Radiotherapy combined with gefitinib for patients with locally advanced non-small cell lung cancer who are unfit for surgery or concurrent chemoradiotherapy: A phase Ⅱ clinical trial

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Research

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Abstract

Background: The objectives of this study were to determine the objective effective response rate, survival, and safety of radiotherapy combined with gefitinib in patients with locally advanced non-small cell lung cancer (NSCLC) who were unfit for surgery or concurrent chemoradiotherapy.

Methods: The patients with the locally advanced NSCLC who were unfit to receive surgery or concurrent chemoradiotherapy, received thoracic intensity-modulated radiotherapy (IMRT) combined with gefitinib 250 mg daily.

Results: Twenty-nine patients were enrolled between July 2014 and March 2017. Of the 29 patients, 21 (72.4%) experienced a partial response, 6 (20.7%) had stable disease, and 2 (6.9%) experienced progression of disease. The objective response rate was 72.4%, and the disease control rate was 93.1%. The median follow-up time was 51 months. The disease progression showed in 26 (89.7%) patients, including local progression in 20 (69.0%) and distant metastasis in 16 (55.2%). The median survival time (MST) and progression-free survival time (PFS) were 26 and 11 months, respectively. The 3-, 4-, 5-year survival rates were 37.6%, 29%, and 29%, respectively. The PFS rates were 17.2%, 9.2%, and 9.2%. Two patients developed grade 3 acute adverse events, and two patients developed grade 2 acute irradiation pneumonitis.

Conclusions: For patients with locally advanced NSCLC who are not eligible for surgery or concurrent chemoradiotherapy, IMRT combined with gefitinib can improve the objective effective rate and is generally well-tolerated.

Background

Lung cancer is a malignant tumor with one of the highest morbidity and mortality rates in the world, and non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancers [1]. Approximately 30% of NSCLC are at a locally advanced stage at the time of diagnosis. Concurrent chemoradiotherapy (CRT) is the standard treatment for unresectable locally advanced NSCLC; however, not all patients with unresectable stage NSCLC are able to tolerate concurrent CRT. Previous clinical trials have shown that among patients treated with concurrent CRT, the incidence of grade 3 and more irradiation pneumonitis and esophagitis ranged from 0–18% and 3.4–32%, respectively [2–11].

Among patients who are unable to tolerate concurrent CRT, the conventional treatment regimens are sequential chemotherapy and radiotherapy, or radiotherapy only, and the median survival time (MST) is 11–16 months [2–9].

Coupled with further development of lung cancer genomics, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) provide an effective treatment for patients with the advanced lung adenocarcinoma. There is currently a lot of interest in targeted therapy, which has a higher efficiency and a lower toxicity.

Several trials have shown that EGFR inhibitors have a radiotherapy sensitization effect when combined with radiotherapy. The Cancer and Leukemia Group B (CALGB30106) trial [12], which evaluated the feasibility of poor-risk patients receiving radiotherapy and gefitinib (Group A) and those with a more favorable risk profile receiving concurrent CRT and gefitinib (Group B), showed that Group A had a longer MST than Group B. In RTOG 0972, a phase clinical trial of induction chemotherapy followed by thoracic radiotherapy (TRT) and erlotinib in 75 poor-risk patients with stage NSCLC, showed the MST and progression-free survival time (PFS) were 17 and 11 months, respectively, and the 1-year overall survival (OS) was 75% [13].

These trials demonstrate that radiotherapy combined with targeted therapy may be a potentially beneficial treatment for patients with locally advanced NSCLC who are unable to tolerate concurrent CRT. We conducted a phase trial to evaluate the effectiveness of radiotherapy combined with gefitinib in patients with locally advanced NSCLC who were unfit for surgery or concurrent CRT. The primary objective of this study was to determine the objective response rate. The secondary objectives included assessing the OS, MST, PFS, and the safety of radiotherapy combined with gefitinib.

Patients And Methods

2.1 Patient selection

The inclusion criteria were: (1) histologically or cytologically confirmed unresectable stage NSCLC; (2) no thoracic radiotherapy history; (3) tumor objectively measured; (4) age ≥18 years; (5) Karnofsky Performance Status ≥70; (6) predicted survival ≥3 months; (7) without severe disease of the vital organs; and (8) provision of written informed consent.

The exclusion criteria were: (1) neurological disease; (2) history of recent treatment for another malignant tumor; (3) previous participation in clinical trials of other new drugs; and (4) previous targeted therapy.

2.2 Treatment

Patients were treated with a combination of radiotherapy and gefitinib:

- **Radiotherapy:** Photon beams were applied with an intensity of 6-MV. The gross tumor volume was defined as the volume of the primary disease as well as any involved regional lymph nodes (the short axis of at least 1 cm on computed tomography scan). The clinical target volume (CTV) included the primary tumor plus a margin of 6-8 mm, including the ipsilateral hilum and the mediastinal lymph nodes. The planning target volume (PTV) included the CTV plus a margin of 5 mm in 3 dimensions. The prescription dose was 95% PTV 54–66 Gy/2 Gy/27–33f.
- **Gefitinib:** An oral dose of 250 mg was administered daily, starting on Day 1. If the treatment was effective, it was continued after radiotherapy had been completed.

2.3 Response and toxicity criteria

The Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.0 was used to evaluate the short-term effectiveness. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 was used to evaluate the toxicity.

2.4 Study design

The study was a single-arm, phase Ⅱ open-label clinical trial.

2.5 Calculation of sample size

In the JCOG0301 trial [14], the objective effective rate of concurrent CRT was 51.5%. We expected that the objective effective rate of TRT with gefitinib would be 68%. According to the sample size calculations, at least 27 patients would be required. The target sample size was increased by 10% to 30 patient to allow for participant withdrawals.

2.6 Statistical analysis

The statistical analysis was performed using SPSS version 20.0 (IBM Corp, Armonk, NY, USA). Kaplan-Meier plots were used for survival analysis. Log-rank tests were used to assess the significance of associations in the univariate analysis. Cox regression was using to assess factors associated with survival in the multivariate analysis. Results with $p<0.05$ were considered statistically significant.

Results

3.1 Patient characteristics

From July 2014 to March 2017, 30 patients were enrolled, of which 29 were included in the analysis. One patient did not receive the protocol treatment and so was excluded from the analysis. The median age of the participants was 63 years. Of the participants, 7 (24.1%) and 22 (75.9%) were diagnosed with stages Ⅲ A and Ⅲ B NSCLC, respectively. Seventeen participants (58.6%) had previously received platinum-based induction chemotherapy (Table 1).

3.2 Treatment regimens

Of the 29 participants, 22 received intensity-modulated radiotherapy and 7 received volumetric-modulated arc therapy. 28 patients completed TRT with a dose of 54–60 Gy. One patient completed TRT with a reduced does of 34 Gy because of fever.

Response to treatment and toxicity

Of the 29 patients, 21 (72.4%) experienced a partial response (PR), 6 (20.7%) had stable disease (SD), and 2 (6.9%) experienced progression of disease (PD). None of the patients experienced a complete response (CR). The objective response rate (CR+PR) was 72.4%, and the disease control rate (CR+PR+SD) was 93.1%. Twenty-six participants (89.7%) experienced a relapse: 20 (69.0%) experienced a local relapse, and

16 (55.2%) experienced a distant relapse, including 10 participants (34.5%) who experienced both a local and a distant relapse.

Overall, the toxicity results demonstrated the feasibility of this approach (Table 2). One patient (3.4%) experienced Grade 3 liver dysfunction, esophagitis, and diarrhea, respectively. Seven participants (24.1%) experienced grade 2 pneumonitis.

3.3 Survival

Follow-up was censored on 15 December 2019. The median follow-up time was 51 months. The median PFS was 11 months, and the MST was 26 months. The 3-, 4- and 5-year survival rates were 37.6%, 29%, and 29%, respectively. The 3-, 4- and 5-year PFS rates were 13.8%, 9.2%, and 9.2%, respectively. (Figure 1).

Univariate analysis showed that only disease stage was associated with OS (p=0.016, 95%CI 0.072-0.767), and with PFS (p=0.004, 95%CI 0.043-0.539).

The MST of participants with stages □ A and □ B disease were 12 and 27 months, respectively. Participants with stage □ B disease had a significantly better OS and PFS than patients with stage □ A disease.

3.4 Epidermal growth factor receptor mutation

Molecular data were available for 13 participants. The EGFR-activating mutation was detected in 6 of the 13 participants (46.2%). The 6 participants with the EGFR-activating mutation had a significantly better MST (39 months) than the 21 participants with the EGFR wild-type or non-adenocarcinoma (21 months) without significant difference.

Discussion

In this trial, the PR rate and the objective effective response rate were both 72.4%, and the disease control rate was 93.1%, and no participants experienced a CR. In previous clinical trials of concurrent CRT the CR rate was 9–28%, the PR rate was 28–81%, and the objective effective response rate was 43–85% [2–11,14]. Among participants in previous studies who received radiotherapy only, or sequential chemotherapy and radiotherapy, the CR rate was 1.3–30%, the PR rate was 30–65%, and the objective effective response rate was 39–66%. Although none of the participants in our study experienced a CR, the PR rate and the objective effective response rate were comparable to those of previous studies.

The reason for the absence of any participants with a CR in this study may be attributable to: the high proportion of participants with stage □ B disease (76%); older age (50% were aged ≥65 years); high PTV (62% had a PTV volume >450 ml); the relatively small proportion of participants with adenocarcinoma (41%). The relatively high PR rate and objective effective response rate compared to previous studies may be attributable to the higher rates of completion of radiotherapy (97%) and targeted therapy (83%).

In the CALB30106 trial [12] the high-risk group (radiotherapy and gefitinib) had a MST of 19.0 months and median PFS of 13.4 months; while the low-risk group (concurrent CRT and gefitinib) had a MST of 13 months and a median PFS of 9.2 months. The survival time of high-risk patients who received sequential CRT with gefitinib is promising. Spanish researchers [15] studied 90 patients with locally advanced NSCLC. The MST was 11.4 months among those who received radiotherapy only, and 8.9 months among those who received radiotherapy with erlotinib, and the median PFS was 15.3 months and 12.9 months, respectively. Wang et al reported that EGFR-TKI concurrent with thoracic radiotherapy in treating stage ⅢB/Ⅳ NSCLC had local control rate of 96% for thoracic tumor and 1-year PFS rate of 42% [16]. Zheng et al reported that the 1-year PFS rate of 57.1%, the median PFS 13 months and the median time to progression of irradiated lesion 20.5 months in TIK combined with radiotherapy as first line treatment for patients with stage Ⅳ NSCLC harboring EGFR active mutations [17]. In the RTOG 9410 trial [4], the MST was 17 months among participants who received 60 Gy of CRT, and 15.6 months among those who received 70 Gy of CRT. Compared with radiotherapy only and concurrent CRT, the survival of participants who received radiotherapy combined with targeted therapy is comparable to that of the participants in our study.

In our study, the OS and PFS of participants with stage Ⅲ B disease was higher than that of participants with stage Ⅲ A disease. Possible reasons for this paradoxical result include: (1) participants with stage Ⅲ A disease had more risk factors than those with Ⅲ B disease including older age, greater weight loss, more comorbidities, less healthy lifestyles, and larger primary tumors; (2) participants with stage Ⅲ B disease were more likely to have adenocarcinoma and EGFR mutations than those with stage Ⅲ A disease; (3) participants with stage Ⅲ B disease received more induction chemotherapy; and (4) participants with stage Ⅲ A disease suffered more acute toxicities.

In our study, participants with the EGFR-activating mutation had a better MST than those with the EGFR wild-type and those with non-adeno carcinomatous tumors. This result suggests that there is an association between the EGFR mutation state and response to radiotherapy combined with targeted therapy. Previous studies have shown that among patients with NSCLC, approximately 80% have squamous cell carcinoma, and 65% of patients with adenocarcinomas have overexpression of EGFR protein, which is an important factor leading to radiation resistance [18–19]. A meta-analysis conducted in 2002 suggested that a high EGFR expression could be related to the prognosis of NSCLC [20]. However, the CALGB 30106 trial [12] did not find an association between the presence of EGFR mutations and the prognosis of NSCLC. Although the relationship between EFGR-mutation and prognosis in advanced lung adenocarcinoma was relatively clear, the heterogeneity was relatively large among participants with locally advanced lung adenocarcinoma who were able to receive radiotherapy and chemotherapy. For locally advanced lung cancer, there are no prospective studies that have assessed whether individuals with EGFR-activating mutations could benefit from targeted therapy as the first-line treatment. Our study suggests that radiotherapy combined with gefitinib could improve the survival of patients with locally advanced EGFR-activating mutation lung adenocarcinoma.

In this study, the majority of acute adverse events (93%) were grades 1 and 2; only 7% of participants experienced a grade 3 acute adverse event, and no participants experienced a grade 4 acute adverse event. These results indicate that radiotherapy combined with gefitinib was well tolerated.

Irradiation pneumonia is an important adverse event among patients treated with TRT. In our study, the incidence of grade 2 acute irradiation pneumonitis was 24%, but there were no cases of more than grade 3 acute irradiation pneumonitis. Compared with concurrent CRT (which has a reported rate of grade 3 acute irradiation pneumonitis of 0–18%) [2–11], targeted therapy combined with radiotherapy did not significantly increase the incidence of related adverse events. Although irradiation pneumonia did not cause any treatment-related deaths among participants in our study, the pulmonary toxicity associated with EGFR-TKIs is a cause for concern. Zheng et al reported that the most common grade 3 adverse events were radiation pneumonitis (20%) and rash (10%) in TIK combined with radiotherapy as first line treatment for patients with stage NSCLC harboring EGFR active mutations [17]. A study [21] of the relationship between radiotherapy combined with erlotinib and acute irradiation pneumonitis among 24 patients with NSCLC, suggested that 9 patients (37.5%) experienced greater than grade 2 acute irradiation pneumonitis. Other studies have shown that erlotinib can damage the lung stroma [22–23], and erlotinib combined with TRT may increase the occurrence of acute irradiation pneumonitis. Some small sample studies [24–25] also reported there was a higher incidence of acute irradiation pneumonitis among patients treated with erlotinib combined with TRT.

This trial had several limitations. First, some patients received induction chemotherapy, but the induction chemotherapy regimens and chemotherapy cycles were not standardized. Second, this study was a single-arm, phase clinical trial with no control group. Third, the sample was small.

Conclusions

For patients with locally advanced NSCLC who couldn’t receive surgery or concurrent chemoradiotherapy, TRT combined with gefitinib could improve the objective effective rate and be tolerated well.

List Of Abbreviations

CR, complete response; CRT, chemoradiotherapy; CTCAE, Common Terminology Criteria for Adverse Events; CTV, clinical target volume; EGFR, epidermal growth factor receptor; IMRT, intensity-modulated radiotherapy; MST, median survival time; NCI, National Cancer Institute; NSCLC, non-small cell lung cancer; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PTV, planning target volume; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TKI, tyrosine kinase inhibitor; TRT, thoracic radiotherapy

Declarations

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This trial had approved by Ethics Committee of Cancer Institute and Hospital , Chinese Academy of Medical Sciences. Approval No. 14-091/881.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data and materials of this study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

The authors have declared no conflicts of interest.

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AUTHORS' CONTRIBUTIONS

Dr. Jun Liang had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Acquisition, analysis, or interpretation of data: Xu Yang, Wenqing Wang, Lei Deng, Tao Zhang, Nan Bi, Xiaozhen Wang, Dongfu Chen, Zongmei Zhou. Drafting of the manuscript: Zhixue Fu. Supervision: Luhua Wang, Jun Liang

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Tables

Table 1. Patients' characteristics

Characteristics	N（%）
Sex	
Male	25（86.2）
Female	4 （13.8）
Age	
Median	63
Range	42-77
Smoking index	
0	7 （24.1）
1-400	1 （3.5 ）
≥400	21（72.4）
KPS status	
70	2 （6.9）
80	17（58.6）
90	9 （31.1）
100	1 （3.4）
Weight loss within 6 months before the treatment	
0	19（65.5）
<5%	4 （13.8）
≥5%	6 （20.7）
T stage	
T1	1 （3.4）
T2	11（37.9）
T3	9 （31.1）
T4	8 （27.6）

N stage	
N1	3 （10.3）
N2	9 （31.1）
N3	17（58.6）
Clinical stage	
（A	7 （24.1）
（B	22（75.9）
Histological type	
• Squamous cell carcinoma	16（55.2）
Adenocarcinoma	12（41.4）
Neuroendocrine carcinoma	1 （3.4）
Inducing chemotherapy before TRT	
Yes	17（58.6）
No	12（41.4）

Table2（ Acute adverse events

Toxicity	Toxicity Grade			
	1	2	3	4
	N（%）	N（%）	N（%）	N（%）
Skin				
Rash	9 （31.0）	0	0	0
Radiation dermatitis	19（73.1）	0	0	0
Hematologic toxicity				
Anemia	9 （31.0）	0	0	0
Leukopenia	9 （31.0）	0	0	0
Thrombocytopenia	0	0	0	0
Gastrointestinal toxicity				
Nausea	7 （24.1）	3（10.3）	0	0
Vomiting	1 （3.4）	1（3.4）	0	0
Diarrhea	1 （3.4）	0	1（3.4）	0
Esophagitis	10（34.5）	9（31.0）	1（3.4）	0
Hypohepatia	9 （31.0）	0	1（3.4）	
Renal function	6 （20.6）	0	0	0
Pneumonitis	3 （10.3）	7（24.1）	0	0

Figures

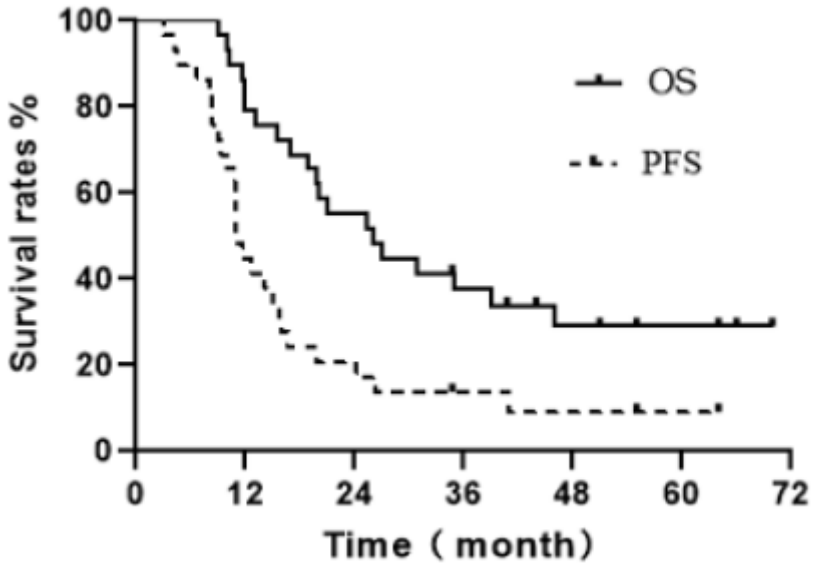

Figure 1

The OS and PFS curves of the whole group