**Name of journal: World Journal of Clinical Oncology**

**ESPS Manuscript NO: 11079**

**Columns: TOPIC HIGHLIGHT**

WJCO 5th Anniversary Special Issues (1): Lung cancer

**Erlotinib usage after prior treatment with gefitinib in advanced non-small cell lung cancer: A clinical perspective and review of published literature**

Singh N *et al.* Erlotinib usage in advanced NSCLC

Navneet Singh, Aditya Jinda, Digambar Behera

**Navneet Singh, Aditya Jinda, Digambar Behera,** Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

**Author contributions:** All the authors equally contributed to this work.

**Correspondence to: Navneet** **Singh MD, DM, FACP, FCCP, FICS, Assistant Professor,** Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Sector 12, Chandigarh 160012, India. [singh.navneet@pgimer.edu.in](mailto:singh.navneet@pgimer.edu.in)

**Telephone*:*** +91-172-2756826 **Fax*:*** +91-172-2745959

**Received:** May 3, 2014 **Revised:** July 19, 2014

**Accepted:** October 1, 2014

**Published online:**

**Abstract**

Erlotinib and gefitinib are among the most widely researched, used and available molecularly targeted therapies for treatment of advanced non-small cell lung cancer (NSCLC). They are both tyrosine kinase inhibitors (TKIs) of the epidermal growth factor receptor (EGFR). In the past decade, there have been reports on clinical benefit from use of erlotinib after gefitinib failure in NSCLC patients. A review of published literature on this focussed topic is provided herein. Pooled analysis of published literature shows that majority of patients were female (60.6%), non-smokers (64.5%), had adenocarcinoma histology (88.3%) and were of East Asian ethnicity (92.3%). Presence of sensitizing EGFR mutation was detected in 48.4% of subjects. Disease control rates with prior gefitinib therapy and with subsequent erlotinib treatment were 79.4% and 45.4% respectively. Based upon our review, the most important predictive factor for clinical benefit from erlotinib identified was previous response to gefitinib. The exact explanations for the potential benefit from erlotinib use in this patient population is still not known and further studies are required to determine the role of molecular mechanisms especially those related to resistance to initial EGFR TKI therapy.

© 2014 Baishideng Publishing Group Inc. All rights reserved.

**Key words:** Gefitinib; Erlotinib; Non-small cell lung cancer; Epidermal growth factor receptor; Tyrosine kinase inhibitor

**Core tip:** This manuscript is focused on the controversial yet interesting topic of whether erlotinib provides clinical benefit amongst patients who have experienced disease progression after prior therapy with gefitinib-both drugs being tyrosine kinase inhibitors of the epidermal growth factor receptor. We have reviewed available literature on this topic, carried out a pooled analysis on available data and hope readers find it useful in clearing the confusion related to this topic.

Singh N, Jinda A, Behera D. Erlotinib usage after prior treatment with gefitinib in advanced non-small cell lung cancer: A clinical perspective and review of published literature. *World J* *Clin Oncol* 2014; In press

**INTRODUCTION**

Lung cancer remains among the most commonly occurring cancers in the world with majority of the cases being of non-small cell lung cancer (NSCLC)[1,2]. As in other malignancies, molecularly targeted therapies are being increasingly researched and approved for clinical use in case of NSCLC especially adenocarcinoma. Among the molecularly targeted therapies available for advanced NSCLC, the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) occupy a central place and form part of the standard treatment algorithms[3]. Gefitinib, erlotinib and recently afatinib are the available, orally active agents in this group. Gefitinib was approved for use after two randomised trials–the Iressa Dose Evaluation in Advanced Lung Cancer 1 and 2 (IDEAL 1 and 2) studies–showed survival benefit as compared to placebo amongst patients with advanced NSCLC who had progressed after initial platinum based chemotherapy[4,5]. However, based on a subsequent trial, *i.e.*, the Iressa Survival Evaluation in Lung Cancer study, which did not show an improvement in overall survival (OS), the use of gefitinib was disallowed in the United States by the Federal Drugs Authority (FDA)[6]. Erlotinib was demonstrated to have efficacy in advanced NSCLC in the BR.21 trial. This was a randomised, double blind, placebo controlled trial in which the administration of erlotinib to patients with advanced NSCLC who had received prior chemotherapy led to an improvement in response rates (RR), progression free survival (PFS) and OS with an acceptable toxicity profile[7]. Subsequently, erlotinib was approved by the FDA for use in advanced NSCLC. In all of the above studies, the clinical benefit and treatment response was more evident in certain subgroups namely female gender, non-smoker status, Asian ethnicity and adenocarcinoma. Subsequently, these subgroups were proven to have a higher incidence of sensitizing EGFR mutations which till date remains the most important predictive factor for clinical benefit with EGFR TKIs[8].

Almost a decade ago, there was an initial report on the use of erlotinib after gefitinib failure in patients of non-small cell lung cancer[9]. Following this, several case reports, case series, retrospective reviews and even a few prospective trials have been published related to use of erlotinib in patients who had received prior therapy with gefitinib. This is surprising, considering that the mechanism of action of both drugs is similar. No satisfactory explanation has been found till date, though many have been postulated. In the current article, we have reviewed published literature on this focused area and carried out a pooled analysis with the data available.

**MECHANISM OF ACTION OF TKIS**

EGFR is a transmembrane protein which functions as the receptor for the epidermal growth factor (EGF) pathway[8]. The EGFR protein consists of three domains: an extra-cellular binding site for the EGF molecule, a transmembrane unit which spans the cell membrane and an intracellular unit which has tyrosine kinase activity. The binding of EGF causes conformational changes in the receptor which further leads to phosphorylation/dephosphorylation of the intracellular tyrosine kinase domain and subsequent downstream signalling. Mutations in the EGFR lead to a constitutive activation of the EGF pathway and subsequent activation of cell survival pathways[10].

The mutations underlying the activation of this pathway were elucidated in the earlier part of the last decade[11-13]. Based on the experience with imatinib in chronic myeloid leukaemia, inhibitors of the EGFR tyrosine kinase pathway were developed. The first of these was gefitinib, which acts by interfering with the tyrosine kinase activity of the intracellular domain of the EGFR. It was followed by erlotinib, which has a somewhat similar mechanism of action. These molecules function as ATP (adenosine triphosphate) mimetic molecules, in that they bind to the intracellular domain of the EGFR and block receptor phosphorylation and subsequent downstream signalling and activation of dependent pathways[14].

**LITERATURE REVIEW**

We carried out a PubMed search for all published literature in the English language on this topic till 2013. Multiple case reports, retrospective reviews and prospective studies were identified that have been listed in Table 1. The studies included in this review used standard treatment protocols for gefitinib and erlotinib, *i.e.,* 250 mg/d and 150 mg/d respectively. Tumour response was assessed according to the Response Evaluation Criteria in Solid Tumours[15]. The outcome measures reported in the studies included: RR, defined as combination of complete response (CR) and partial response (PR); Disease control rate (DCR), defined as the combination of CR, PR and stable disease (SD); PFS, defined as the period from the start of treatment to the date when disease progression or death was observed and OS, defined as the period from the start of treatment to the date of death (Tables 2 and 3).

Use of erlotinib after gefitinib failure was first reported in 2005[9]. Subsequently, sporadic case reports were published which demonstrated similar findings[16-18]. A prospective phase II study evaluated the use of erlotinib in patients of NSCLC who had been treated with chemotherapy followed by gefitinib and then had failure on gefitinib. A total of 21 patients were included in this study. Out of these 21 patients, who had progressed on gefitinib, 2 patients achieved PR and 4 patients SD while the remaining 15 patients had progressive disease (PD). The DCR was 28.6% (95%CI: 9.3% to 47.9%) while the median PFS and OS were 60 d (95%CI: 43 to 77 d) and 158 d (95%CI: 141 to 175 d), respectively. An interesting point noted was that the only predictor of a response to erlotinib was the presence of a prior response to gefitinib. Surprisingly, the presence of EGFR mutations was not associated with a response to erlotinib. In fact, 4 out of 6 responders to erlotinib did not have the EGFR mutation[19].

A retrospective study analysed 14 patients who had received erlotinib after failure of gefitinib over a two year period. The initial DCR for gefitinib was 64.3% (9 of 14), while it was 35.7% (5 of 14) for erlotinib. Predictors for good clinical response to erlotinib included never smoker status, adenocarcinoma subtype, good response to initial gefitinib and presence of EGFR mutations[20].

23 patients of metastatic or advanced NSCLC who had documented progression on gefitinib were studied in an open label, single institution, phase II study. All patients were never smokers and 22 out of the 23 patients were of the adenocarcinoma subtype. The initial DCR on gefitinib was 65.3% (15 out of 23). 2 patients responded to erlotinib, giving a DCR of 8.7% and a RR of 4.3%, while the rest 21 patients developed PD within 3 mo [21].

Another study included 4 males and 4 females in their study, with a mean age of 70 years. All of these patients had received chemotherapy at least twice, followed by gefitinib. 4 patients had achieved PR with gefitinib and 4 patients SD, and the median PFS was 17 mo. Two (25%) patients achieved PR and 3 (37.5%) patients SD, while 3 developed PD. The median PFS and OS were 5.9 and 14.6 mo, respectively with erlotinib. The authors observed that patients who had a longer PFS on initial gefitinib therapy had better disease control with erlotinib[22].

Another retrospective study published in 2008 included 18 patients. These patients had received primary chemotherapy and had subsequently been given gefitinib. The initial response to gefitinib included 14 patients with either CR or PR, 2 patients with SD and 2 with PD. After treatment with erlotinib, 14 out of the 18 patients developed PD, while 3 patients had SD and only 1 PR. The median PFS was 2 mo and no patient had a PFS over 6 mo[23].

The utility of established prognostic factors for response to EGFR TKIs namely female sex, adenocarcinoma subtype, Asian ethnicity and never smoking status, for predicting the use of erlotinib after progression on initial gefitinib treatment were studied. They included 14 patients and noted a DCR of 68.8% (95%CI: 0.44-0.86) on initial gefitinib treatment and a rate of 25.0% (95%CI: 0.10-0.50) after treatment with erlotinib. The median PFS was 6.3 mo for gefitinib and 1.7 mo for erlotinib. The prognostic factors were found to be unfavourable for predicting response to erlotinib after treatment failure with gefitinib[24].

A more heterogeneous population of 10 (47.6%) smokers, 9 (42.9%) patients with squamous cell carcinoma, 8 (38.1%) with adenocarcinoma and 4 (19%) with other NSCLC subtypes, totalling 21 were included in another trial. All of them had progressed on gefitinib therapy after chemotherapy. 6 of the 21 patients responded, with 2 (9.5%) showing PR and 4 (19.0%) showing SD, giving an overall RR of 9.5% and a DCR of 28.5%. The median PFS was 55 d and the median OS was 135 d. All of these 6 patients had also had a response to prior gefitinib therapy, either PR or SD[25].

All of the previously mentioned trials included patients who had received chemotherapy prior to initial gefitinib therapy. A retrospective review of 21 patients who had received gefitinib as first line therapy instead of chemotherapy was conducted. The patient population was selected based on clinical characteristics *i.e.*, never smokers, females, Asian ethnicity and adenocarcinoma subtype. Only 3 of these 21 patients had EGFR mutation status known. Disease control was achieved in 18 patients (85.7%) with first line gefitinib therapy and in 12 out of these 18 patients (66.7%) who received erlotinib as salvage therapy. The overall DCR for erlotinib was 57.1% (12 out of 21). All 3 patients who progressed on gefitinib did not respond to erlotinib[26].

In a retrospective review of 42 patients with lung adenocarcinoma receiving erlotinib with history of prior gefitinib treatment, PFS (4.7 mo *vs* 1.8 mo) and OS (9.2 mo *vs* 4.7 mo) were better in patients who had experienced prior response with gefitinib as compared to those who had not[27]. On multivariate analyses for prognostic factors for OS, only prior response to gefitinib was found to be significant but not presence of EGFR mutations. Interestingly in this cohort, 69% of patients had a sensitizing EGFR mutation (exon 19 deletion or L858R mutation exon 21).

A systematic review included 3 prospective studies, 3 retrospective studies and 7 case reports leading to a total of 106 patients. Out of these 9.9% patients had PR, 18.9% SD and 70.8% PD. The DCR was 37.5% in patients who had EGFR mutations and 21.7% in patients without EGFR mutations, which was not statistically different. The mean PFS varied from 1.7 to 5.9 mo. Analysis showed that the only factors which predicted response to erlotinib were the presence of SD on initial treatment with gefitinib and the presence of PFS to initial gefitinib for more than 6 mo[28].

In a large retrospective analysis of 125 patients all of whom had experienced disease progression following initial gefitinib therapy, the RR was 9%, DCR 44% and median PFS 2 mo with erlotinib treatment. Multivariate analysis showed that disease control was predicted by three factors: good performance status [Eastern Cooperative Oncology Group (ECOG) PS 0/1], EGFR mutation-positive status (or unknown) and benefit from prior gefitinib therapy. Longer PFS was predicted by insertion of cytotoxic chemotherapies between gefitinib and erlotinib therapies in addition to ECOG PS 0/1 and benefit from prior gefitinib therapy[29].

In another retrospective review published recently, 44 of the 54 patients had a sensitizing EGFR gene mutation (exon 19 deletion or L858R mutation exon 21) and all 54 patients had received gefitinib initially. DCR of 63% was observed with subsequent erlotinib treatment. The authors observed no significant differences in erlotinib efficacy between EGFR-mutated NSCLC who had developed gefitinib resistance as compared to another 50 patients of NSCLC with wild-type EGFR in whom gefitinib had not been given earlier. This study also showed that presence of skin rash was associated with better outcomes–an observation that has been reported by others also[30].

**POOLED ANALYSIS**

We also carried out pooled analysis of published literature involving patients who had received erlotinib treatment following prior gefitinib therapy. This has been summarized in Table 4. It was not possible to analyse objective RRs and SD separately since some of the publications included in this review had only provided DCRs which is the sum of objective responses (CR/PR) and SD. There are three important observations that are apparent from the pooled analysis. First, majority of the patients were of East Asian ethnicity, females, non-smokers and had adenocarcinoma histology all of which are clinical surrogates for presence of sensitizing EGFR mutations. Second, approximately one of every two subjects in the pooled population had a sensitizing EGFR mutation (exon 19 deletion or exon 21 L858R mutation). However, the true prevalence in this population database is likely to be higher than the figure of 48.4% that arose on pooled analysis because in several of the publications, results of EGFR mutation testing were either not mentioned or were performed in subgroup of patients included in the article. An indirect indicator that this was a highly enriched pooled population is the fact that approximately four of five patients had initial disease control with gefitinib. Third, despite progressing on gefitinib treatment, approximately 45% of patients achieved disease control with erlotinib. However, it was not possible to carry out molecular analysis regarding the mechanisms that led to gefitinib failure or resistance since these have not been provided in majority of the publications.

**RATIONALE**

A satisfactory explanation as to cause of responsiveness to erlotinib after failure of gefitinib is yet to be given. However, several hypotheses have been put forward. One possibility is that gefitinib is usually given at a clinical dose of 250 mg, which is around one third of the maximum tolerated dose, about 750 mg. In contrast, the clinical dose of erlotinib is 150 mg, which is very close to the maximum tolerated dose. Therefore, the biological dose of these two drugs may not be equal. However, in the IDEAL 1 and 2 trials, higher doses of gefitinib were not associated with a better RR[4,5,19].

Another possibility invokes the presence of both EGFR TKI sensitive and resistant clones at the start of treatment with gefitinib. The administration of gefitinib leads to the selective dying out of the sensitive clones and subsequent development of resistance. When the TKI is stopped, the sensitive clones again propagate and are the reason for the response to the subsequent TKI[21]. This is borne out by case reports demonstrating that readministration of gefitinib to some patients after progression may sometimes lead to disease control similar to that achieved with erlotinib[31].

Patients who develop resistance to EGFR TKIs, acquire common mutations such as T790M secondary mutation or amplification of the MET oncogene. Other secondary mutations have also been reported. Some mutations, such as the L748S or E884K mutation, may result in differing sensitivities to the oral EGFR TKIs, resulting in different tumour responses[12,19,21].

An overview of the potential factors predicting clinical benefit with erlotinib is provided in Table 5. The most consistent predictive factor has been prior response to gefitinib. However the predictive role of presence of EGFR mutations in this setting has not been as strong as it is for first line therapy. The clinical surrogates for presence of EGFR mutations namely, female gender, Asian ethnicity, adenocarcinoma histology and non-smoking status, are the other factors that remain associated with clinical benefit from erlotinib in this setting.

**CONCLUSION**

Oral EGFR TKIs are widely available drugs that are an important component of the therapeutic armamentarium against advanced NSCLC. The use of sequential EGFR TKIs, especially of erlotinib after prior treatment with gefitinib has remained a controversial area so far. Given the disease control rate of approximately 45% in the current pooled analysis, such an approach can be considered in carefully selected patients especially those in whom alternate treatment options are not being considered. The exact explanation of this response is still not known. Possible predictive factor for clinical benefit with erlotinib includes previous response to gefitinib. The predictive value of sensitizing EGFR mutations requires further evaluation and further studies are required to determine the underlying molecular mechanisms for observed clinical benefit with erlotinib in this setting.

**REFERENCES**

1 **Singh N**, Aggarwal AN, Gupta D, Behera D, Jindal SK. Unchanging clinico-epidemiological profile of lung cancer in north India over three decades. *Cancer Epidemiol* 2010; **34**: 101-104 [PMID: 20079703 DOI: 10.1016/J.CANEP.2009.12.015]

2 **Singh N**, Aggarwal AN, Gupta D, Behera D, Jindal SK. Quantified smoking status and non-small cell lung cancer stage at presentation: analysis of a North Indian cohort and a systematic review of literature. *J Thorac Dis* 2012; **4**: 474-484 [PMID: 23050111]

3 **Singh N**, Aggarwal AN, Behera D. Management of advanced lung cancer in resource-constrained settings: a perspective from India. *Expert Rev Anticancer Ther* 2012; **12**: 1479-1495 [PMID: 23249112 DOI: 10.1586/era.12.119]

4 **Fukuoka M**, Yano S, Giaccone G, Tamura T, Nakagawa K, Douillard JY, Nishiwaki Y, Vansteenkiste J, Kudoh S, Rischin D, Eek R, Horai T, Noda K, Takata I, Smit E, Averbuch S, Macleod A, Feyereislova A, Dong RP, Baselga J. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial) [corrected]. *J Clin Oncol* 2003; **21**: 2237-2246 [PMID: 12748244 DOI: 10.1200/JCO.2003.10.038]

5 **Kris MG**, Natale RB, Herbst RS, Lynch TJ, Prager D, Belani CP, Schiller JH, Kelly K, Spiridonidis H, Sandler A, Albain KS, Cella D, Wolf MK, Averbuch SD, Ochs JJ, Kay AC. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. *JAMA* 2003; **290**: 2149-2158 [PMID: 14570950 DOI: 10.1001/jama.290.16.2149]

6 **Thatcher N**, Chang A, Parikh P, Rodrigues Pereira J, Ciuleanu T, von Pawel J, Thongprasert S, Tan EH, Pemberton K, Archer V, Carroll K. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet* 2005; **366**: 1527-1537 [PMID: 16257339 DOI: 10.1016/S0140-6736(05)67625-8]

7 **Shepherd FA**, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, Campos D, Maoleekoonpiroj S, Smylie M, Martins R, van Kooten M, Dediu M, Findlay B, Tu D, Johnston D, Bezjak A, Clark G, Santabárbara P, Seymour L. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005; **353**: 123-132 [PMID: 16014882 DOI: 10.1056/NEJMoa050753]

8 **Singh N**, Bal A, Aggarwal AN, Das A, Behera D. Clinical outcomes in non-small-cell lung cancer in relation to expression of predictive and prognostic biomarkers. *Future Oncol* 2010; **6**: 741-767 [PMID: 20465389 DOI: 10.2217/fon.10.30]

9 **Garfield DH**. Modern treatment of lung cancer: case 2. Response to erlotinib after failure of gefitinib in a patient with advanced non-small-cell lung carcinoma. *J Clin Oncol* 2005; **23**: 7738-7740 [PMID: 16234533 DOI: 10.1200/JCO.2005.02.4471]

10 **Lam KC**, Mok TS. Targeted therapy: an evolving world of lung cancer. *Respirology* 2011; **16**: 13-21 [PMID: 20723139 DOI: 10.1111/j.1440-1843.2010.01821.x]

11 **Lynch TJ**, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, Louis DN, Christiani DC, Settleman J, Haber DA. 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 [PMID: 15118073 DOI: 10.1056/NEJMoa040938]

12 **Paez JG**, Jänne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, Naoki K, Sasaki H, Fujii Y, Eck MJ, Sellers WR, Johnson BE, Meyerson M. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004; **304**: 1497-1500 [PMID: 15118125 DOI: 10.1126/science.1099314]

13 **Pao W**, Miller V, Zakowski M, Doherty J, Politi K, Sarkaria I, Singh B, Heelan R, Rusch V, Fulton L, Mardis E, Kupfer D, Wilson R, Kris M, Varmus H. 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 U S A* 2004; **101**: 13306-13311 [PMID: 15329413 DOI: 10.1073/pnas.0405220101]

14 **Brandes AA**, Franceschi E, Tosoni A, Hegi ME, Stupp R. Epidermal growth factor receptor inhibitors in neuro-oncology: hopes and disappointments. *Clin Cancer Res* 2008; **14**: 957-960 [PMID: 18281526 DOI: 10.1158/1078-0432.CCR-07-1810]

15 **Therasse P**, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**: 205-216 [PMID: 10655437 DOI: 10.1093/jnci/92.3.205]

16 **Viswanathan A**, Pillot G, Govindan R. Lack of response to erlotinib after progression on gefitinib in patients with advanced non-small cell lung cancer. *Lung Cancer* 2005; **50**: 417-418 [PMID: 16129510 DOI: 10.1016/j.lungcan.2005.07.004]

17 **Walther JC**, Khorshid M, Gaya A, Plowman PN. Cross-over response to erlotinib of brain metastatic disease from bronchial adenocarcinoma after gefitinib failure, and an unusual rash. *Clin Oncol (R Coll Radiol)* 2006; **18**: 637-639 [PMID: 17051957 DOI: 10.1016/j.clon.2006.07.002]

18 **Chang JW**, Chou CL, Huang SF, Wang HM, Hsieh JJ, Hsu T, Cheung YC. Erlotinib response of EGFR-mutant gefitinib-resistant non-small-cell lung cancer. *Lung Cancer* 2007; **58**: 414-417 [PMID: 17618013 DOI: 10.1016/j.lungcan.2007.05.018]

19 **Cho BC**, Im CK, Park MS, Kim SK, Chang J, Park JP, Choi HJ, Kim YJ, Shin SJ, Sohn JH, Kim H, Kim JH. Phase II study of erlotinib in advanced non-small-cell lung cancer after failure of gefitinib. *J Clin Oncol* 2007; **25**: 2528-2533 [PMID: 17577030 DOI: 10.1200/JCO.2006.10.4166]

20 **Wong AS**, Soong R, Seah SB, Lim SW, Chuah KL, Nga ME, Chin TM, Soo RA. Evidence for disease control with erlotinib after gefitinib failure in typical gefitinib-sensitive Asian patients with non-small cell lung cancer. *J Thorac Oncol* 2008; **3**: 400-404 [PMID: 18379359 DOI: 10.1097/JTO.0b013e318168c801]

21 **Lee DH**, Kim SW, Suh C, Yoon DH, Yi EJ, Lee JS. Phase II study of erlotinib as a salvage treatment for non-small-cell lung cancer patients after failure of gefitinib treatment. *Ann Oncol* 2008; **19**: 2039-2042 [PMID: 18644828 DOI: 10.1093/annonc/mdn423]

22 **Vasile E**, Tibaldi C, Chella A, Falcone A. Erlotinib after failure of gefitinib in patients with advanced non-small cell lung cancer previously responding to gefitinib. *J Thorac Oncol* 2008; **3**: 912-914 [PMID: 18670311 DOI: 10.1097/JTO.0b013e318180275e]

23 **Costa DB**, Nguyen KS, Cho BC, Sequist LV, Jackman DM, Riely GJ, Yeap BY, Halmos B, Kim JH, Jänne PA, Huberman MS, Pao W, Tenen DG, Kobayashi S. Effects of erlotinib in EGFR mutated non-small cell lung cancers with resistance to gefitinib. *Clin Cancer Res* 2008; **14**: 7060-7067 [PMID: 18981003 DOI: 10.1158/1078-0432.CCR-08-1455]

24 **Sim SH**, Han SW, Oh DY, Lee SH, Kim DW, Im SA, Chung DH, Kim TY, Lee JS, Kim YW, Heo DS, Bang YJ. Erlotinib after Gefitinib failure in female never-smoker Asian patients with pulmonary adenocarcinoma. *Lung Cancer* 2009; **65**: 204-207 [PMID: 19110337 DOI: 10.1016/j.lungcan.2008.11.006]

25 **Zhou ZT**, Xu XH, Wei Q, Lu MQ, Wang J, Wen CH. Erlotinib in advanced non-small-cell lung cancer after gefitinib failure. *Cancer Chemother Pharmacol* 2009; **64**: 1123-1127 [PMID: 19322567 DOI: 10.1007/s00280-009-0973-1]

26 **Wong MK**, Lo AI, Lam B, Lam WK, Ip MS, Ho JC. Erlotinib as salvage treatment after failure to first-line gefitinib in non-small cell lung cancer. *Cancer Chemother Pharmacol* 2010; **65**: 1023-1028 [PMID: 19680652 DOI: 10.1007/s00280-009-1107-5]

27 **Asami K**, Kawahara M, Atagi S, Kawaguchi T, Okishio K. Duration of prior gefitinib treatment predicts survival potential in patients with lung adenocarcinoma receiving subsequent erlotinib. *Lung Cancer* 2011; **73**: 211-216 [PMID: 21272953 DOI: 10.1016/j.lungcan.2010.12.014]

28 **Kaira K**, Naito T, Takahashi T, Ayabe E, Shimoyama R, Kaira R, Ono A, Igawa S, Shukuya T, Murakami H, Tsuya A, Nakamura Y, Endo M, Yamamoto N. Pooled analysis of the reports of erlotinib after failure of gefitinib for non-small cell lung cancer. *Lung Cancer* 2010; **68**: 99-104 [PMID: 19540616 DOI: 10.1016/j.lungcan.2009.05.006]

29 **Hata A**, Katakami N, Yoshioka H, Fujita S, Kunimasa K, Nanjo S, Otsuka K, Kaji R, Tomii K, Iwasaku M, Nishiyama A, Hayashi H, Morita S, Ishida T. Erlotinib after gefitinib failure in relapsed non-small cell lung cancer: clinical benefit with optimal patient selection. *Lung Cancer* 2011; **74**: 268-273 [PMID: 21529987 DOI: 10.1016/j.lungcan.2011.03.010]

30 **Singh N,** Vishwanath G, Aggarwal AN, Behera D. Clinical Experience on Use of Oral EGFR-TKIs as First-line Treatment of Advanced NSCLC from a Tertiary Care Centre in North India and Implications of Skin Rash. *Indian J Chest Dis Allied Sci* 2014; **56:** 79-82

31 **Asahina H**, Oizumi S, Inoue A, Kinoshita I, Ishida T, Fujita Y, Sukoh N, Harada M, Maemondo M, Saijo Y, Dosaka-Akita H, Isobe H, Nukiwa T, Nishimura M. Phase II study of gefitinib readministration in patients with advanced non-small cell lung cancer and previous response to gefitinib. *Oncology* 2010; **79**: 423-429 [PMID: 21474967 DOI: 10.1159/000326488]

32 **Gridelli C**, Maione P, Galetta D, Colantuoni G, Del Gaizo F, Ferrara C, Guerriero C, Nicolella D, Rossi A. Three cases of long-lasting tumor control with erlotinib after progression with gefitinib in advanced non-small cell lung cancer. *J Thorac Oncol* 2007; **2**: 758-761 [PMID: 17762344 DOI: 10.1097/JTO.0b013e3180cc25b0]

33 **Kim HK**, Ahn MI, Yoo J, Kim CH, Yang HJ, Shim BY. Sequential responses of adenocarcinoma of the lung to erlotinib after gefitinib in never smoker Korean woman. *Cancer Res Treat* 2007; **39**: 37-39 [PMID: 19746235 DOI: 10.4143/crt.2007.39.1.37]

34 **Wong AS**, Seto KY, Chin TM, Soo RA. Lung cancer response to gefitinib, then erlotinib, then gefitinib again. *J Thorac Oncol* 2008; **3**: 1077-1078 [PMID: 18758318 DOI: 10.1097/JTO.0b013e318183afb0]

35 **Wu SG**, Shih JY, Yu CJ, Yang PC. Lung adenocarcinoma with good response to erlotinib after gefitinib treatment failure and acquired T790M mutation. *J Thorac Oncol* 2008; **3**: 451-452 [PMID: 18379370 DOI: 10.1097/JTO.0b013e318169e32a]

36 **Katayama T**, Shimizu J, Suda K, Onozato R, Fukui T, Ito S, Hatooka S, Sueda T, Hida T, Yatabe Y, Mitsudomi T. Efficacy of erlotinib for brain and leptomeningeal metastases in patients with lung adenocarcinoma who showed initial good response to gefitinib. *J Thorac Oncol* 2009; **4**: 1415-1419 [PMID: 19692934 DOI: 10.1097/JTO.0b013e3181b62572]

37 **Masuda T**, Hattori N, Hamada A, Iwamoto H, Ohshimo S, Kanehara M, Ishikawa N, Fujitaka K, Haruta Y, Murai H, Kohno N. Erlotinib efficacy and cerebrospinal fluid concentration in patients with lung adenocarcinoma developing leptomeningeal metastases during gefitinib therapy. *Cancer Chemother Pharmacol* 2011; **67**: 1465-1469 [PMID: 21274533 DOI: 10.1007/s00280-011-1555-6]

38 **Shoji F**, Kawano D, Ito K, Morodomi Y, Yano T, Maehara Y. Effectiveness of erlotinib against recurrent pulmonary adenocarcinoma unresponsive to gefitinib: report of a case. *Surg Today* 2011; **41**: 255-257 [PMID: 21264764 DOI: 10.1007/s00595-009-4259-3]

39 **Song ZB**, Yu YF, Chen ZW, Lu S. Erlotinib as a salvage treatment for patients with advanced non-small cell lung cancer after failure of gefitinib treatment. *Chin Med J (Engl)* 2011; **124**: 2279-2283 [PMID: 21933557]

40 **Takenaka T**, Yamagata M, Fukuda A, Sonoda T. Long-term survival of a patient with carcinomatous meningitis due to non-small cell lung cancer treated with erlotinib following gefitinib. *BMJ Case Rep* 2011; **2011**: [PMID: 22679236 DOI: 10.1136/bcr.08.2011.4586]

41 **Saito H**, Murakami S, Kondo T, Oshita F, Noda K, Yamada K. Effectiveness of erlotinib in advanced non-small cell lung cancer in cases of gefitinib resistance after treatment of more than 6 months. *Onkologie* 2012; **35**: 18-22 [PMID: 22310340 DOI: 10.1159/000335736]

42 **Tetsumoto S**, Osa A, Kijima T, Minami T, Hirata H, Takahashi R, Kuhara H, Nagatomo I, Takeda Y, Kida H, Goya S, Tachibana I, Kawase I. Two cases of leptomeningeal metastases from lung adenocarcinoma which progressed during gefitinib therapy but responded to erlotinib. *Int J Clin Oncol* 2012; **17**: 155-159 [PMID: 21594553 DOI: 10.1007/s10147-011-0256-9]

43 **Koyama N**, Uchida Y. Clinical significance of erlotinib monotherapy for gefitinib-resistant non-small cell lung cancer with EGFR mutations. *Anticancer Res* 2013; **33**: 5083-5089 [PMID: 24222153]

**P-Reviewer:** Garfield DH, Metro G, Perego P **S-Editor:** Tian YL

**L-Editor: E-Editor:**

**Table 1 Baseline characteristics of subjects in studies evaluating response to erlotinib after gefitinib**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Type of study** | **No. of patients** | **Gender (M/F)** | **Smoking status (smokers/NS)** | **Histology (A/S/other)** |
|  | | | | | | | |
| Garfield *et al*[9] | 2005 | United States | Case report | 1 | 1/0 | 1/0 | 0/0/1 |
| Vishwanathan *et al*[16] | 2005 | United States | Case report | 5 | 1/4 | 2/3 | NA |
| Walther *et al*[17] | 2006 | United Kingdom | Case report | 1 | 0/1 | 0/1 | 1/0/0 |
| Chang *et al*[18] | 2007 | Taiwan | Case report | 1 | 1/0 | 1/0 | 1/0/0 |
| Cho *et al*[19] | 2007 | South Korea | Prospective | 21 | 10/11 | 10/11 | 16/3/2 |
| Gridelli *et al*[32] | 2007 | Italy | Case report | 3 | 0/3 | 0/3 | 3/0/0 |
| Kim *et al*[33] | 2007 | South Korea | Case report | 1 | 0/1 | 0/1 | 1/0/0 |
| Costa *et al*[23] | 2008 | United States | Retrospective | 18 | 7/11 | 7/11 | 16/0/2 |
| Lee *et al*[21] | 2008 | South Korea | Prospective | 23 | 4/19 | 0/23 | 22/0/1 |
| Vasile *et al*[22] | 2008 | Italy | Prospective | 8 | 4/4 | 1/7 | 6/0/2 |
| Wong *et al*[20] | 2008 | Singapore | Retrospective | 14 | 4/10 | 1/13 | 10/1/3 |
| Wong *et al*[34] | 2008 | Singapore | Case report | 1 | 0/1 | 0/1 | 1/0/0 |
| Wu *et al*[35] | 2008 | Taiwan | Case report | 1 | 0/1 | 0/1 | 1/0/0 |
| Katayama *et al*[36] | 2009 | Japan | Retrospective | 7 | 2/5 | NA | 7/0/0 |
| Sim *et al*[24] | 2009 | South Korea | Retrospective | 16 | 0/16 | 0/16 | 16/0/0 |
| Zhou *et al*[25] | 2009 | China | Prospective | 21 | 14/7 | 10/11 | 8/9/4 |
| Wong *et al*[26] | 2010 | China | Retrospective | 21 | 2/19 | 1/20 | 19/0/2 |
| Asami *et al*[27] | 2011 | Japan | Retrospective | 42 | 13/29 | 14/28 | 42/0/0 |
| Hata *et al*[29] | 2011 | Japan | Retrospective | 125 | 49/76 | 55/70 | 117/NA/8 |
| Masuda *et al*[37] | 2011 | Japan | Case report | 3 | 3/0 | NA | 3/0/0 |
| Shoji *et al*[38] | 2011 | Japan | Case report | 1 | 1/0 | NA | 1/0/0 |
| Song *et al*[39] | 2011 | China | Retrospective | 20 | 9/11 | 5/15 | 18/0/2 |
| Takenaka *et al*[40] | 2011 | Japan | Case report | 1 | 0/1 | 0/1 | 1/0/0 |
| Saito *et al*[41] | 2012 | Japan | Retrospective | 21 | 9/12 | 9/12 | 19/0/2 |
| Tetsumoto *et al*[42] | 2012 | Japan | Case report | 2 | 0/2 | 0/2 | 2/0/0 |
| Koyama *et al*[43] | 2013 | Japan | Retrospective | 1041 | 56/48 | 50/54 | 90/6/8 |

1Of the 104 patients, only 54 had prior treatment with gefitinib. A: Adenocarcinoma; S: Squamous cell carcinoma; M: Male; F: Female; NA: Not available; smokers: Includes current and ex smokers; NS: Non-smokers.

Table 2 Prevalence of epidermal growth factor receptor mutations and comparison of responses to gefitinib and erlotinib *n* (%)

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **No. of patients** | **EGFR mutations no** | **E19 Del /E21 L858R** | **Response to prior gefitinib** | | | | **Response to erlotinib** | | | |
|  |  |  | | **CR** | **PR** | **SD** | **PD** | **CR** | **PR** | **SD** | **PD** |
| Garfield *et al*[9] | 1 | NA | |  |  |  | 1(100) |  | 1(100) |  |  |
| Vishwanathan *et al*[16] | 5 | NA | |  | 4(80.0) | | 1(20.0) |  |  |  | 5(100) |
| Walther *et al*[17] | 1 | NA | |  |  |  | 1(100) |  | 1(100) |  |  |
| Chang *et al*[18] | 1 | 1 (100) | 1/0 |  | 1(100) |  |  |  | 1(100) |  |  |
| Cho *et al*[19] | 21 | 5 (23.8) | 5/0 |  | 6(28.6) | 4(19.0) | 11(52.4) |  | 2(9.5) | 4(19.0) | 15(71.5) |
| Gridelli *et al*[32] | 3 | NA | |  |  | 3(100) |  |  | 1(33.3) | 2(66.7) |  |
| Kim *et al*[33] | 1 | NA | |  | 1(100) |  |  |  | 1(100) |  |  |
| Costa *et al*[23] | 181 | 17 (94.4) | 13/4 |  | 11(84.6) | 2(15.4) |  |  | 1(7.7) | 2(15.4) | 10(76.9) |
| Lee *et al*[21] | 23 | 3 (13.0) | 3/0 |  | 15(65.2) | 2(8.7) | 6(26.1) |  | 1(4.3) | 1(4.3) | 21(91.4) |
| Vasile *et al*[22] | 8 | NA | |  | 4(50.0) | 4(50.0) |  |  | 2(25.0) | 3(37.5) | 3(37.5) |
| Wong *et al*[20] | 14 | 7 (50.0) | 4/3 |  | 9(64.3) | | 5(35.7) |  |  | 5(35.7) | 9(64.3) |
| Wong *et al*[34] | 1 | 1 (100) | 1/0 |  | 1(100) |  |  |  |  | 1(100) |  |
| Wu *et al*[35] | 1 | 1 (100) | 0/1 |  | 1(100) |  |  |  |  | 1(100) |  |
| Katayama *et al*[36] | 7 | 6 (85.7) | 4/2 | 2(28.6) | 2(28.6) | 3(42.8) |  |  | 3(42.9) | 3(42.9) | 1(14.3) |
| Sim *et al*[24] | 16 | 5 (31.3) | 2/3 |  | 9(56.3) | 2(12.5) | 5(31.2) |  | 1(6.3) | 3(18.7) | 12(75.0) |
| Zhou *et al*[25] | 21 | 7 (33.3) | NA/NA | 2(9.5) | | 8(38.1) | 11(52.4) |  | 2(9.5) | 4(19.1) | 15(71.4) |
| Wong *et al*[26] | 21 | 3 (14.3) | 0/3 |  | 18(85.7) | | 3(14.3) |  | 12(57.1) | | 9(42.9) |
| Asami *et al*[27] | 42 | 28 (66.7) | 14/14 |  | 22(52.4) | 17(40.5) | 3(7.1) |  | 1(2.4) | 24(57.1) | 17(40.5) |
| Hata *et al*[29] | 1252 | 63 (50.4) | NA/NA | 3(2.5) | 68(56.2) | 22(18.2) | 28(23.1) |  | 11(8.8) | 44(35.2) | 70(56.0) |
| Masuda *et al*[37] | 3 | 3 (100) | 2/1 |  | 3(100) |  |  |  | 3(100) |  |  |
| Shoji *et al*[38] | 1 | 0 (0) | |  |  |  | 1(100) |  | 1(100) |  |  |
| Song *et al*[39] | 20 | 5 (25.0) | 3/2 |  | 5(25.0) | 9(45.0) | 6(30.0) |  |  | 7(35.0) | 13(65.0) |
| Takenaka *et al*[40] | 1 | 1 (100) | 1/0 |  |  | 1(100) |  |  | 1(100) |  |  |
| Saito *et al*[41] | 21 | 12 (57.1) | 0/12 |  | 16(76.2) | 5(23.8) |  |  | 2(9) | 6(19) | 13(62) |
| Tetsumoto *et al*[42] | 2 | 2 (100) | 1/1 |  | 2(100) |  |  |  | 2(100) |  |  |
| Koyama *et al*[43] | 54 | 44 (81.5) | 22/22 | 4(7.4) | 32(59.3) | 13(24.0) | 5(9.3) | 0 (0) | 4(7.4) | 30(55.6) | 20(37.0) |

1Response to gefitinib and erlotinib was evaluable for 13 patients only; 2Response to gefitinib was evaluable for 121 patients only. EGFR: Epidermal growth factor receptor; PR: Partial response; CR: Complete response; PD: Progressive disease; SD: Stable disease; E19: Exon 19; E21: Exon 21; Del: Deletion; NA: Not available.

Table 3 Response rates and survival rates with erlotinib following gefitinib therapy

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **RR** | **DCR** | **PFS** | **OS** |
|  | | | | |
| Cho *et al*[19] | 9.5% | 28.6% | 60 d | 158 d |
| Costa *et al*[23] |  |  | 2 mo |  |
| Lee *et al*[21] | 4.3% | 8.7% |  |  |
| Vasile *et al*[22] | 25% | 62.5% | 5.9 mo | 14.6 mo |
| Wong *et al*[20] |  | 35.7% | 97 d |  |
| Sim *et al*[24] |  | 25% | 1.7 mo |  |
| Zhou *et al*[25] | 9.5% | 28.5% | 55 d | 135 d |
| Wong *et al*[26] |  | 57.1% | 14.9 wk | 40 mo |
| Asami *et al*[27] | 2.4% | 59.5% | 3.4 mo | 7.1 mo |
| Hata *et al*[29] | 9% | 44% | 2 mo | 11.8 mo |
| Song *et al*[39] | 0 | 35% | 31 d | 4.2 mo |
| Saito *et al*[41] |  | 38.1% |  | 369 d |
| Koyama *et al*[43] | 7.4% | 63.0% | 135 d | 333 d |

RR: Response rate; DCR: Disease control rate; PFS: Progression free survival: OS: Overall survival.

**Table 4 Pooled analysis of demographic profile, prevalence of epidermal growth factor receptor mutations and disease control rates with erlotinib following prior gefitinib therapy**

|  |
| --- |
| Female gender : 60.6% (292 of 482)  Adenocarcinoma histology: 88.3% (421 of 477)  Non smokers: 64.5% (304 of 471)  East Asian ethnicity: 92.3% (445 of 482)  EGFR mutation positive status1: 48.4% (224 of 463)  Disease control rate with prior gefitinib treatment: 79.4% (336 of 423)  Disease control rate with subsequent erlotinib treatment: 45.4% (194 of 427) |

1Indicates presence of sensitizing epidermal growth factor receptor mutations exon 19 deletion or exon 21 L858R mutation. EGFR: Epidermal growth factor receptor.

**Table 5 Potential factors predicting response to erlotinib following prior gefitinib therapy**

|  |
| --- |
| Previous response to gefitinib (most important)  Longer duration of response to prior gefitinib  Female gender  Adenocarcinoma histology  Non smokers  East Asian ethnicity  EGFR mutation positive status1  Good performance status  Chemotherapy cycles in between gefitinib and erlotinib |

1Indicates presence of sensitizing EGFR mutations exon 19 deletion or exon 21 L858R mutation. EGFR: Epidermal growth factor receptor.