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Gefitinib combined with γ-ray stereotactic body radiation therapy has better efficacy than gefitinib alone for senile lung adenocarcinoma patients with EGFR mutations as first-line regimen*

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Abstract ***Objective:*** The senile lung adenocarcinoma patients harboring an activating epidermal growth factor receptor (EGFR) mutation shows good and rapid response to EGFR tyrosine kinase inhibitors (TKIs). Whether gefitinib combined with γ-ray stereotactic body radiation therapy has better efficacy than gefitinib alone for senile lung adenocarcinoma patients with EGFR mutations as first-line regimen is still under investigation. ***Methods:*** The 42 senile lung adenocarcinoma patients with EGFR mutations were divided into 2 groups according to the therapy method. Group A was the 22 patients treated with gefitinib combined with γ-ray stereotactic body radiation therapy (SBRT). Group B was the 20 patients treated with gefitinib alone. All of the patients received gefitinib of 250 mg/d from the first day until disease progression or other reasons. The patients of Group A were treated with γ-ray stereotactic body radiation therapy from the second day. Radiation fields included the primary lesions and the integration of lymph nodes. Dose curve of this group was 50%–80%. Encircled dose was 4.0–6.5 Gy per fraction and the range of total dose was 40–52 Gy. We treated the patients 8–12 times and treated five times every week. ***Results:*** All the patients were examined by enhanced double helix CT at the second month. The tumor response rate (RR) of group A was 81.8% (18/22). Disease control rate (DCR) was 90.9% (20/22). The median overall survival (OS) was 24.2 months (range 8–58 months) and the progression-free survival (PFS) was 18.6 months. The overall 1-year survival rate was 72.3% (16/22) and 2-year survival rate was 54.5% (12/22). The main side effects included skin rash and diarrhea. The RR of group B was 50.0 % (10/20). DCR was 75.0% (15/20). OS was 17.4 months (range 6–32 months) and PFS was 12.1 months. The overall 1-year survival rate was 60.0% (12/20) and 2-year survival rate was 40.0% (8/20). The main side effects included skin rash and diarrhea. The group A who were treated with gefitinib combined with γ-ray stereotactic body radiation therapy had a higher short term therapeutic effects (RR) and long term therapeutic effects (OS) than group B who were treated with gefitinib alone respectively (81.8% vs 50.0%, $P = 0.029 < 0.05$, $\chi^2 = 4.773$ and 24.2 vs 17.4, $P = 0.024 < 0.05$, $\chi^2 = 5.098$). ***Conclusion:*** Gefitinib combined with γ-ray stereotactic body radiation therapy has better efficacy than gefitinib alone for senile lung adenocarcinoma patients with EGFR mutations as first-line regimen. The side affects are acceptable.

Key words gefitinib; γ-ray stereotactic body radiation therapy (SBRT); epidermal growth factor receptor (EGFR) mutations; senile; first-line regimen

Lung cancer is one of the most commonly malignant tumors for human being and the major cause of cancer death in the world. With the elongation of the lifetime of mankind and the increase of the incidence of lung cancer, the incidence of senile lung cancer has increased prominently and reaches the peak at the age of seventy to seventy four. The senile lung cancer patients have their own characteristics. The adenocarcinoma accounts for about fifty percent of lung cancer in senile patients. So, the combined modality therapy of lung adenocarcinoma has a very important research value for senile patients. Radiotherapy and biological targeting therapy have become an important method for senile patients with adenocarcinoma of lung for the miopragia of the organs and the descent of the repair ability of the cellular damage of senile patients. Gefitinib (ZD1839, Iressa) is an inhibitor of tyrosine kinase of epidermal growth factor receptor (EGFR) which has a good effect and low subsidiary reaction for non-small lung cancer (NSCLC) in Asia [1] and has been used in elderly or poor performance status patients with

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advanced NSCLC as first-line regimen especially for the patients with EGFR mutations [2]. The γ-ray stereotactic body radiotherapy (γSBRT) has a good effect in the near future for senile NSCLC patients. At the same time EGFR inhibitor has shown efficacy as a radiosensitizer [3]. There was few systematic study about the treatment of senile lung adenocarcinoma patients with EGFR mutations. We have verified that gefitinib combined with γ-ray stereotactic radiotherapy is feasible and effective for treatment in senile patients with adenocarcinoma of lung as the first-line regimen in preliminary study [4]. To evaluate whether gefitinib combined with γ-ray stereotactic body radiation therapy has better efficacy than gefitinib alone for senile lung adenocarcinoma patients with EGFR mutations as first-line regimen, we enrolled 42 senile lung adenocarcinoma patients with EGFR mutations from July 2007 to August 2009.

Materials and methods

For respecting the right to choose of the patients and the family member, our research did not use randomization but to solicit their opinions and enroll the corresponding therapeutic group. Selected standard included the following eight points: (1) Adenocarcinoma of lung approved by histology and harboring either exon 19 or 21 mutation. (2) Operation and chemotherapy were rejected by the patients and the family member specifically. (3) The age of patients was more than seventy years old and the performance status of Zubrod-ECOG-WHO (ZPS) was 0 to 3. (4) There was at least one measurable lesion and the total number was less than three (integration of lymph nodes accounts for one lesion). (5) The function of heart, liver and kidney was primary normal basically. (6) Without moderate or abundant malignant hydrothorax. (7) Without typical interstitial pneumonia or pulmonary fibrosis. (8) Patient and family member signed the informed consent.

There were 42 patients in our groups. Male was 14 and female was 28. The age range of these patients was from 72 to 82 years and the average age was 75.2 years. All of these patients were adenocarcinoma of lung approved by histology and harboring either exon 19 or 21 mutation. According to the American Joint Committee on Cancer (AJCC seventh edition) TNM Staging for lung cancer, there were 12 patients belonging to stage II and 30 patients belonging to stage III in our groups. The total longitude of all the lesions of the patient was from 3 to 10 centimeter and the average length was 6.1 centimeter. The performance status of Zubrod-ECOG-WHO (ZPS) was 0 to 3 and the average score was 2.1 score. There was no statistical variance in age and clinical stage between the two groups (Table 1).

Group A was the 22 patients treated with gefitinib combined with γ-ray stereotactic body radiation therapy (SBRT). Group B was the 20 patients treated with gefitinib alone. All of the patients received gefitinib of 250 mg/d from the first day until disease progression or other reasons. The patients who were treated with γ-ray SBRT from the second day. Radiation fields included the primary lesions and the integration of lymph nodes. Dose curve of this group was 50%–80%. Encircled dose was 4.0–6.5 Gy per fraction and the range of total dose was 40–52 Gy. We treated patients 8–12 times and treated five times every week. Antiasthma, eliminate sputum, dephlogisticate and some other directional treatments were used to deal with the symptoms such as cough, expectoration, panting and so on in the two groups.

The patients in our groups were followed up by the telephone once every month and clinic service once every 3 months. The objective effectiveness of the two groups were according to the calculation of the double helix CT at two months.

Efficacy was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for solid tumors. Each patient experienced either a complete response (CR), partial response (PR) or achieved stable disease (SD) or progressive disease (PD). The response rate (RR) was calculated using the formula: RR = CR + PR. The disease control rate (DCR) was calculated as DCR = CR + PR + SD. Toxicity was evaluated according to the standard for adverse reactions (grades 1–4) issued by the National Cancer Institute of the USA. The calculation of therapeutic effect was from the effectiveness to the progression and total survival rate was from the enrollment to the death. The time of disease progress was from the enrollment to the obvious progress.

The objective therapeutic effects were calculated with χ^2 test and the live time assessment used Kaplan-Meier test. All of the patients enrolled in our research have been analyzed.

Results

Efficacy

Table 2 described therapeutic effect of tumor lesions

Table 1 Characteristics of patients

Characteristics	Gefitinib-SBRT (n = 22)	Gefitinib (n = 20)	P value
Average age (years)	74.6	75.9	0.290
Male (n)	9	5	0.275
Female (n)	13	15	
Average performance status (ECOG)	1.9	2.3	0.855
Average stage	2.6	2.8	0.342
Average longitude of the lesions (centimeter)	5.8	6.4	0.636

Table 2 The therapeutic effects of all patients who were treated with different therapeutic methods (*n*, %)

	Gefitinib-SBRT		Gefitinib		*P* value
	n = 22	%	*n* = 20	%	
CR	3	13.6	1	5.0	0.341
PR	15	68.2	9	45.0	0.129
SD	2	9.1	5	25.0	0.167
PD	2	9.1	5	25.0	0.167
RR	18	81.8	10	50.0	0.029
DCR	20	90.9	15	75.0	0.167
PFS (months)	18.6		12.1		0.045
OS (months)	24.2		17.4		0.024
1-year survival rate (%)	72.3		60.0		0.382
2-year survival rate (%)	54.5		40.0		0.346

CR, response rate; PR, partial response; SD, stable disease; PD, progressive disease; RR, response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival

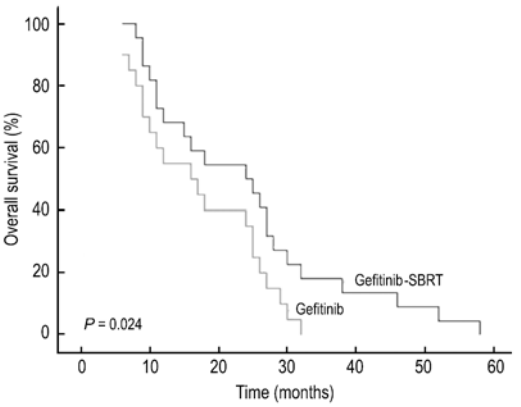

Fig. 1 Kaplan-Meier curves of overall survival for all patients from start of treatment

examined by enhanced double helix CT at the second month, including progression-free survival (PFS), median overall survival (OS) and overall survival rate. The survival analysis was described as Fig. 1. The tumor response rate (RR) of group A was 81.8% (18/22). Disease control rate (DCR) was 90.9% (20/22). The median overall survival (OS) was 24.2 months (range 8–58 months) and the PFS was 18.6 months. The overall 1-year survival rate was 72.3% (16/22) and 2-year survival rate was 54.5% (12/22). The RR of group B was 50.0% (10/20). DCR was 75.0% (15/20). OS was 17.4 months (range 6–32 months) and PFS was 12.1 months. The overall 1-year survival rate was 60.0% (12/20) and 2-year survival rate was 40.0% (8/20). The group A who were treated with gefitinib combined with γ-ray SBRT had a higher short term therapeutic effects (RR) and long term therapeutic effects (OS) than group B who were treated with gefitinib alone respectively (81.8% vs 50.0%, $P = 0.029 < 0.05$, $\chi^2 = 4.773$ and 24.2 vs 17.4, $P = 0.024 < 0.05$, $\chi^2 = 5.098$).

Safety

All 42 patients were included in the toxicity evaluation (Table 3). Adverse effects of patients were acceptable. The main side effects included skin rash and diarrhea between grade 1 to grade 3 that could be treated with symptomatic treatment. Dyspnea was another common symptom for the senile patients but had more relationship with cancer itself, not always the adverse effects of therapy. There were no significant differences about adverse effects between the gefitinib-SBRT group and the gefitinib group. Generally speaking, the side effects of gefitinib combined with γ-ray SBRT are acceptable, even in the senile patients.

Discussion

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related death in the world. The aim of treatment, in this setting of disease, is to slow down the progression of the disease, to relieve the patients from the lung cancer symptoms and, whenever possible, to increase the overall survival (OS). In first-line treatment doublets containing platinum compounds represent the standard of care in advanced NSCLC, reporting a response rate (RR) racing from 20% to 35% with a median survival time (MST) of about 10 months [5].

The major progresses in the understanding cancer biology and mechanism of oncogenesis have allowed to identify several potential molecular targets for cancer treat-

Table 3 The adverse effects of all patients who were treated with different therapeutic methods (*n*, %)

Adverse effects	Gefitinib-SBRT								Gefitinib								*P* value
	0		1		2		3		0		1		2		3		
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	
Leukopenia	17	77	4	18	0	0	1	5	0	0	19	95	1	5	0	0	0.101
Thrombocytopenia	20	91	2	9	0	0	0	0	0	0	19	95	1	5	0	0	0.607
Anemia	18	82	3	14	0	0	1	5	0	0	18	90	2	10	0	0	0.449
Rash	5	23	14	64	1	5	2	9	1	5	6	30	12	60	1	5	0.592
Diarrhea	8	36	12	55	0	0	1	5	1	5	8	40	11	55	1	5	0.808
Nausea/vomiting	16	73	5	23	0	0	1	5	0	0	17	85	2	10	1	5	0.333
Dyspnea	14	64	7	32	0	0	1	5	0	0	16	80	3	15	1	5	0.241

ment such as vascular endothelial growth factor (VEGF) and its receptors (VEGFRs) and epidermal growth factor receptor (EGFR). The EGFR small molecules inhibitors such as gefitinib and erlotinib are now available in clinical practice in first or second-line treatment [6].

Gefitinib is a compound of aniline quinazoline. It can be used to promote apoptosis, resist angiogenesis, and restrain differentiated proliferation or migration of cancer cells with a powerful ability to restrain epidermal growth factor receptor tyrosine kinase. It is widely used as the second or third line therapy in advanced non-small cell lung carcinoma (NSCLC) after the failure of platinum [7]. Although the ISEL research [8] can not confirm the prominent advantage in promoting patient's life span, the subordinate analysis demonstrated an obvious elongation in life span which chosen Asiatic Race as the research object. The median survival time (MST) of gefitinib group and placebo group was 9.5 months and 5.5 months respectively. Wu *et al*[9] had reported that the application of gefitinib to Chinese advanced NSCLC patients and demonstrated that it had good therapeutic effects and little adverse effects for Chinese advanced NSCLC patients. Recently, Gao *et al* [10] reported the clinical observation of gefitinib as a first-line therapy in sixty-eight patients with advanced NSCLC and get the conclusion that first-line therapy with gefitinib is an effective and tolerable treatment regimen for advanced NSCLC.

In 2004, three research groups have identified somatic gene mutations within the kinase domain of EGFR, related to the response to EGFR TKIs [11–13]. EGFR mutations were most frequently detected in a subpopulation of NSCLC patients with characteristics associated with a better treatment outcome: female sex, non smokers, Asian origin, adenocarcinoma histology. Approximately 90% of EGFR gene mutations affect small region of the gene within the exons (18 to 24) which code for the TK domain. The more common mutations are an in frame deletion in exon 19 around codons 746 to 750 (45%– 50% of all somatic EGFR mutations) and a missense mutation leading to leucine to arginine substitution at codon 858 (L858R) in exon 21 (35%–45% of all EGFR mutations) [14].

In the First-SIGNAL study, Korean advanced NSCLC patients (adenocarcinoma histology and never smokers) were randomized to gefitinib or standard chemotherapy (gemcitabine/cisplatin) as first-line treatment. OS was similar in both groups, although PFS at 1 year was superior in the gefitinib compared to chemotherapy group (20.3% and 5.0% respectively) and also quality of life (QoL) is improved in gefitinib group. Moreover a subgroup analysis showed an OS of 30.6 months in EGFR mutations positive patients and 18.4 months in those without mutations (HR 0.845; $P = 0.643$) treated with gefitinib and a PFS of 8.4 and 2.1 months, respectively (HR 0.394; $P = 0.0006$); the ORR was also dramatically better in this subgroup of patients (84.6% and 25.9%; respectively) [15]. In the WJTOG3405 trial, chemotherapy-naive advanced NSCLC patients harbouring EGFR mutations were randomly assigned to receive gefitinib or chemotherapy (cisplatin/docetaxel). In gefitinib arm a longer PFS was reported compared to chemotherapy group (9.2 and 6.3 months; HR 0.489, log-rank $P < 0.0001$, respectively); as well the RR was higher in patients treated with gefitinib (62.1% and 32.2%, respectively) [16]. In a recent trial (NEJ002) gefitinib was compared to carboplatin/paclitaxel in EGFR mutated advanced NSCLC patients. After a planned interim analysis this trial has been interrupted since a significantly longer median PFS (10.8 vs 5.4 months; HR, 0.30; $P < 0.001$), as well as a higher RR (73.7% vs 30.7%, $P < 0.001$) was reported in patients treated with gefitinib. However the median OS was 30.5 months in the gefitinib group and 23.6 months in the chemotherapy group ($P = 0.31$) [17]. NEJ 003 study suggest that first-line gefitinib may be preferable to standard chemotherapy for the patients aged 75 or older with advanced non-small cell lung cancer harboring epidermal growth factor receptor mutations [18]. These three phase III trials performed in EGFR mutated patients confirm once more gefitinib to be superior to chemotherapy in terms of PFS and RR suggesting that the EGFR gene mutational status play an important role in the treatment choice of advanced NSCLC. Finally, based on these results the EMEA approved gefitinib for the treatment of advanced NSCLC patients harboring EGFR mutations even in first-line setting.

The complications of ordinary radiotherapy confine the application in senile lung cancer patients for the poor general body states. In recent years, with the development of stereotactic radiological technology, we can concentrate radiological dose into the diseased region and avoid the irradiation of surrounding normal tissues and organs. In this way, we can improve the radiological dose of the tumor and protect the normal tissues. As the result, the complication of radiotherapy was reduced, the time of therapy was shortened, and so the stereotactic body radiation therapy can be used in the senile patients with lung cancer successfully. Just as we know, the stereotactic body radiation therapy has a high tumor control rate as a kind of local treatment, but on the other hand, it almost has little therapeutic effect for the recurrence or metastasis of tumor. So, we imagine that the combination of gefitinib and stereotactic body radiation therapy should be a suitable method to the local therapeutic effect and systemic control for the senile NSCLC. That is to say, the combined modality therapy of micromolecular targeted drug and stereotactic body radiation therapy is feasible in theoretically.

The four large randomized phase III trials of chemotherapy with or without an EGFR tyrosine kinase inhibi-

tor in unselected patients with advanced-stage NSCLC, altogether totaling > 4000 patients, did not demonstrate improvement in clinical outcomes with the combination [19]. But the preclinical research of Tanaka *et al* [20] demonstrate that gefitinib enhances the radio response of NSCLC cells by suppressing cellular DNA repair capacity, thereby prolonging the presence of radiation-induced DNA double strand breaks (DSBs). It suggests that the combination of gefitinib and radiotherapy is worth us researching in clinical work. Recently, Zhuang *et al* [21] found that the best radio sensitizing effect was obtained when gefitinib was delivered before irradiation. In our research, gefitinib was used from the first day and the radiation began with the second day for the position fixing of γ-ray stereotactic body radiation therapy in the first day. So gefitinib can improve the efficiency of radiotherapy at the most degree in our study coincidently. Another phenomenon that local treatment combined with systemic therapy would have a better efficacy than them alone in clinical work. Zeng *et al* [22] retrospectively reviewed 90 patients with BM from NSCLC who received gefitinib alone (250 mg/day, gefitinib group) or with concomitant WBRT (40 Gy/20 f/4 w, gefitinib-WBRT group). The objective response rate of BM was significantly higher in gefitinib-WBRT group (64.4%) compared with gefitinib group (26.7%, $P < 0.001$). The disease control rate of BM was 71.1% in gefitinib-WBRT group and 42.2% in gefitinib group ($P = 0.006$). The median time to progression of BM was 10.6 months in gefitinib-WBRT group and 6.57 months in gefitinib group ($P < 0.001$). The median overall survival (OS) of gefitinib-WBRT and gefitinib alone group was 23.40 months and 14.83 months, respectively (HR, 0.432, $P = 0.002$). So get the conclusion that gefitinib plus concomitant WBRT had higher response rate of BM and significant improvement in OS compared with gefitinib alone in treatment of BM from NSCLC. Wang *et al* [23] reported the prospective study of epidermal growth factor receptor tyrosine kinase inhibitors concurrent with individualized radiotherapy for patients with locally advanced or metastatic NSCLC. The 26 patients with Stage III/IV NSCLC were enrolled in this prospective study. With a median follow-up of 10.2 months, a local control rate of 96% was achieved for thoracic tumor. Median time to progression, median PFS, and median survival time were 6.3, 10.2, and 21.8 months, respectively. The 1- and 2-year PFS rates were both 42%, and 1-, 2-, and 3-year overall survival rates were 57%, 45%, and 30%, respectively.

How about the efficacy and safety for senile patients with EGFR mutations? Our research will answer this question. Stinchcombe *et al* [24] reported that the induction chemotherapy with carboplatin, irinotecan, and paclitaxel followed by high dose three-dimension conformal thoracic radiotherapy (74 Gy) with concurrent carboplatin, paclitaxel, and gefitinib had a good response in unresectable stage IIIA and stage IIIB non-small cell lung cancer. But unfortunately, the combination of gefitinib, radiotherapy and chemotherapy had prominent side effects such as radioactive esophagitis and cardiac toxicity. So, we did not combine chemotherapy in our research, especially when our patients were senile.

There was no patient died in our research for therapeutic related side effects and the side effects occurred was acceptable and treatable. The response rate of gefitinib combined with γ-ray stereotactic body radiation therapy group and gefitinib group was 81.8% and 50.0% respectively when we examined tumors with enhanced double helix CT at the second month. It suggested that γ-ray stereotactic body radiation therapy can improve the local control ratio of gefitinib. In NEJ002 trial [17], the RR of gefitinib group was 73.7%. The RR of gefitinib group in our research was lower than that in NEJ002 trial. Perhaps the reason was the higher age in our group. The γ-ray stereotactic body radiation therapy can improve the RR to 81.8% which will offset the disadvantage of senile age. On the other hand, The PFS of the two groups in our research (18.6 and 12.1 months) was longer than NEJ002 (10.8 months) but the OS of our research (24.2 and 17.4 months) was shorter than NEJ002 (30.5 months) even with the efforts of γ-ray stereotactic body radiation therapy. That is to say, the senile patients had a longer PFS but a shorter OS than the conventional crowds. The main reason lines in the shorter survival time after the tumor progress because of the poor general body states. It suggested that gefitinib combined with γ-ray stereotactic body radiation as the first-line therapy worth us enrolling conventional patients in the next step.

Generally speaking, gefitinib combined with γ-ray stereotactic body radiation therapy has better efficacy than gefitinib alone for senile lung adenocarcinoma patients with EGFR mutations as first-line regimen and worth us researching it further.

Conflicts of interest

The authors indicated no potential conflicts of interest in this work.

References

1. Cappuzzo F, Ligorio C, Jänne PA, *et al*. Prospective study of gefitinib in epidermal growth factor receptor fluorescence *in situ* hybridization-positive/phospho-Akt-positive or never smoker patients with advanced non-small-cell lung cancer: the ONCOBELL trial. J Clin Oncol, 2007, 25: 2248–2255.
2. Lin CC, Yang CH. Epidermal growth factor receptor tyrosine kinase inhibitors in elderly or poor performance status patients with advanced non-small cell lung cancer. Target Oncol, 2009, 4: 37–44.
3. Magné N, Chargari C, Castadot P, *et al*. The efficacy and toxicity of EGFR in the settings of radiotherapy: Focus on published clinical tri-

als. Eur J Cancer, 2008, 44: 2133–2143.
4. Pan DJ, Wang B, Zhou XJ, *et al.* Clinical study on gefitinib combined with γ-ray stereotactic radiotherapy for senile patients with adenocarcinoma of lung as the first-line regimen. Chinese-German J Clin Oncol, 2011, 10: 386–390.
5. Waters JS, O'Brien ME. The case for the introduction of new chemotherapy agents in the treatment of advanced non small cell lung cancer in the wake of the findings of The National Institute of Clinical Excellence (NICE). Br J Cancer, 2002, 87: 481–490.
6. Bareschino MA, Schettino C, Rossi A, *et al.* Treatment of advanced non small cell lung cancer. J Thorac Dis, 2011, 3: 122–133.
7. Yoneda S. Outpatient chemotherapy for lung cancer. Gan To Kagaku Ryoho (Japanese), 2007, 34: 533–537.
8. Chang A, Parikh P, Thongprasert S, *et al.* Gefitinib (IRESSA) in patients of Asian origin with refractory advanced non-small cell lung cancer: subset analysis from the ISEL study. J Thorac Oncol, 2006, 1: 847–855.
9. Wu YL, Yang JJ, Lin JY, *et al.* Gefitinib target treatment in non-small cell lung cancer. Chin J Tubere Respir Dis (Chinese), 2007, 30: 98–102.
10. Gao Z, Han B, Wang H, *et al*. Clinical observation of gefitinib as a first-line therapy in sixty-eight patients with advanced NSCLC. Oncol Lett, 2012, 3: 1064–1068.
11. Lynch TJ, Bell DW, Sordella R, *et al.* Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med, 2004, 350: 2129–2139.
12. Paez JG, Jänne PA, Lee JC, *et al.* EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science, 2004, 304: 1497–1500.
13. Pao W, Miller V, Zakowski M, *et al.* EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci USA, 2004, 101: 13306–13311.
14. Shigematsu H, Lin L, Takahashi T, *et al.* Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. J Natl Cancer Inst, 2005, 97: 339–346.
15. Lee JS, Park K, Kim SW, *et al.* A randomized phase III trial of gefitinib (IRESSA) versus standard chemotherapy (gemcitabine plus cisplatin) as a first-line treatment for never-smokers with advanced of metastatic adenocarcinoma of the lung. J Thorac Oncol, 2009, 4: s283–s284.
16. Mitsudomi T, Morita S, Yatabe Y, *et al.* Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol, 2010, 11: 121–128.
17. Maemondo M, Inoue A, Kobayashi K, *et al.* Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med, 2010, 362: 2380–2388.
18. Fukuoka M, Wu YL, Thongprasert S, *et al.* Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). J Clin Oncol, 2011, 29: 2866–2874.
19. Gandara DR, Davies AM, Gautschi O, *et al.* Epidermal growth factor receptor inhibitors plus chemotherapy in non-small-cell lung cancer: biologic rationale for combination strategies. Clin Lung Cancer, 2007, 8 Suppl 2: S61–S67.
20. Tanaka T, Munshi A, Brooks C, *et al.* Gefitinib radiosensitizes non-small cell lung cancer cells by suppressing cellular DNA repair capacity. Clin Cancer Res, 2008, 14: 1266–1273.
21. Zhuang HQ, Sun J, Yuan ZY, *et al*. Radiosensitizing effects of gefitinib at different administration times *in vitro*. Cancer Sci, 2009, 100: 1520–1525.
22. Zeng YD, Zhang L, Liao H, *et al.* Gefitinib alone or with concomitant whole brain radiotherapy for patients with brain metastasis from non-small-cell lung cancer: a retrospective study. Asian Pac J Cancer Prev, 2012, 13: 909–914.
23. Wang J, Xia TY, Wang YJ, *et al.* Prospective study of epidermal growth factor receptor tyrosine kinase inhibitors concurrent with individualized radiotherapy for patients with locally advanced or metastatic non-small-cell lung cancer. Int J Radiat Oncol Biol Phys, 2011, 81: e59–e65.
24. Stinchcombe TE, Morris DE, Lee CB, *et al.* Induction chemotherapy with carboplatin, irinotecan, and paclitaxel followed by high dose three-dimension conformal thoracic radiotherapy (74 Gy) with concurrent carboplatin, paclitaxel, and gefitinib in unresectable stage IIIA and stage IIIB non-small cell lung cancer. J Thorac Oncol, 2008, 3: 250–257.