J Hong Kong Col Radiol. 2010;13(Suppl):S10-5

ORIGINAL ARTICLE

Personalised Therapy with Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Non–small-cell Lung Cancer: Consensus and Controversy

ML Zhuo, J Wang

Department of Thoracic Medical Oncology Peking University Cancer Hospital, Beijing 100036, China

ABSTRACT

The epidermal growth factor receptor tyrosine kinase inhibitors, including gefitinib and erlotinib, have been proven to provide significant benefit in progression-free survival and overall survival in patients who have received at least one line of prior chemotherapy. Subgroup analyses of previous placebo-controlled clinical trials demonstrated that epidermal growth factor receptor mutation–positive status was associated with improved outcomes with epidermal growth factor receptor tyrosine kinase inhibitor therapy, leading to further investigation of these agents in the first-line setting. However, selection by clinical characteristics has proved inadequate for identifying all patients with epidermal growth factor receptor mutation–positive disease. Recently, several randomised and multicentre phase III clinical trials investigated the efficacy and tolerability of first-line gefitinib or erlotinib versus standard chemotherapy regimens in patients with confirmed epidermal growth factor receptor–activating mutation non–small-cell lung cancer. The results demonstrated that epidermal growth factor receptor mutation is a key to achieving exceptional outcomes with tyrosine kinase inhibitor therapy, regardless of patient clinical characteristics. However, there are also some dilemmas in genotype-based personalised tyrosine kinase inhibitor treatment. It is not yet clear whether this approach should only be applied after standard first-line chemotherapy or be used as first-line therapy to start with. In addition, as a non-invasive and repeatable source of genotypic information, it is uncertain whether repeated determination of epidermal growth factor receptor mutation status in peripheral blood could be helpful. In future, more clinical studies combined with prospective molecular analysis are warranted to verify the best strategy for individualised target therapy in selected patients with non–small-cell lung cancer.

Key Words: *Carcinoma, non-small-cell lung; Lung neoplasms; Protein-tyrosine kinases; Receptor, epidermal growth factor; Survival rate*

中文摘要

表皮生長因子受體酪胺酸激酶抑制劑對非小細胞肺癌患者的個體化治療：共識與爭議

卓明磊、王洁

表皮生長因子受體（EGFR）酪胺酸激酶抑制劑（TKI）類藥物，包括gefitinib及erlotinib，已被證實為至少已經接受一線化療的病人提高無惡化生存期及總生存時間。採用安慰劑對照的臨床研究的亞組分析顯示，EGFR突變狀況與EGFR-TKI治療帶來的改善有關，令至有更多關於使用EGFR-TKI作一線治療的研究。儘管如此，純粹用臨床特徵辨別所有具EGFR突變的病人並不足夠。最近有幾個隨機及多中心III期臨床研究探討在確認有EGFR突變的非小細胞肺癌患者中，比較標準化療及使用

Correspondence: *Dr Jie Wang, Department of Thoracic Medical Oncology Peking University Cancer Hospital, Beijing 100036, China.*
Email: wangjie_cc@yahoo.com

gefitinib或erlotinib作為一線治療的療效與耐受性。結果顯示EGFR突變是TKI治療達至理想效果的一個關鍵，與病人的臨床特徵無關。可是，以基因型為基礎的個體化TKI治療有些兩難局面。究竟這種療法應該在標準一線治療後才施用，還是本身應作為一線治療的藥物，並未有清晰結論。並且作為一種非創傷性及可重複性的基因型資訊，重複外周血液測試EGFR突變狀況未知是否真的有幫助。以後需要有更多的包括分子分析的前瞻性臨床研究來驗證非小細胞肺癌患者的最佳個體化標靶治療。

INTRODUCTION

Lung cancer is still the leading cause of cancer death worldwide[1]; non–small-cell lung cancer (NSCLC) is the most common form and accounts for approximately 85% of cases.[2,3] Traditional chemotherapies have reached a plateau in terms of efficacy.[4-6] Developments in molecular research show that we can no longer assume one therapeutic regimen is fit for all such patients. Survival rates not only depend on the efficacy of treatments but also on the genetic makeup of each individual and the type of tumour that one has. With the study and discovery of biomarkers and epidermal growth factor receptor (EGFR) therapy, survival rates for patients with NSCLC have been increasing.

In some tumours including NSCLC, it is evident that EGFR is over-expressed. Activation of EGFR tyrosine kinase leads to activation of several signal pathways including the Ras/MAPK pathway and the PI3K/Akt pathway, which drive malignant transformation. In a subset of patients with NSCLC, treatment with reversible EGFR tyrosine kinase inhibitors (TKIs) results in dramatic antitumour activity. Sequencing of the *EGFR* gene revealed that the majority of tumours responding to EGFR TKIs harboured mutations in the TK domain of EGFR.[7-9]

EGFR-activating mutation–based EGFR-TKI first-line therapy has become the model of personalised treatment, which indicates that we are entering an era of individualised therapy for NSCLC. In this article, the latest data on EGFR-TKI studies are reviewed, and consensus and controversies about personalised EGFR-TKI therapy are discussed.

EGFR MUTATIONS IN CHEMOTHERAPY-NAÏVE NSCLC: TARGETING NEW DISEASE

Selection of therapy for patients with advanced-stage NSCLC remains largely empiric. Although a number of potential predictive biomarkers for both chemotherapy and targeted therapies have been reported within the last several years, till now very few have proven to be 'practice-changing'. However, with the advent of first-line EGFR-TKI therapy for the patients with known activating mutations in EGFR, this situation has now changed.

The large phase IIII trial of gefitinib versus paclitaxel/carboplatin in Asia (IPASS) recruited 1217 patients in East Asian countries, who were selected on the basis of clinical (including adenocarcinoma) characteristics, non-smoker or light-smoker status.[10] This study achieved its primary endpoint by demonstrating gefitinib's noninferiority, and with respect to its impact on progression-free survival (PFS), it was also superior (hazard ratio [HR] for gefitinib vs paclitaxel/carboplatin = 0.74; 95% confidence interval [CI], 0.65-0.85; $p < 0.001$). HR in this paper refers to the risk of adversity relative to the comparator. The 12-month rates for PFS were 24.9% with gefitinib and 6.7% with standard chemotherapy. In the subgroup of patients harbouring the *EGFR* mutation, gefitinib achieved a significantly longer PFS than chemotherapy (HR = 0.48; $p = 0.0001$). By contrast, in patients who were negative for the mutation, PFS was significantly longer in chemotherapy group (HR = 2.85; $p < 0.001$). The objective response rates were 71.2% and 1.1% for first-line gefitinib in patients with and without *EGFR* mutation, respectively. Such results indicated that gefitinib could be used as first-line therapy for patients carrying EGFR-activating mutation, while those without the mutation should receive standard chemotherapy.

A Korean study (First-SIGNAL) with a similar design to IPASS randomised 313 patients with adenocarcinoma who were non- or light-smokers into gefitinib or a gemcitabine-plus-cisplatin regimen.[11] The primary endpoint was overall survival (OS). Despite there being no significant difference in OS in the 2 treatment arms, the study provided supportive evidence about the importance of *EGFR* mutation–positive status, as such patients enjoyed a higher tumour response rate and prolonged PFS with gefitinib therapy.

In both the First-SIGNAL and IPASS studies, however, the selection of patients was based on clinical characteristics and did not depend on the EGFR-activating mutation, which could be regarded as important limitations. It is well known that selection by clinical characteristics proved inadequate for identifying patients with *EGFR* mutation–positive disease. Subsequently a single-arm study and 3 other randomised studies based on prospective and sensitive screening for the *EGFR* mutation, all confirmed the important findings related to this mutation noted in IPASS and First-SIGNAL.

In a Spanish study (acronym SLOC),[12] 2105 patients with non-squamous NSCLC were screened for the *EGFR* mutation, of whom 315 (16.6%) tested positive. However, the study population entailed considerable numbers of women and never-smokers, so it may have included a higher proportion of EGFR-activating mutation patients than the general Caucasian population with non-squamous NSCLC. Regarding the 217 out of these 315 patients treated with erlotinib 150 mg daily (113 as first-line and 104 as second- or third-line therapy), the objective response rate, median PFS and OS were 70.6%, 14 months and 27 months, respectively.[12] This result was a striking improvement over findings in patients with lung cancer reported previously. In multivariate analyses, male sex and the presence of the L858R mutation (vs exon 19 deletion) were associated with both poor PFS and OS.

Two randomised studies from Japan compared EGFR-TKI therapy with chemotherapy in a genotype-selected population positive for *EGFR* mutation.[13,14] In the first phase III study (NEJSG002) for advanced NSCLC patients with the EGFR-activating mutation,[13] 228 eligible patients were randomised into first-line gefitinib or chemotherapy with paclitaxel/carboplatin. The results showed that in gefitinib therapy arm, PFS was significantly prolonged (HR = 0.36; 95% CI, 0.25-0.51; $p < 0.001$) and the overall response rate (ORR) was increased in comparison to those having chemotherapy (74.5 vs 29.0%; $p < 0.001$). There was also a trend towards prolonged OS with gefitinib compared to carboplatin/paclitaxel recipients (HR = 0.79; 95% CI, 0.49-1.30; $p = 0.35$), although there was a high crossover rate in the chemotherapy arm; 96% of the participants received gefitinib following the period of study treatment.[13] Another phase III study in Japan compared gefitinib (250 mg/day) with cisplatin (80 mg/m^2) plus docetaxel (60 mg/m^2) administered at 3-weekly intervals as first-line treatment for advanced NSCLC patients carrying EGFR-activating mutations (exon 19 deletion or L858R in exon 21; West Japan Thoracic Oncology Group [WJTOG] 3405).[14] The primary endpoint was PFS. Gefitinib significantly prolonged PFS compared to cisplatin / docetaxel (HR = 0.49; 95% CI, 0.34-0.71; $p < 0.001$; n = 172); there was no statistically significant difference in PFS between patients with exon 19 deletions and those with the L858R mutation. The ORR was significantly higher in the gefitinib arm compared to those on cisplatin / docetaxel (62.1 vs 32.2%; $p < 0.001$; n = 117). Data for OS were still immature (27 patients [15.7%] had died, follow-up was ongoing); the HR for gefitinib was 1.638 (95% CI, 0.75-3.58).

The OPTIMAL study was the first prospective head-to-head study comparing first-line erlotinib with platinum-doublet chemotherapy conducted in Chinese NSCLC patients with the EGFR-sensitive mutation.[15] 165 patients with confirmed EGFR-activating mutation were randomised into either erlotinib or standard first-line chemotherapy with gemcitabine plus carboplatin (the

Table. Randomised studies confirming the role of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) as first-line therapy.

Author(s)	Study	No. (EGFR+)	Patients	Primary endpoint	RR (TKI vs chemotherapy)	HR (95% CI)	
						PFS	OS
Mok et al[10]	IPASS	261	Adenocarcinoma, non- or light-smokers	PFS	71% vs 47%	0.48 (0.36-0.64)	0.48 (0.36-0.64)
Lee et al[11]	First-SIGNAL	42	Adenocarcinoma, non- or light-smokers	OS	85% vs 38%	0.61 (0.31-1.22)	NA
Mitsudomin et al[14]	WJTOG3405	198	*EGFR* mutation(+)	PFS	62% vs 32%	0.49 (0.34-0.71)	1.64 (0.75-3.58)
Maemondo et al[13]	NEJSG002	230	*EGFR* mutation(+)	PFS	74% vs 31%	0.30 (0.22-0.41)	NA
Zhou et al[15]	OPTIMAL	150	*EGFR* mutation(+)	PFS	83% vs 36%	0.16 (0.10-0.26)	NA
Rosell et al[12]	EURTAC	130	*EGFR* mutation(+)	PFS	NA	NA	NA

Abbreviations: RR = relative risk; HR = hazard ratio; CI = confidence interval; PFS = progression-free survival; OS = overall survival; NA = not applicable.

most commonly used regimen in China). The primary endpoint was PFS. The study met its primary endpoint of PFS with a HR of 0.16 and highly significant p value of less than 0.0001 in favour of erlotinib. Median PFS increased by 8.5 months from 4.6 months with chemotherapy to 13.1 months with erlotinib. Similar PFS benefits were observed across the clinical subgroups analysed with all HR of less than 0.27, and these results clearly demonstrate that *EGFR* mutation is the key factor in providing the exceptional response to erlotinib therapy, regardless of patients' clinical characteristics.

The above facts verified that the detection of *EGFR* with mutations is fundamental in determining first-line therapy strategy (Table). If patients with *EGFR* mutation–positive tumours are treated with EGFR-TKI, they have superior PFS and ORR than if they receive primary chemotherapy. Therefore, the detection of *EGFR* mutations in patients with NSCLC appears to be the first molecular predictive factor that can offer patients more effective and convenient targeted therapy than conventional chemotherapy regimens. This should therefore be the first step in management, and could lead to individualised treatment for patients with advanced NSCLC that could improve both disease outcomes and quality of life (QoL).

CAN *EGFR* MUTATION PREDICT THE OUTCOME OF SECOND- OR THIRD-LINE EGFR-TKI THERAPY?

The TKIs were originally introduced for chemotherapy-resistant NSCLC patients. In the phase III BR.21 trial, a total of 731 patients were randomised to receive either erlotinib 150 mg daily or placebo in 2:1 ratio.[16] The response rate (RR) was 8.9% in the erlotinib group and less than 1% in the placebo group ($p < 0.001$); PFS was 2.2 months and 1.8 months respectively (HR = 0.61, $p < 0.001$), and the OS was 6.7 months and 4.7 months respectively (HR = 0.70; $p < 0.001$), in favour of erlotinib. The ISEL study, however, did not show a survival benefit for gefitinib in the overall group of patients studied; the median OS was 5.6 months for gefitinib and 5.1 months for placebo.[16] The possible reason could be the high percentage of refractory disease patients in the ISEL trial in comparison to the BR.21 study.

However, controversies exist as to whether *EGFR* mutation can predict outcome of EGFR-TKI therapy when these agents were given to the patients who failed previous chemotherapy. In the BR.21 study, univariate analysis revealed that survival was longer in the erlotinib group than in the placebo group when EGFR was expressed (HR for death = 0.68; $p = 0.02$) or there was a high number of copies of EGFR (HR = 0.44; $p = 0.008$). Yet in the multivariate analyses, survival after treatment with erlotinib was not influenced by the status of EGFR expression, the number of EGFR copies, or *EGFR* mutations.[17] Similarly, subgroup analysis in ISEL study[16] indicated that *EGFR* mutations status was not associated with PFS and OS in the patients who received gefitinib as second- or third-line therapy. In the INTEREST study, however, gefitinib was compared with docetaxel in NSCLC patients pretreated with platinum-based chemotherapy,[18] PFS was significantly longer with the former in *EGFR* mutation–positive patients in the pretreated setting (HR = 0.16; 95% CI, 0.05-0.49; $p = 0.001$; $n = 38$). Subgroup analysis, in non-Asian patients only, has also shown that PFS was significantly longer with gefitinib compared with docetaxel in *EGFR* mutation–positive patients (HR = 0.12; 95% CI, 0.03-0.51; $p = 0.005$), although patient numbers were small.

Furthermore, for patients with *EGFR* mutation, the RR of EGFR-TKI therapy was about 70 to 80% after first-line therapy but only 40 to 50% in the second-line setting.[19-21] It is difficult to explain such discrepancies with imbalanced subsequent treatments. In the above studies, EGFR biomarkers were determined in the primary tumour from initial diagnostic samples. Therefore, there was a gap between the initial diagnosis and onset of second-line therapy. We believe that the *EGFR* gene of the tumour may have changed after chemotherapy, which prevented the above analysis from reaching valid conclusions. Several studies have supported our hypothesis that *EGFR* mutation status may change during the course of disease.[22-26] In our unpublished study, the *EGFR* mutation rate in all 61 patients were 41.0% (25/61) at baseline and dropped to 29.5% (18/61) after neoadjuvant chemotherapy.

WHAT IS THE OPTIMAL SEQUENCE OF TREATMENT IN PATIENTS WITH *EGFR* MUTATIONS?

Recent data suggest that the presence of an *EGFR* mutation is the decisive predictor for first-line EGFR-TKI therapy. Yet up to now, the results of all clinical trials involving first-line EGFR-TKI versus standard chemotherapy — including IPASS, First-SIGNAL, NEJSG002 and WJTOG3405 — could not resolve what

strategy to use. Thus, for patients with EGFR-activating mutations it is unclear whether to offer first-line EGFR-TKI followed by second-line chemotherapy or vice versa. The phase III TORCH trial, reported at the 2010 ASCO meeting, tried to answer the question on this therapeutic sequence. It was designed to test whether OS in the experimental arm (first-line erlotinib [150 mg/d orally] followed at progression by cisplatin and gemcitabine [CG]) was not inferior to standard first-line CG followed by erlotinib at disease progression. However, the study was based on unselected patients and showed that in these patients chemotherapy should be given first.[27] We therefore need to conduct prospective trials to compare EGFR-TKIs with standard chemotherapy using the OS as primary endpoint in genotype-defined populations. Such studies will challenge investigators because, unlike current trials, not only the first-line therapy but also all subsequent lines of therapy would need to be defined in the protocol.

EGFR MUTATION TESTING IN PERIPHERAL BLOOD SAMPLES, IS TRAP OR SURROGATE OF TISSUES *EGFR* MUTATION?

EGFR mutation testing in tissues has been used routinely to select patients for treatment with an EGFR-TKI. However, such approach has a major limitation because of the difficulty to obtain tumour tissues for the analyses, particularly in those with refractory NSCLC. Even in prospectively conducted clinical trials, tumours from less than 40% of the patients were available for the mutation analysis,[10,16] because plasma samples of patients with cancer often contain circulating DNA derived from tumour tissues. The use of surrogate (non-tumour) samples — including serum and plasma — has been explored,[28-30] but current methods lack sufficient sensitivity and have false-negative rates of approximately 20 to 50%. In the screening study conducted in Spain, which used a polymerase chain reaction–based screening technique, exon 19 deletions were detected in 62% (135/217) of tumour samples compared to 39% (64/164) of serum samples, whilst the L858R mutation was noted in 38% (82/217) of tumour samples compared to 20% (33/164) in serum samples.[12]

Our recently published study evaluated the value of a plasma-based *EGFR* mutation analysis in predicting tumour response in patients with NSCLC by denaturing high-performance liquid chromatography (DHPLC).[28] In all, 230 stage IIIB-IV NSCLC patients with circulating DNA in plasma samples and matched tumours were analysed for mutations in EGFR exon 19 and 21, using DHPLC whilst being blinded to clinical outcome data. The results showed that 81 mutations were detected in 79 (35%) of the 230 plasma samples; 63 (80%) such mutations were also detected in the matched tumours, whereas 18 (8%) of the plasma samples and 16 (7%) of the tumour samples showed unique mutations. In the 105 patients treated with gefitinib, 22 (60%) of the 37 with mutations in the plasma samples achieved objective partial responses, whereas only 15 (22%) of the 68 without the mutations did so ($p = 0.0002$). Patients with mutations evident in plasma samples had a significantly longer PFS than in those without the mutations ($p = 0.04$).

Rosell et al[12] used a polymerase chain reaction–based screening technique to detect the *EGFR* mutation in peripheral blood samples and protein nucleic acid (PNA) clamp method designed to inhibit the amplification of the wild-type allele.This method has allowed us to detect *EGFR* mutations in serum and plasma in a population of 211 mutated patients with a 57% sensitivity and almost 100% specificity.[31] Using the amplification refractory mutation system (ARMS) technique to analyse serum samples from Japanese patients in the IPASS trial, Yamamoto et al[32] also detected mutations in the serum of 29 out of 51 patients deemed *EGFR* mutation–positive by tumour-tissue testing (false-negative rate, 56.9%). Another publication[26] described the use of a microfluidic device containing microposts coated with antibodies against epithelial cells to purify circulating tumour cells. This had been used with an ARMS technique to detect *EGFR* mutations with a sensitivity of 92% (11/12 patients) compared to of 33% (4/12 patients) in matched free-plasma DNA ($p = 0.009$). However, this study had relatively small samples and this device is not yet suitable for large-scale use.

CONCLUSION

NSCLC is a heterogeneous disease associated with a high mortality. Personalised therapy may improve treatment outcomes by identification of a specific genotypic anomaly and target-specific therapy. The most significant development in recent years was the discovery of activated *EGFR* mutations at exons 19 and 21. Patients with *EGFR* mutations respond dramatically to EGFR-TKIs such as gefitinib or erlotinib, resulting in longer PFS. Multiple randomised studies — including the IPASS, two Japanese studies and OPTIMAL — have confirmed the role of EGFR-TKIs as standard first-line therapy for patients with an activating *EGFR* mutation. Controversy still exists, however, and warrants further research.

REFERENCES

1. Revised global burden of disease (GBD) 2002 estimates: incidence, prevalence, mortality, YLL, YLD and DALYs by sex, cause and region, estimates for 2002 as reported in the World Health Report 2004. Geneva: World Health Organisation; 2004.
2. Navada S, Lai P, Schwartz AG, Kalemkerian GP. Temporal trends in small cell lung cancer: analysis of the national Surveillance Epidemiology and End-Results (SEER) database. J Clin Oncol. 2006;24:384S.
3. Sher T, Dy GK, Adjei AA. Small cell lung cancer. Mayo Clin Proc. 2008;83:355-67.
4. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med. 2002;346:92-8.
5. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006;355:2542-50.
6. Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol. 2003;21:3016-24.
7. 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;350:2129-39.
8. Paez JG, Jänne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science. 2004;304:1497-500.
9. Gazdar AF. Activating and resistance mutations of EGFR in non-small-cell lung cancer: role in clinical response to EGFR tyrosine kinase inhibitors. Oncogene. 2009;28 Suppl 1: S24-31.
10. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361:947-57.
11. Lee JS, Park K, Kim S-W, et al. A randomized phase III study of Gefitinib versus Standard chemotherapy (Gemcitabine plus Cisplatin) as a first-line treatment for never-smokers with advanced or metastatic adenocarcinoma of the Lung [abstract]. J Thorac Oncol. 2009;4(Suppl 1):PRS.4.
12. Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med. 2009;361:958-67.
13. 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;362:2380-8.
14. 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;11:121-8.
15. Zhou C, Wu YL, Lu S, et al. Efficacy results from the randomised phase III OPTIMAL (CTONG 0802) study comparing first-line erlotinib versus carboplatin plus gemcitabine, in chinese advanced non-small-cell lung cancer patients with EGFR activating mutations. ESMO 2010; Abstract LBA13.
16. Thatcher N, Chang A, Parikh P, et al. 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;366:1527-37.
17. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med. 2005;353:123-32.
18. Kim ES, Hirsh V, Mok T, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. Lancet. 2008;372:1809-18.
19. Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial). J Clin Oncol. 2003;21:2237-46.
20. Kris MG, Natale RB, Herbst RS, et al. 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;290:2149-58.
21. Pérez-Soler R, Chachoua A, Hammond LA, et al. Determinants of tumor response and survival with erlotinib in patients with non--small-cell lung cancer. J Clin Oncol. 2004;22:3238-47.
22. Gow CH, Chang YL, Hsu YC, et al. Comparison of epidermal growth factor receptor mutations between primary and corresponding metastatic tumors in tyrosine kinase inhibitor-naive non-small-cell lung cancer. Ann Oncol. 2008;20:696-702.
23. Bozzetti C, Tiseo M, Lagrasta C, et al. Comparison between epidermal growth factor receptor (EGFR) gene expression in primary non-small cell lung cancer (NSCLC) and in fine-needle aspirates from distant metastatic sites. J Thorac Oncol. 2008;3:18-22.
24. Italiano A, Vandenbos FB, Otto J, et al. Comparison of the epidermal growth factor receptor gene and protein in primary non-small-cell-lung cancer and metastatic sites: implications for treatment with EGFR-inhibitors. Ann Oncol. 2006;17:981-5.
25. Kobayashi S, Boggon TJ, Dayaram T, et al. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. N Engl J Med. 2005;352:786-92.
26. Maheswaran S, Sequist LV, Nagrath S, et al. Detection of mutations in EGFR in circulating lung-cancer cells. N Engl J Med. 2008;359:366-77.
27. Gridelli C, Ciardiello F, Feld R, et al. International multicenter randomized phase III study of first-line erlotinib (E) followed by second-line cisplatin plus gemcitabine (CG) versus first-line CG followed by second-line E in advanced non-small cell lung cancer (aNSCLC): The TORCH trial [abstract]. J Clin Oncol. 2010;28(Suppl):S15.
28. Bai H, Mao L, Wang HS, et al. Epidermal growth factor receptor mutations in plasma DNA samples predict tumor response in Chinese patients with stages IIIB to IV non-small-cell lung cancer. J Clin Oncol. 2009;27:2653-9.
29. Sozzi G, Conte D, Leon M, et al. Quantification of free circulating DNA as a diagnostic marker in lung cancer. J Clin Oncol. 2003;21:3902-8.
30. Esteller M, Sanchez-Cespedes M, Rosell R, Sidransky D, Baylin SB, Herman JG. Detection of aberrant promoter hypermethylation of tumor suppressor genes in serum DNA from non-small cell lung cancer patients. Cancer Res. 1999;59:67-70.
31. Molina-Vila MA, Bertran-Alamillo J, Mayo C, Rosell R. Screening for EGFR mutations in lung cancer. Discov Med. 2009;8:181-4.
32. Yamamoto N, Ichinose Y, Nishiwaki Y, et al. EGFR mutations based on circulating free DNA in the subset of Japanese patients from IPASS (IRESSA Pan Asia Study), a Phase III study of first-line gefitinib vs carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer. Presented at: EORTC-NCI-ASCO. Brussels, Belgium 15–17 October 2009 (Poster 78).