-mutant NSCLC and received second-line EGFR-TKI combined with thoracic radiation. Despite with the low number of patients, the outcome was surprising and the PFS and OS were 291 days and 523 days respectively. Therefore, we presume that the results of our present work may be promising and hopeful.

There are also several limitations about this study. It is a single-arm study with a small sample size and the lack of random assignment and a control group may reduce the reliability of the results. Thoracic radiation therapy may induce radiation pneumonitis and interstitial lung disease is one of adverse events of EGFR-TKI [24]. Thus, the addition of radiotherapy to EGFR-TKI may increase the incidence rate and severity of pneumonitis. That's why we adopt palliative dose of TRT and make the lung dose lower than usual.

Conclusions

To our knowledge, this is an original trial which integrates EGFR-TKI concurrent with thoracic radiotherapy as the first-line treatment in NSCLC for the first time and needs to be explored and verified urgently. We anticipate the promising results from it. In the future, randomized clinical trials need to be conducted to confirm our practice.

Acknowledgements

This work was supported by grant from Chongqing Natural Science Foundation (cstc2012jjA10096), Clinical Innovation Foundation of the Third Military Medical University (yclkt-201408) and Wu Jieping Medical Foundation (320.6799.15037). The authors thank in advance all the patients and investigators who will be involved in this study.

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