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Are erlotinib and gefitinib interchangeable, opposite or complementary for non-small cell lung cancer treatment? Biological, pharmacological and clinical aspects

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Contents

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Abstract

Gefitinib and erlotinib are the two anti-epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) approved for treatment of advanced NSCLC patients. These drugs target one of the most important pathways in lung carcinogenesis and are able to exploit the phenomenon of 'oncogene addiction', with different efficacy according to EGFR gene mutational status in tumor samples. Gefitinib has been approved only for EGFR mutation bearing patients regardless the line of treatment, while erlotinib is also indicated in patients without EGFR mutation who undergo second- or third-line treatment. Some studies evaluated the main differences between these drugs both for direct comparison and to improve their sequential use. In particular, toxicity profile resulted partially different, and these observations may be explained by several molecular and pharmacokinetic features. Therefore, this review integrates preclinical data with clinical evidences of TKIs to guide the optimization of currently available treatments in advanced NSCLC patients.

Keywords: Lung cancer; Gefitinib; Erlotinib; Tyrosine kinase; EGFR; NSCLC

1. Introduction

1.1. Definition of EGFR-TKIs drugs

The management of NSCLC patients can today take advantage from the use of innovative targeted agents, such as erlotinib and gefitinib. The rationale for the efficacy of these small tyrosine kinase inhibitor (TKI) molecules lies in the so called "oncogene addiction" hypothesis, according to which some mutations that occur in specific oncogenes may render cancer cell survival strictly dependent on that aberrant gene [1,2]. Thus, drugs that are able to inactivate the mutated gene offer a new important strategy in the treatment of selected subgroups of tumors.

Gefitinib and erlotinib are orally active EGFR TKIs with different structure, as also reflected by the different molecular weight (446.9 Da and 429.9 Da, respectively). These drugs are ATP competitors at the ATP-binding pocket in the intracellular domain of EGFR [3]. As a consequence of this inhibition, cellular proliferation, angiogenesis, tumor invasion, and metastatic potential are inhibited. Gefitinib is available as film-coated tablets that contain 250 mg of active compound. Erlotinib tablets are available in three dose strengths: 25 mg, 100 mg, and 150 mg.

1.2. EGFR Pathway

Epidermal growth factor receptor (EGFR) is a transmembrane protein with cytoplasmic kinase activity that transduces growth signaling from the extracellular environment to the cell. The EGFR gene is located on the short arm of chromosome 7 (7p11.2) and encodes a 170 kDa type I transmembrane growth factor receptor [4]. EGFR belongs to the HER/*erb*B family receptor tyrosine kinases, which includes HER1 (EGFR/*erb*B1), HER2 (*neu*, *erb*B2), HER3 (*erb*B3) and HER 4 (*erb*B4). The interaction of EGFR extracellular domain with specific ligands induces a homo-dimerization (or hetero-dimerization with other HER family members) that causes the activation of the TK domain resulting in tyrosine autophosphorylation. Multiple signaling pathways are then activated, including RAS/RAF/ERK/MAPK and PI3K/AKT pathways [5]. These pathways regulate several intracellular processes such as proliferation, invasion, cellular repair, protection from injury and anti-apoptosis [6].

2. Biological bases of EGFR-TKIs treatment

2.1. EGFR mutational status and resistance mutations

Until April 2004 it was unclear how to identify NSCLC patients who would benefit from the use of erlotinib or gefinitib. The data from the retrospective analysis of BR.21 trial about erlotinib in pretreated patients suggest that never-smokers and patients with EGFR-positive tumors might experience an enhanced benefit from erlotinib compared to placebo [7]. Higher response rates were also associated with patient characteristics such as never-smoking status, female gender, adenocarcinoma histotype, and East Asian race. Nevertheless it was clear from the outset that not all patients responded in the same way to the treatment with these drugs. Then, two research groups from Boston revealed that EGFR gene mutations in the kinase domain are strongly associated with TKIs sensitivity [8–10].

The sensitizing mutations to TKIs treatment fall within EGFR kinase domain and are activating mutations. To date four main types of EGFR activating mutations have been identified: point mutation in exon18 (G719X, G719S, G719A), deletions in exon19, insertions in exon20, and point mutation in exon21 (L858R and L861Q). The most frequent mutations are exon19 deletions (over 20 variant types) and leucine-to-arginine mutation at codon 858 in exon21 (L858R), accounting for 90% of all EGFR mutations. Several cell-based studies demonstrated that these mutations increased autophosphorylating activity on intracellular tyrosines determining the activation of a subset of downstream effectors. In addition, the mutant kinases are more sensitive to inhibition by gefitinib and erlotinib, which seems to reflect their increased drug affinity [11].

Despite the efficacy of EGFR-targeted therapy in NSCLC, almost all patients develop resistance to these drugs, with a mean duration of the response ranging between 3 and 7 months [12,13]. Beyond all the activating mutations that confer sensitivity to TKIs, there are indeed other point

mutations that may determine resistance to TKIs treatment. The most common resistance mutation is the T790M (substitution of threonine to methionine on codon 790), which falls into exon20. This mutation cause the insertion of a bulky methionine over the ATP binding pocket, blocking access to EGFR-TKIs but not to ATP [14]. Because of its significant role in affecting TKIs activity, the T790M should also be evaluated before the beginning of the treatment. This mutation has been thought to cause resistance by sterically blocking binding of TKIs such as gefitinib and erlotinib, but this explanation is in contrast with the fact that it remains sensitive to structurally similar irreversible inhibitors. Subsequent studies showed that T790M mutation increased the affinity of the receptor for ATP [15] and that T790M mutants retain low-nanomolar affinity for TKIs, in particular gefitinib [14]. This mutation occurs in cis of the same allele as the original activating mutations (it may be either an exon19 deletion or an exon21 L858R mutation). Interestingly, data from a recent study have unraveled the predictive value of T790M [16]. This study analyzed 95 patients enrolled in EURTAC trial for T790M end P53 mutations, EML4-ALK translocation and BIM mRNA expression levels. The results showed that OS for patients with T790M mutations was 40.1 months in those with high BIM levels and 15.4 months in patients with low/intermediate BIM levels ($P = 0.04$). These findings should lead to the design of studies of treatment based on the presence of the EGFR T790M mutation and BIM expression levels. In addition to the EGFR T790M mutation, there are other uncommon secondary resistance mutations, such as T854A in exon21 [17], as well as L747S [18], and D761Y [19], both in the exon19. T854A mutation has a comparable effect to that of T790M; L747S is thought to shift the equilibrium toward the active conformation of the receptor, while D761Y may affect the catalytic cleft of the receptor [20] (Figs. 1–4).

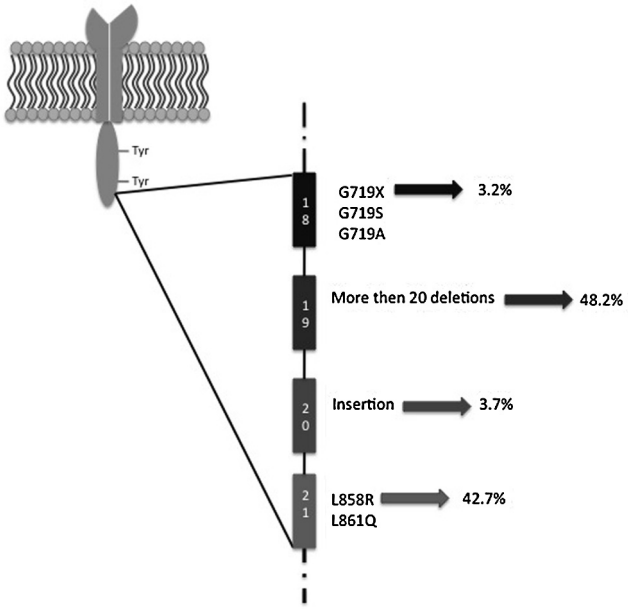

Fig. 1. EGFR activating mutation. The main mutation types identified in EGFR gene are: point mutation in exon18 (G719X, G719S, G719A), deletions in exon19, insertions in exon20, and point mutation in exon21 (L858R and L861Q). Point mutation in exon18 and insertions in exon20 account for 4% of all EGFR mutations; the most frequent mutations are exon19 deletions (over 20 variant types) and leucine-to-arginine mutation at codon 858 in exon21 (L858R), accounting for 90% of all EGFR mutations.

2.2. *EGFR-TKIs mechanisms of action*

Both gefitinib and erlotinib exert their action by interacting with EGFR ATP binding pocket and thereby blocking the signal transduction. EGFR mutations make the cancer cells more sensitive to these drugs through the phenomenon of "oncogene addiction", which provides a rationale for molecular targeted therapy. The blockade of this pathway leads to tumor cell death, while sparing EGFR wild type cells. Despite many studies support the concept of this phenomenon, the underlying biological and molecular mechanisms are not yet clear. Zhou and collaborators have recently developed a mathemathic model of EGFR-associated signaling network to investigate possible molecular mechanisms of tumor cell death [21].

EGFR activation results in the initiation of different cellular pathways. In response to several stimuli (toxic environmental stimuli or receptor occupation by the ligands EGF, transforming growth factor-α and neuregulins), the EGFR forms homo- or heterodimers with other family members and all the possible complexes between ErbB family members have been already identified [22]. The three heterodimers that are most frequently formed are ErbB-2/ErbB-3, ErbB-2/ErbB-4, and ErbB1/ErbB-4 and the different ability to form homo- and heterodimers is dictated by receptors expression levels. Receptor dimerization is followed by activation of intrinsic protein tyrosine kinase activity and tyrosine phosphorylation. These lead to the formation of phospho-tyrosine residues that enable receptor to recruit adaptor proteins such as Shc and Grb2 [23]. Several studies have also shown that the phosphorylation of specific tyrosine residues is able to recruit specific cytosolic proteins, and then activate different pathways [11]. For example Purvis and collaborators [24] assumed that phosphorylated Y1068 (pY1068) binds mainly to Gab-1 and Grb2 while phosphorylated Y1173 (pY1173) binds preferentially to Shc. This introduces the concept that differential signaling is headed by the phosphorilation of different tyrosine residues that transduce signal through distinctive/diverse pathways. Once bound to the receptor Shc and Grb2 recruit SOS that promotes the replacement of GDP by GTP in Ras, thereby activating Ras. This activation in turns lead to the phosphorylation of Raf and hence the MAPK pathway is activated. Conversely, the interaction of the EGFR with Gab-1 leads to the recruitment of phosphatidylinositol 3-kinase (PI3K), which induces the activation of AKT pathway by transforming PIP2 in PIP3 [25–29]. An internal process of negative feedback regulates both these pathways. In fact, activated ERK can also phosphorylate the protein SOS

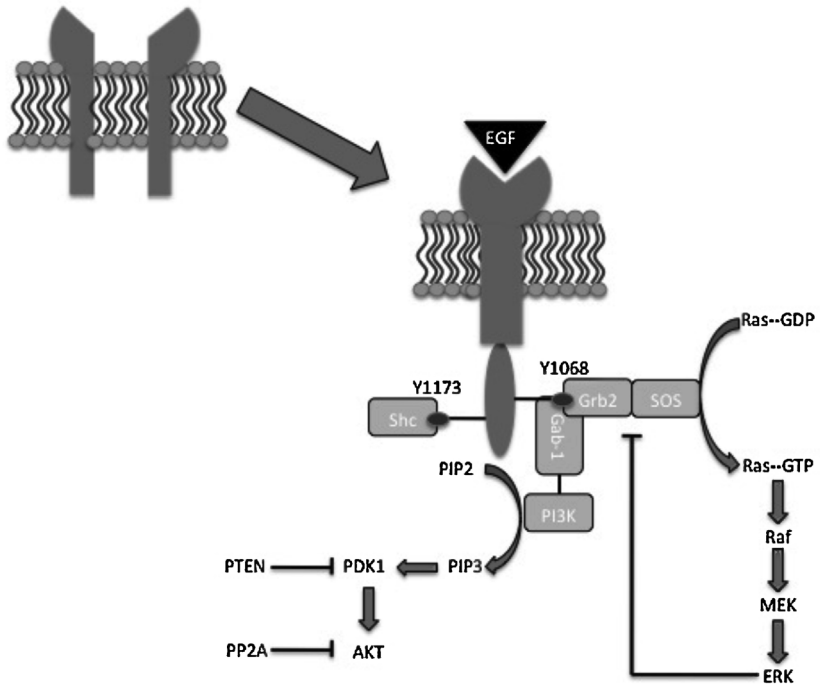

Fig. 2. EGFR pathway: Receptor dimerization lead to the activation of intrinsic protein tyrosine kinase activity and tyrosine phosphorylation. The phosphorylation of different tyrosine residues enables the receptor to recruit adaptor protein such as Shc and Grb2. Phosphorylated Y1068 (pY1068) binds mainly to Gab-1 and Grb2 while phosphorylated Y1173 (pY1173) binds preferentially to Shc. The recruitment of SOS promotes the replacement of GDP by GTP in Ras, thereby activating Ras. This activation in turns lead to the phosphorylation of Raf and hence the MAPK pathway is activated. Instead the interaction of the EGFR with Gab-1 leads to the recruitment of phosphatidylinositol 3-kinase (PI3K), that by transforming PIP2 in PIP3 induces the activation of AKT pathway.

inducing the dissociation of Grb2-SOS from the receptor. PIP3 and Akt are instead dephosphorylated by PTEN and PP2A, respectively. P38 is an important pro-apoptotic effector that can be activated by a variety of environmental stresses, among them the most important is the stress due to reactive oxygen species (ROS). Numerous studies have shown that stimulation of neoplastic cells with EGF can induce ROS production thus activating P38 [30]. The acute inactivation of EGFR results in a drastic decline of p-ERK and AKT and a delayed increase of P38. This finally results in a rapid decrease of proliferative stimuli and an increase of pro-apoptotic signals in addicted cancer cells [31].

Orally administered gefitinib or erlotinib are taken up by cancer cells, and they reversibly and competitively inhibit the binding of ATP to the phosphate-binding loop. By the inhibition of ATP binding to EGFR, the EGFR-TKIs therefore block auto-phosphorylation and the activation of downstream signaling pathways, leading to the inhibition of cell proliferation and the induction of apoptosis in cancer cells [32].

2.3. Biological hypotheses to explain the differences between erlotinib and gefitinib

The analysis of clinical data suggests a difference in the effectiveness of erlotinib and gefitinib. We present hypotheses on the biological basis of this difference to improve the understanding of TKIs' biological function. We hypothesize that the different response to gefitinib and erlotinib may depend on

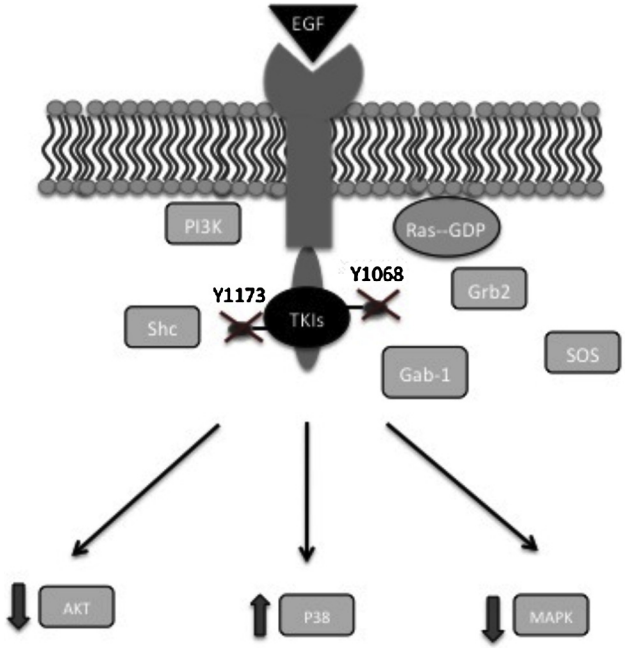

Fig. 3. TKIs supposed mechanism of action. Orally administered gefitinib (or erlotinib) is taken up by cancer cells, and it reversibly and competitively inhibits the binding of ATP to the phosphate-binding loop. By the inhibition of ATP binding to EGFR, EGFR-TKIs therefore block auto-phosphorylation and the activation of downstream signaling pathways, leading to the inhibition of cell proliferation and the induction of apoptosis in cancer cells.

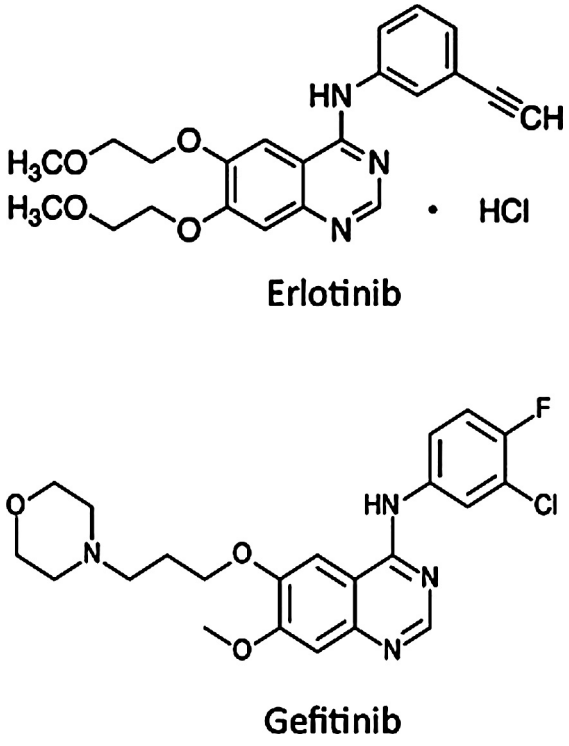

Fig. 4. Erlotinib and gefitinib chemical structures. Erlotinib and gefitinib (molecular mass 429.9 and 446.9 respectively) are both based on a 4-anilino-quinazoline kinase pharmacophore and exhibit similar pharmacokinetic characteristics in patients after oral administration, with extensive metabolism primarily by cytochrome P450 3A4 in liver.

the effects of various EGFR mutations on receptor structure, primarily on catalytic site. This hypothesis is supported by Yun and collaborators, stating that the effect of the mutations on inhibitor binding site is important, because they cluster around the catalytic cleft and differences in inhibitor sensitivity of the mutants have been reported [15]. This study suggests that mutations L858R and G719S have a different effect on the sensitivity to gefitinib, showing that L858R binds more tightly to gefitinib compared to G719S mutant. This markedly tighter binding of gefitinib to L858R mutant could explain its effectiveness against cells bearing this mutation. In particular L858R transformed Ba/F3 cells are significantly more gefitinib-sensitive than G719S transformed cells [32]. These data show that intrinsic differences in the inhibitor binding affinity of the altered EGFR kinases might explain the differential sensitivity of cell lines and tumor cells bearing L858R and G719S proteins.

Moreover, the combination of two different mutations could confer resistance to a TKI but improve sensitivity to the other one. In particular, an EGFR mutation E884K, in combination with L858R, was identified in a patient with advanced lung cancer who progressed on erlotinib maintenance therapy, and subsequently had leptomeningeal metastases that responded to gefitinib [33].

Several other EGFR mutations might also play a relevant role in this context and further studies are necessary to investigate this possibility. More than 75 different EGFR kinase domain residues have been reported to be altered in NSCLCs. Using transfection of an YFP-tagged fragment of the EGFR intracellular domain (YFP-EGFR-ICD), followed by immunofluorescence microscopy analysis, recent studies demonstrated that the exon 20 insertions Ins770SVD, Ins774HV N771GY and A767-V769 confer increased kinase activity, but no sensitivity to erlotinib at clinically available concentrations [34]. However, a more recent study showed that sensitivity to erlotinib and gefitinib differed among several EGFR mutations at exon 19 [35]. Moreover, gefitinib and erlotinib seems to have slightly different activity also for the wild-type EGFR receptor, since esponse rates of gefitinib in NSCLC with wild-type EGFR range from 0 to 6.6% in several phase III trials [36–39], while the response rate of erlotinib in NSCLC with wild-type EGFR was 7% in the BR.21 study [40]. Although one should be cautious in interpreting these results since the detection method of EGFR mutations varied from study to study, further studies with standardized methods may help the clinician in patient management and may also improve the research of new and more potent TKIs selective for specific mutations.

Finally, several research groups are investigating the possible role of EGFR polymorphisms in the response and toxicity to TKIs treatment [41]. Germline polymorphisms can be easily assessed in blood samples, and candidate polymorphisms in EGFR have been correlated with outcome in NSCLC patients treated with gefitinib or erlotinib [42]. In particular, EGFR -191C/A, -216 G/T, and R497K polymorphisms have been associated with gastrointestinal toxicity both in gefitinib and erlotinib-treated patients, while AKT1-SNP4 A/A genotype seems to be a candidate biomarker of primary resistance, when using gefitinib in NSCLC patients [43], but not in the pharmacogenetic analysis of the BR.21 randomized phase III clinical trial of erlotinib [44]. Despite these intriguing findings, the small sample size, together with the interethnic differences, and the retrospective nature of most pharmacogenetic studies, make it difficult to draw any clear conclusions regarding the role of these biomarkers in determining the differential clinical outcome or toxicity in gefitinib and erlotinib treatment. Hopefully, the accurate planning of new prospective trials, the increased knowledge of key mechanisms affecting drug distribution/activity, and the use of novel technologies, including genome-wide approaches, may provide critical and essential tools to improve our insights in EGFR-TKIs mechanisms of action, in order to optimize these treatments in selected NSCLC patients.

3. Pharmacokinetics

3.1. Bioavailability

After oral assumption erlotinib is slowly absorbed and reaches its maximum plasma concentration after 3–4 h with a mean bioavailability of 60%. One study provided an estimate of the absolute bioavailability of 59%. At a dose of

150 mg daily erlotinib keep an area under curve (AUC) of 38.420 ng.h/ml [45]. This value is about seven-fold higher than those which could be obtained by administering therapeutic doses of gefitinib. Thus, the standard dose of erlotinib yields a higher exposure, and a patient should receive >3-fold recommended dose of gefitinib, which is 250 mg, to obtain drug concentrations equivalent to those achievable by erlotinib.

The solubility of both erlotinib and gefitinib is pH-dependent. Agents that alter gastric pH, such as H2-receptor antagonists and proton-pump inhibitors can substantially reduce the plasma levels of EGFR TKIs, and their concomitant use should be avoided. Moreover, both the bioavailability and the AUC of erlotinib increase considerably when the drug is ingested with food [46]. Erlotinib has an oral bioavailability of 60% when taken on an empty stomach. Conversely, when taken with food, erlotinib has a bioavailability of nearly 100%, which potentiates side effects. Therefore, erlotinib should be taken at least 1 h before or 2 h after a meal. After 7–8 days erlotinib concentrations reach steady-state and its elimination half-life is 31 h. Erlotinib is evenly distributed in the plasma and tumor tissue (plasma: tumor ratio = 1:1). Binding to plasma proteins is approximately 95% bound to serum albumin and alpha-1 acid glycoprotein (AAG) of the serum. For erlotinib a 30% dose reduction is allowed. This dose reduction regards 6–16% of patients because of side effects.

In contrast, food does not affect the absorption of gefitinib. The absorption after oral administration is moderately slow and peak plasma concentrations are obtained after 3–7 h from administration, with elimination half-life of 48 h, and mean bioavailability of 60%. This drug is distributed extensively in tissues, and plasma protein binding is approximately 90% [47].

3.2. Metabolism and clearance

Erlotinib and gefitinib are metabolized primarily by CYP3A4 and less by CYP3A5 and CYP1A1 [48]. Erlotinib is metabolized primarily in the liver by different cytochrome enzymes (especially by CYP3A4), but intestinal and lung cancer cells could partly contribute to its catabolism. Moreover, cigarette smoking induces CYP1A1 and has been correlated with a reduction in erlotinib exposure after a therapeutic dose [49].

Erlotinib excretion is >90% by stools and the rest by kidney. Less than 2% of delivered dose is excreted as unchanged drug. Also gefitinib is excreted mainly as metabolites in stools, with renal elimination accounting for <4% of the administered dose.

However, erlotinib lipophilicity is about 3-times lower than gefitinib. This could help to explain some of the differences in pharmacokinetic and pharmacodynamic properties of the two compounds, since a greater lipophilicity also leads to a higher susceptibility to the action of catabolic mechanisms, an increase in biliary excretion and a decrease in plasma concentrations of free drug. In fact erlotinib is less exposed to hepatic cytochrome enzyme action, resulting in a slower clearance.

The factors related to the patient that showed a correlation with the pharmacokinetics of erlotinib were serum total bilirubin, Alpha-1 Acid Glycoprotein (AAG) and current smoking. Increased serum concentrations of total bilirubin and AAG concentrations were associated with a reduced erlotinib clearance. An interesting data on the pharmacokinetics of erlotinib is given by its interaction with smoke, so that smoker's drug exposure is reduced by 50–60% and the maximum tolerated dose is increased to 300 mg [49]. For this reason smoking cessation should be suggested before treatment starts.

4. Clinical aspects

EGFR-TKIs represent the mainstream target therapy in NSCLC lung cancer, leading to improvements in PFS and OS when used as upfront treatment in patients whom tumors harbor EGFR mutations [50]. Instead of chemotherapy, which induces limited benefit on a large proportion of NSCLC patients, targeted drugs are able to obtain a higher benefit on a limited number of selected patients, with a lower toxicity and a better quality of life. Therefore targeted drugs improve the concept of tailored therapy, which will lead to new algorithms taking into account clinical characteristics, histology, molecular profiling such as genomics, and individual genes pattern. It represents the new frontier of cancer treatment without using chemotherapeutic drugs, even if, at this time, these progresses have had only a limited impact on the overall outcome, and chemotherapy remains the only possible treatment for the most part of NSCLC patients [51].

The first clinical trials evaluating the TKIs efficacy in the treatment of NSCLC patients date back to 2003–2005. On the basis of encouraging pre-clinical results, some phase III studies were designed to evaluate the efficacy of gefitinib and erlotinib in combination with the chemotherapeutic second-line treatment [12,52] and the first-line [53–55]. However these results were clearly negative. More recently, a further phase III study [56], evaluated the addition of erlotinib to first-line cisplatin-gemcitabine chemotherapy in stage IIIB–IV NSCLC patients. The authors concluded that erlotinib with concurrent cisplatin-gemcitabine shows no benefit compared to chemotherapy-naive NSCLC patients.

4.1. Comparison of clinical trials results (first line, second line and maintenance)

4.1.1. Use in pretreated patients

On the basis of encouraging results emerging from phase II studies, which showed a good activity profile of gefitinib and erlotinib as second/third line treatment in terms of response rate (RR), two randomized phase III trials comparing the efficacy of both drugs versus placebo were conducted [57,58].

Table 1
Randomized phase III trials of comparison of TKI vs. placebo in pre-treated patients with advanced NSCLC.

Clinical trials	BR.21 [36]	ISEL [37]
Treatment	Erlotinib vs. placebo	Gefitinib vs. placebo
Median OS 6.7 vs. 4.7 months (HR: 0.73; *p*: 0.001)	5.6 vs. 5.1 months (HR: 0.89; *p*: 0.1)	

In particular BR21 study, which enrolled 731 patients with NSCLC in second/third line treatment, achieved the primary endpoint, overall survival (OS), with an extension of 42% of the median survival in the erlotinib group compared with placebo (OS: 6.7 vs. 4.7 months, HR: 0.73, *p*: 0.001).

A multivariate subsequent analysis of the study showed a greater RR in the erlotinib arm in a subgroup of patients selected on the basis of certain clinical characteristics (women, non-smokers, Asian race, adenocarcinoma). These characteristics are associated with a higher probability of EGFR gene mutation, but BR21 data showed a statistically significant benefit even in the subgroup of male patients, smokers, squamous histology, leading to the drug registration with indication for treatment of 2–3 line in NSCLC patients not selected on the basis of clinical or biomolecular features.

With regard to gefitinib, the phase III trial which compared gefitinib vs. placebo in the treatment of 2nd–3rd line NSCLC patients, ISEL [58], didn't reached the primary endpoint (OS: 5.6 months in the gefitinib arm vs. 5.1 in the placebo arm, HR: 0.89, *p*: 0.1), although subgroup of analysis showed a statistically significant advantage in favor of gefitinib in patients with certain clinical characteristics (i.e. women, Asian, not smokers, adenocarcinoma), as described above. Indeed the rate of responses obtained with gefitinib in the ISEL study (8%) is very similar to the one obtained with erlotinib in BR21 (9%), and the progression-free survival (PFS) as well as the OS data seem overlapping.

The different final results achieved in these two studies could be attributed to the different chemosensitivity of the two selected populations. In fact, one of the inclusion criteria of the ISEL trial was that patients had a progressive disease within 90 days from the last cycle of performed chemotherapy, so that about 45% of patients in the ISEL study had a PD as the best response to treatment compared to 18% of the patients in BR21 study (Table 1).

Four following clinical trials compared gefitinib versus docetaxel in second line treatment. The INTEREST study [59], designed as a noninferiority trial, enrolled 1466 patients after 1–2 chemotherapy regimens not selected on the basis of clinical or molecular characteristics, reaching their objective in full (HR: 1.02 96% CI: 0.905–1.15), with a median survival of 7.6 months for gefitinib vs. 8 months for CT. Also the study SIGN [60] showed similar results in terms of OS (7.5 months vs. 7.1 months for gefitinib and docetaxel respectively), as well as the two Asian studies ISTANA [61] and V15-32 [38], in which the higher median survival (14.1 months), can be regarded as the general treatment outcomes in unselected East Asian patients, while the results of INTEREST may represent general treatment outcomes in Western countries. A recent meta-analysis [62] summarizes and reinforces the results that emerge from individual studies, not showing a statistically significant difference in OS and PFS between treatment with gefitinib and docetaxel in the 2nd–3rd line; but a higher RR%, a better toxicity profile and a better quality of life were associated with gefitinib treatment, so that the authors conclude that it would be preferable to docetaxel.

Next, three randomized phase III trials compared erlotinib and chemotherapy in the treatment of 2nd–3rd line NSCLC patients not selected on the basis of clinical or biomolecular characteristic. In the TITAN trial [63], which compared erlotinib vs. docetaxel or pemetrexed, OS (primary endpoint) was similar in the two treatment arms (5.3 months in erlotinib arm vs. 5.5 months in the CT arm, HR: 0.95, *p*: 0.73). In a similar study [64], in patients treated with erlotinib vs. pemetrexed, time to progression (TTP) seems not different between the two treatment arms, while primary endpoint data (OS) of TAILOR study, comparing erlotinib vs. docetaxel, are not yet available, although some partial results of the study, concerning the secondary endpoint (PFS) presented at ASCO 2012, seem to highlight a benefit in favor of docetaxel (HR: 0.69, 95% CI: 0.52–0.93) (Table 2).

4.1.2. *Use for first-line treatment*

The strong evidences concerning EGFR gene activating mutations and their correlation with the efficacy of TKI, prompted several clinical trials to evaluate the use of these drugs in the first-line treatment of NSCLC patients in Asia. The Phase III study IPASS [39] compared gefitinib vs. carboplatin–paclitaxel in a population of patients selected on the basis of clinical features (Asian, non-smoking, adenocarcinoma), demonstrating non-inferiority of gefitinib vs. standard chemotherapy in terms of PFS (5.7 vs. 5.8 months), which was the primary endpoint, as well as for OS (18.6 vs. 17.3 months), with a tolerability profile and a better quality-of-life in patients treated with gefitinib.

Table 2
Randomized phase III trials of comparison of TKI vs chemotherapy in pre-treated patients with advanced NSCLC.

Clinical trials	INTEREST [38]	SIGN [39]	ISTANA [40]	V15-32 [41]	TITAN [43]	TAILOR
Treatment	Gefitinib vs. docetaxel	Gefitinib vs. docetaxel	Gefitinib vs. docetaxel	Gefitinib vs. docetaxel	Erlotinib vs. doc/pem	Erlotinib vs. docetaxel
Median OS	7.6 vs. 8 months (HR: 1.02)	7.5 vs. 7.1 months	14.1 vs. 12.2 months (HR: 0.87)	11.5 vs. 14 months (HR: 1.12)	5.3 vs. 5.5 months (HR: 0.95)	Not yet available

Subsequently the analysis of subgroups selected on the basis of molecular factors [65] showed a statistically significant advantage in favor of gefitinib in the subgroup of patients harboring EGFR gene activating mutations, both in terms of PFS (HR: 0.48, $p < 0.0001$) and RR (43% vs. 32%, $p < 0.001$), whereas no difference was observed regarding OS. Similar results were reported in a randomized phase III Korean study, FIRST SIGNAL [66], which compared gefitinib vs. cisplatin–gemcitabine combination, not showing any difference between the two treatment arms (PFS 6.1 vs. 6.6 months) in the general population selected on the basis of clinical features, while a statistically significant difference in favor of gefitinib was observed in the subgroup of EGFR mutated patients (PFS 8.7 vs. 6.7 months).

In 2010 two randomized Japanese trials, NEJ002 and WJTOG [67,68], compared in first-line treatment of NSCLC gefitinib vs. carboplatin–paclitaxel and gefitinib vs. cisplatin–docetaxel, respectively. Patients were selected for the presence of EGFR gene activating mutations, and the results showed the clear superiority of gefitinib in this subset of patients (median PFS 10.8 months vs. 5.4 months HR: 0:30, $p < 0.001$, in the NEJ002 study, and median PFS 9.2 vs. 6.3 HR: 0.489, $p < 0.0001$ in WJTOG 3405), which determined the premature end of the trial, during the interim analysis.

In all these studies, the OS was similar in both arms, probably because of the high cross-over rate, so that almost all the patients who progressed after a first-line chemotherapy received a TKI as second-line treatment. A recent meta-analysis [69] confirms the results of studies comparing chemotherapy and gefitinib in first-line treatment showing a higher RR (72% vs. 38% OR: 4.04) and a statistically significant increase in PFS (HR: 0.45) in patients treated with gefitinib selected for EGFR gene activating mutations. On the basis of this evidence in July 2009 EMA approved gefitinib for the treatment of locally advanced or metastatic NSCLC in all treatment lines limited to patients bearing EGFR gene activating mutations. To date gefitinib is considered the best first-line option for this molecularly selected subgroup of patients.

Erlotinib was also compared to chemotherapy in first-line treatment of NSCLC patients. Two phase III randomized trials were conducted on a selected population for the presence of EGFR gene activating mutations: the OPTIMAL study [70] enrolled 154 patients in China, comparing erlotinib vs. carboplatin–gemcitabine combination, while in the EURTAC study [71] 174 Caucasian enrolled patients were randomized to erlotinib vs. platinum-based regimens. In both studies the primary endpoint has been reached with a median PFS 13.1 months in arm with erlotinib vs. 4.6 months HR: 0.16, $p < 0.0001$ (OPTIMAL study), and a median PFS 9.7 vs. 5.2 months HR: 0.37, $p < 0.0001$ (EURTAC study). Therefore erlotinib has also proven effective in first-line treatment of NSCLC patients with EGFR mutation. Moreover, it is the only EGFR TKI, which has been directly tested against chemotherapy in Caucasian patients.

A recent meta-analysis [69] included 13 randomized trials which compared TKIs and chemotherapy in first and second-line treatment of 10433 patients selected for the presence of EGFR gene activating mutations, showing a clear superiority of TKIs both in terms of ORR (67,6% vs. 32,8% RR: 2.06) and PFS (HR: 0.30), while no difference was observed regarding OS. These results are likely to be influenced by crossover treatments that formally abrogate any survival gain. Moreover, the increased benefit is statistically maintained both in untreated and in treated patients, while erlotinib appear to have a greater effect on RR and progression delay than gefitinib.

Some phase II trials have compared erlotinib vs. chemotherapy in patients with unknown EGFR mutation status, with conflicting results. A phase II trial [72] compared erlotinib vs. carboplatin–paclitaxel in the first line treatment in NSCLC patients with performance status (PS) 2, with relevant results for chemotherapy arm (RR 2% vs. 12% PFS1.9 vs. 3.5 months, HR: 1.45, p: 0.6). However these results may be influenced by patient PS, which is known to influence the effectiveness of TKI, as observed in another phase II study [73], in which >75 year-old or PS2 patients were treated with erlotinib as first-line treatment, with very disappointing results (ORR: 21%, median PFS: 1.5 months; median OS: 3.2 months).

Another study on elder people (>0 years, PS0/1) [74], comparing erlotinib vs. carboplatin–vinorelbine, showed greater efficacy of chemotherapy (PFS: 4.6 vs. 2.4 months, p: 0.000.5, RR: 28.3% vs. 7.8%, p: 0.000.1). On the other hand, the results of a recent phase II study [75], which compared erlotinib versus single-agent chemotherapy with oral vinorelbine in elderly patients (> 70 years), showed a statistically significant advantage in favor of erlotinib (RR: 22.8% vs. 8.9%, PFS: 4:57 vs. 2:53 months, p: 0.02), with an increase in median PFS that was greater in patients with EGFR activating mutations gene in treatment erlotinib (n: 9, median 8.4 months), followed by the same mutated patients treated with vinorelbine (n: 15, median 3.97 months), and then in descending order by patients without mutation treated with vinorelbine and erlotinib (median 3.83 and 1.47 months respectively). These data suggest a possible prognostic value of EGFR, in additional to the already known predictive value. Furthermore, it raises the possibility of treating with biologic drugs selected subset of patients (elderly PS 0–1, ineligible for double platinum) regardless of the mutational status of EGFR, saving them from all the toxic effects of chemotherapy, and even getting a higher efficacy, is promising (Table 3).

4.1.3. Use as maintenance treatment

Two recent phase III trials evaluated the use of TKI on maintaining strategy with good results. In particular, SATURN study [76] evaluated the erlotinib efficacy in maintenance after 4 cycles of platinum-based chemotherapy, in a population of unselected patients, showing a statistically significant benefit in terms of PFS (median PFS: 12 vs. 11 weeks, HR: 0.71, $p < 0.0001$) and OS (median OS: 12

Table 3
Randomized phase III trials of comparison of TKI vs chemotherapy in first-line treatment of patients with advanced NSCLC.

Clinical trials	IPASS [45]	FIRST-SIGNAL [47]	NEJ002 [48]	WJTOG 3405[49]	OPTIMAL [51]	EURTAC [52]	
Treatment		Gefitinib vs. carboplatino-paclitaxel	Gefitinib vs. cisplatino–gemcitabina	Gefitinib vs. carboplatino–paclitaxel	Gefitinib vs. cisplatino–docetaxel	Erlotinib vs. carboplatino–gemcitabina	Erlotinib vs. platinum doublet
Median PFS	*Overall population*	5.7 vs. 5.8 months HR: 0.74	6.1 vs. 6.6 months HR: 0.813				
	EGFR-mutation positive	HR: 0.48	8.7 vs. 6.7 months	10.8vs5.4 months	9.2 vs. 6.3 months	13.1 vs. 4.6 months	9.7 vs. 5.2 months
		$p < 0.0001$	HR: 0.544	HR: 0.36	HR: 0.489	HR: 0.16	HR: 0.37
	EGFR mutation negative	HR: 1.38	2.1 vs. 6.4 months HR: 1.419				
Median OS	*Overall population*	18.6vs17.3 months HR: 0.90	21.3vs23.3 months HR:0.932				
	EGFR mutation positive	21.6 vs. 21.9 months HR: 1.00	30.6 vs. 26.5 months HR: 1.043	30.5 vs. 23.6 HR: 0.887	Not available	Not available	Not available
	EGFR mutation negative	11.2 vs. 12.7 months HR: 1.38	HR: 1.00				

vs. 11 months, HR: 0.81). This advantage was higher in patients who had SD at the end of chemotherapy, compared with those who had a RP. The ATLAS study [77] evaluated the addition of bevacizumab to erlotinib after 1st line chemotherapy until progression, highlighting a statistically significant increase in PFS (HR: 0.72) and a small benefit in OS. However the trials for second early line therapy are often based on clinical criteria, such as patients with large tumors, symptomatic, PS 0–1, no severe toxicities to first-line treatment [78]. Moreover a meta-analysis [79] and a pooled analysis [80] showed that erlotinib produced significant clinical benefits (improvements in PFS and OS) with acceptable toxicity as a maintenance strategy in patients with unresectable NSCLC who had not progressed after four cycles of first-line chemotherapy, even if further studies are needed to identify patients that may obtain greater benefits from maintenance with erlotinib, and to compare its use as early second line to standard second line therapy treatment. Gefitinib was also effective on maintaining strategy in an unselected population of patients who had completed 4 cycles of platinum-based chemotherapy, regardless of the response obtained in the first-line treatment [81], with a statistically significant benefit in terms of PFS (4.8 months vs. 2.16, HR: 0.42, $p < 0.0001$) (Table 4). Finally, data suggest that both gefitinib and erlotinib produces a significant survival benefit and maintenance strategy with EGFR TKIs after first line chemotherapy is a good treatment strategy in unselected patients with advanced NSCLC, and an excellent option for patients with EGFR mutation [82].

4.2. Directly comparing studies

There are few studies performing a direct comparison between gefitinib and erlotinib. A randomized Phase II trial [83] compared the second-line treatment with gefitinib and erlotinib, in a population of patients selected on the basis of clinical favorable features (women, non-smokers, adenocarcinoma) or the presence of EGFR activating gene mutations. This trial didn't show statistically significant differences between these two drugs regardless EGFR mutational status. However, the subgroup analysis showed higher activity of both drugs in patients with EGFR-mutated (ORR: 76.5%; PFS: 11.9 months) than patients with EGFR-WT (ORR: 25%, PFS: 2.8 months, p: 0.001, p: 0.08). In patients with unknown EGFR status, the gefitinib arm achieved a 37% RR and a 4.3 months median PFS while patients in the erlotinib arm had RR of 55% and PFS of 3.1 months. The small number of patients greatly reduces the statistical power of this study and doesn't allow the identification of significant differences between the two drugs. Similar results emerge from another study [84] that compared the efficacy of both drugs as third-line treatment in a population of unselected patients either clinically or on the basis of biomolecular factors, concluding that there are no statistically significant differences, although a slight trend was observed in terms of survival in favor of erlotinib in patients treated for more than 6 months. The same

Table 4
Randomized phase III trials on TKI maintenance therapy in patients with advanced NSCLC after first line treatment.

Clinical trials	SATURN [57]	ATLAS [58]	INFORM [60]
Treatment	Erlotinib vs. placebo	Bevacizumab + erlotinib vs. bevacizumab + placebo	Gefitinib vs. placebo
First-line treatment	Platinum-based chemotherapy × 4 cycles	Platinum-based chemotherapy × 4 cycles + bevacizumab	Platinum-based chemotherapy × 4 cycles
Median PFS	12.3 vs. 11.1 weeks HR: 0.71	4.8 vs. 3.7 months HR: 0.72	4.8 vs. 2.6 months HR: 0.42
Median OS	12 vs. 11 months HR: 0.81	15.9 vs 13.9 months HR: 0.90	18.7 vs 16.9 months HR: 0.84

Table 5
Clinical trials on direct comparison between gefitinib and erlotinib in patients with advanced NSCLC.

Clinical trials		Kim ST et al. [61]	Kim ST et al. [63]	Wu WS et al. [64]	Wu JY et al. [65]
Treatment		Gefitinib vs. erlotinib (second-line treatment)	Gefitinib vs. erlotinib (pre-treated patients)	Gefitinib vs. erlotinib (all lines of treatment)	Gefitinib vs. erlotinib (all lines of treatment)
ORR	Overall population	47.9% vs. 39.6% *p*: 0.269	38% vs. 32.2% *p*: 0.273	41.9% vs. 42% *p*: 1.0	46.4% vs. 35.5% *p*: 0.004
	EGFR-mutation positive			51% vs. 57.7%	61.9% vs. 75.4% *p*: 0.069
	EGFR-mutation negative			13.3% vs. 25%	12.8% vs. 13.9% *p*: 0.84
Median PFS	Overall population	4.9 vs. 3.1 months *p*: 0.336	4.7 vs. 2.7 months *p*: 0.06	7.6 vs. 7.9 months *p*: 0.47	5 vs. 2.9 months *p*: 0.102
	EGFR-mutation positive			10.5 vs. 10.3 months *p*: 0.32	
	EGFR-mutation negative			2.3 vs. 4.5 months *p*: 0.03	

results of equal efficacy/toxicity in second/third-line treatment are confirmed by another study [85], conducted on 342 patients not selected on the basis of clinical or molecular factors. Conversely, a retrospective study [86] that compared the efficacy of gefitinib and erlotinib in patients with lung adenocarcinoma and known EGFR mutational status demonstrated a statistically significant difference between the two treatment arms in favor of erlotinib in EGFR-WT patients (RR: 25% vs 4%, *p*: 0064; PFS: 4.5 vs. 2.3 months, *p*: 0.03), while no differences were observed in patients with EGFR gene activating mutations. However, no differences were found in terms of OS.

Finally, a previous retrospective study [87] compared gefitinib and erlotinib treatment in a population of 716 patients with advanced NSCLC in all lines of treatment, showing no statistically significant differences between these two drugs in the different lines, regardless of EGFR mutational status. Additional informations about the current use of these two different drugs in clinical practice, showed that erlotinib would be used much more frequently than gefitinib in the treatment of male patients, smokers, not adenocarcinoma histology ($p < 0.001$); both drugs are used more in 1st line rather than in 2nd or 3rd line, but gefitinib is much more used than erlotinib in this indication (63% vs. 38%, $p < 0.001$). This is certainly due to the fact that erlotinib has not been indicated in first-line treatment of NSCLC patients, although all studies compared with chemotherapy have made a clear superiority of erlotinib in patients with activating mutations of the EGFR gene (Table 5).

This trend in the use of these two TKIs could be explained by the two major comparing studies between TKIs and placebo in 2nd-line treatment (ISEL and BR21), which demonstrated an exclusive benefit of erlotinib in unselected population, and no benefit of gefitinib. However, in contrast to this finding, there are evidences from 4 studies that compared the efficacy of gefitinib versus docetaxel in the second-line for unselected population, as well as the data of the studies that have directly compared erlotinib and gefitinib in 2nd–3rd-line, suggesting the absolute equivalence of the two treatments. In this regard it may be appropriate to review and re-modulate the directions to the rigid use of the two drugs in different lines of treatment with the aim of being able to guarantee to the patient the highest number of treatment options.

Finally, we are eager to know the results of the only Asian trial currently underway evaluating the direct comparison between gefitinib and erlotinib in the treatment of first-line treatment with NSCLC patients.

4.3. Possibility of sequential administration of the two drugs

Several studies (retrospective, prospective, case reports) evaluated erlotinib efficacy in patients who had a PD after

first-line treatment with gefitinib, showing controversial results. Two clinical trials [88,89], in patients selected according to specific clinical characteristics (women, non-smokers, adenocarcinoma) reported very low response and survival rates (RR: 25%, median PFS: 1.5 months). Conversely, another study [90], which assessed erlotinib in patients with the same clinical characteristics, reported significantly higher response rate (RR: 57%), if we consider those patients who had a disease control during treatment with gefitinib. Similar data were reported in two other studies (DCR 55% and 50%) [91,92]. Studies on patients selected for EGFR mutation status showed higher RR (50%) and DCR (75%) in EGFR-WT patients, who obtained a previous response to gefitinib [92], and no statistically significant benefit in patients who developed resistance to gefitinib [93]. A pooled analysis summarizes the data emerging from individual studies evaluating sequential treatment with erlotinib after failure of gefitinib or erlotinib [94]. It concludes that a statistically significant benefit could be achieved in patients selected on the basis of specific clinical features, who experienced a long-term disease control during treatment with gefitinib, intended as a median PFS of at least 6 months. However the authors suggest that the EGFR mutational status couldn't be considered a predictor of response for erlotinib after gefitinib failure. A careful analysis of response and survival data reported in these studies show a slight trend of effectiveness in favor of patients with EGFR-WT. From this observation we could argue that the biomolecular mechanisms of acquired resistance to gefitinib are common to both these TKIs. In particular, the T790M EGFR mutation and MET amplifications are the most frequent causes of acquired resistance to both these EGFR TKIs.

Besides the higher equivalent erlotinib dose (the dose administered coincides with MTD, while the dose of gefitinib is equal to 1/3 MTD) and the lower IC50 compared to gefitinib are possible explanations for the theory of different sensitivity of tumor cells to the two drugs which is observed in patients with EGFR WT. Another hypothesis to explain this phenomenon regards the initial presence of both sensitive and resistant clones to TKI. The resistant clones could increase during TKI treatment inducing acquired drug resistance. The amount of resistant clones could be reduced during subsequent chemotherapy, thus yielding new sensitivity to TKIs. This theory might also explain the results emerging from studies which evaluated the re-administration of gefitinib after failure of the same on the front lines, reporting DCR of 27% and a median PFS 13.8 months [95]. However, we could hypothesize that the clones resistant to gefitinib might not be resistant to erlotinib, or be incompletely resistant, because of the presence of unknown mutations and different profiles of resistance/sensitivity to the two drugs.

4.4. Toxicity

The analysis of data from individual studies about toxic effects of TKIs show a good tolerability profile of both drugs, with an incidence of adverse events significantly lower with respect to chemotherapy (61–13% for chemotherapy vs. gefitinib $p < 0.001$; dose reduction of 35% vs. 16% for gefitinib; in the IPASS study, and 65% vs. 17% for erlotinib; dose reduction of 53% vs. 6% for erlotinib in the OPTIMAL). The treatment with these drugs is associated with a significantly lower incidence of myelosuppression, nausea, vomiting, fatigue, neurotoxicity. The most common toxic effects most frequently encountered in the course of treatment with TKIs are rash, diarrhea and asymptomatic hypertransaminasemia generally mild to moderate, while severe toxicities are uncommon. Although the toxicity profile is almost comparable in both drugs, a phase II study [83] comparing the efficacy/toxicity of these two drugs in the 2nd-line showed a higher incidence of moderate-to-severe rash in patients treated with erlotinib (43% vs. 10.4%), as well as a higher incidence of fatigue. Howevere these toxicities didn't affect the dose-intensity or quality of life in the two treatment arms. A recent meta-analysis [96] has analyzed over 24 trials, showing a statistically significant association between rash and clinical efficacy of treatment with TKIs (OS: HR:0.30, $p < 0.00001$; PFS: HR:0.50, $p < 0.00001$), so that the authors conclude that the rash can be considered an independent predictor of effectiveness for TKI treatment, particularly for patients with EGFR unknown mutational status. However, a careful analysis of the studies reported in this meta-analysis and other studies in the literature including the recent study of Lilembaum et al. [72] highlights a difference regarding skin toxicity. In fact, treatment with erlotinib is associated with a higher incidence of moderate-to-severe skin-rash, which seems to be associated with a statistically significant outcomes (ORR, PFS, OS), not always demonstrable during treatment with gefitinib, which is rather more frequently responsible for mild–minimal skin toxicities. These differences, though slight, there certainly appear relevant and worthy of in-depth in subsequent work.

5. Conclusions

In the last years the introduction of the anti-EGFR TKIs gefitinib and erlotinib represented the most important innovation for the treatment of advanced NSCLC. Infact these drugs are able to target the main pathway involved in lung cancer development and progression, the EGFR-mediated signaling transduction pathway. Furthermore TKIs allow sparing these patients from chemotherapy and subsequent quality-of-life-impairing toxicities. However in the first-line treatment only patients bearing EGFR gene activating mutations could achieve more benefit than chemotherapy.

Since gefitinib and erlotinib have different structure and subsequently different affinity with their receptor, toxicity frequency, but similar efficacy results, we postulated that these drugs could be partially interchangeable in the decision making for EGFR-mutated advanced NSCLC patients who will undergo a cancer treatment. However these two molecules are not identical, and we carefully evaluated

available information about a comparison between these drugs, as well as on a possible complementary role in the overall management of these patients.

The biological, pharmacological and clinical differences of anti-EGFR TKIs should represent the starting point for further studies, at different levels. For instance the clinical results divergence should be related to molecular differences, which might be evaluated using new standardized procedures. This should prompt the development and validation of predictive tests to select the best drug for each patient. The evaluation of the possible sequential use of gefitinib and erlotinib is another key point in the clinical setting, since it would allow widening the treatment options.

Since the main goal of advanced cancer treatment is represented by prolongation of lifetime together with quality-of-life preservation, we envision that novel biological and pharmacological insights leading to the optimal use of currently available targeted drugs could achieve better results than chemotherapy in the future clinical management of NSCLC patients.

Reviewers

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References

[1] Torti D, Trusolino L. Oncogene addiction as a foundational rationale for targeted anti-cancer therapy: promises and perils. EMBO Mol Med 2011;3:623–36.
[2] Bronte G, Rizzo S, La Paglia L, et al. Driver mutations and differential sensitivity to targeted therapies: a new approach to the treatment of lung adenocarcinoma. Cancer Treat Rev 2010;36(Suppl. 3):S21–9.
[3] Brehmer D, Greff Z, Godl K, et al. Cellular targets of gefitinib. Cancer Res 2005;65:379–82.
[4] Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. Nat Rev Mol Cell Biol 2001;2:127–37.
[5] Arteaga CL. Overview of epidermal growth factor receptor biology and its role as a therapeutic target in human neoplasia. Semin Oncol 2002;29:3–9.
[6] Bronte G, Terrasi M, Rizzo S, et al. EGFR genomic alterations in cancer: prognostic and predictive values. Front Biosci (Elite Ed) 2011;3:879–87.
[7] Clark GM, Zborowski DM, Santabarbara P, et al. Smoking history and epidermal growth factor receptor expression as predictors of survival benefit from erlotinib for patients with non-small-cell lung cancer in the National Cancer Institute of Canada Clinical Trials Group study BR.21. Clin Lung Cancer 2006;7:389–94.
[8] 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;101:13306–11.
[9] 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.
[10] Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497–500.
[11] Mulloy R, Ferrand A, Kim Y, et al. Epidermal growth factor receptor mutants from human lung cancers exhibit enhanced catalytic activity and increased sensitivity to gefitinib. Cancer Res 2007;67:2325–30.
[12] 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) [corrected]. J Clin Oncol 2003;21:2237–46.
[13] 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.
[14] Yun CH, Mengwasser KE, Toms AV, et al. The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. Proc Natl Acad Sci USA 2008;105:2070–5.
[15] Yun CH, Boggon TJ, Li Y, et al. Structures of lung cancer-derived EGFR mutants and inhibitor complexes: mechanism of activation and insights into differential inhibitor sensitivity. Cancer Cell 2007;11:217–27.
[16] Rosell R, Massuti Sureda B, Costa C, et al. Concomitant actionable mutations and overall survival (OS) in EGFR-mutant non-small-cell lung cancer (NSCLC) patients (p) included in the EURTAC trial: EGFR L858R, EGFR T790M, TP53 R273H and EML4-ALK (v3). In: ESMO Congress 2012. 2012.
[17] Bean J, Riely GJ, Balak M, et al. Acquired resistance to epidermal growth factor receptor kinase inhibitors associated with a novel T854A mutation in a patient with EGFR-mutant lung adenocarcinoma. Clin Cancer Res 2008;14:7519–25.
[18] Costa DB, Schumer ST, Tenen DG, Kobayashi S. Differential responses to erlotinib in epidermal growth factor receptor (EGFR)-mutated lung cancers with acquired resistance to gefitinib carrying the L747S or T790M secondary mutations. J Clin Oncol 2008;26:1184–6, 1182-1184.
[19] Balak MN, Gong Y, Riely GJ, et al. Novel D761Y and common secondary T790M mutations in epidermal growth factor receptor-mutant lung adenocarcinomas with acquired resistance to kinase inhibitors. Clin Cancer Res 2006;12:6494–501.
[20] Lin L, Bivona TG. Mechanisms of resistance to epidermal growth factor receptor inhibitors and novel therapeutic strategies to overcome resistance in NSCLC patients. Chemother Res Pract 2012;2012:817297.
[21] Zhou JP, Chen X, Feng S, et al. Systems biology modeling reveals a possible mechanism of the tumor cell death upon oncogene inactivation in EGFR addicted cancers. PLoS One 2011;6:e28930.
[22] Gullick WJ. The type 1 growth factor receptors and their ligands considered as a complex system. Endocr Relat Cancer 2001;8:75–82.
[23] Schlessinger J. Cell signaling by receptor tyrosine kinases. Cell 2000;103:211–25.
[24] Purvis J, Ilango V, Radhakrishnan R. Role of network branching in eliciting differential short-term signaling responses in the hypersensitive epidermal growth factor receptor mutants implicated in lung cancer. Biotechnol Prog 2008;24:540–53.
[25] Voice JK, Klemke RL, Le A, Jackson JH. Four human ras homologs differ in their abilities to activate Raf-1, induce transformation, and stimulate cell motility. J Biol Chem 1999;274:17164–70.
[26] Kolch W. Meaningful relationships: the regulation of the Ras/Raf/MEK/ERK pathway by protein interactions. Biochem J 2000;351(Pt 2):289–305.

[27] Meakin SO, MacDonald JI, Gryz EA, et al. The signaling adapter FRS-2 competes with Shc for binding to the nerve growth factor receptor TrkA. A model for discriminating proliferation and differentiation. J Biol Chem 1999;274:9861–70.
[28] Kiyatkin A, Aksamitiene E, Markevich NI, et al. Scaffolding protein Grb2-associated binder 1 sustains epidermal growth factor-induced mitogenic and survival signaling by multiple positive feedback loops. J Biol Chem 2006;281:19925–38.
[29] Rintelen F, Stocker H, Thomas G, Hafen E. PDK1 regulates growth through Akt and S6K in Drosophila. Proc Natl Acad Sci USA 2001;98:15020–5.
[30] Bae YS, Kang SW, Seo MS, et al. Epidermal growth factor (EGF)-induced generation of hydrogen peroxide. Role in EGF receptor-mediated tyrosine phosphorylation. J Biol Chem 1997;272:217–21.
[31] Costa DB, Halmos B, Kumar A, et al. BIM mediates EGFR tyrosine kinase inhibitor-induced apoptosis in lung cancers with oncogenic EGFR mutations. PLoS Med 2007;4:1680, 1669-1679; discussion.
[32] Jiang J, Greulich H, Janne PA, et al. Epidermal growth factor-independent transformation of Ba/F3 cells with cancer-derived epidermal growth factor receptor mutants induces gefitinib-sensitive cell cycle progression. Cancer Res 2005;65:8968–74.
[33] Tang Z, Jiang S, Du R, et al. Disruption of a conserved ion pair E884-R958 in EGFR differentially alters kinase inhibitor sensitivity and downstream signaling: P2-138. J Thorac Oncol 2007:S545–6.
[34] de Gunst MM, Gallegos-Ruiz MI, Giaccone G, Rodriguez JA. Functional analysis of cancer-associated EGFR mutants using a cellular assay with YFP-tagged EGFR intracellular domain. Mol Cancer 2007;6:56.
[35] Furuyama K, Harada T, Iwama E, et al. Sensitivity and kinase activity of epidermal growth factor receptor (EGFR) exon 19 and others to EGFR-tyrosine kinase inhibitors. Cancer Sci 2013.
[36] Douillard JY, Shepherd FA, Hirsh V, et al. Molecular predictors of outcome with gefitinib and docetaxel in previously treated non-small-cell lung cancer: data from the randomized phase III INTEREST trial. J Clin Oncol 2010;28:744–52.
[37] Hirsch FR, Varella-Garcia M, Bunn Jr PA, et al. Molecular predictors of outcome with gefitinib in a phase III placebo-controlled study in advanced non-small-cell lung cancer. J Clin Oncol 2006;24:5034–42.
[38] Maruyama R, Nishiwaki Y, Tamura T, et al. Phase III study V-15-32, of gefitinib versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer. J Clin Oncol 2008;26:4244–52.
[39] Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947–57.
[40] Zhu JQ, Zhong WZ, Zhang GC, et al. Better survival with EGFR exon 19 than exon 21 mutations in gefitinib-treated non-small cell lung cancer patients is due to differential inhibition of downstream signals. Cancer Lett 2008;265:307–17.
[41] Shitara M, Sasaki H, Yokota K, et al. Polymorphisms in intron 1 of the EGFR gene in non-small cell lung cancer patients. Exp Ther Med 2012;4:785–9.
[42] Galvani E, Peters GJ, Giovannetti E. EGF receptor-targeted therapy in non-small-cell lung cancer: role of germline polymorphisms in outcome and toxicity. Future Oncol 2012;8:1015–29.
[43] Giovannetti E, Zucali PA, Peters GJ, et al. Association of polymorphisms in AKT1 and EGFR with clinical outcome and toxicity in non-small cell lung cancer patients treated with gefitinib. Mol Cancer Ther 2010;9:581–93.
[44] Liu G, Cheng D, Ding K, et al. Pharmacogenetic analysis of BR.21, a placebo-controlled randomized phase III clinical trial of erlotinib in advanced non-small cell lung cancer. J Thorac Oncol 2012;7:316–22.
[45] Frohna P, Lu J, Eppler S, et al. Evaluation of the absolute oral bioavailability and bioequivalence of erlotinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in a randomized, crossover study in healthy subjects. J Clin Pharmacol 2006;46:282–90.
[46] Ling J, Fettner S, Lum BL, et al. Effect of food on the pharmacokinetics of erlotinib, an orally active epidermal growth factor receptor tyrosine-kinase inhibitor, in healthy individuals. Anticancer Drugs 2008;19:209–16.
[47] Cantarini MV, McFarquhar T, Smith RP, et al. Relative bioavailability and safety profile of gefitinib administered as a tablet or as a dispersion preparation via drink or nasogastric tube: results of a randomized, open-label, three-period crossover study in healthy volunteers. Clin Ther 2004;26:1630–6.
[48] Li J, Zhao M, He P, et al. Differential metabolism of gefitinib and erlotinib by human cytochrome P450 enzymes. Clin Cancer Res 2007;13:3731–7.
[49] Hamilton M, Wolf JL, Rusk J, et al. Effects of smoking on the pharmacokinetics of erlotinib. Clin Cancer Res 2006;12:2166–71.
[50] Langer CJ. Individualized therapy for patients with non-small cell lung cancer: emerging trends and challenges. Crit Rev Oncol Hematol 2012;83:130–44.
[51] Klastersky J, Awada A. Milestones in the use of chemotherapy for the management of non-small cell lung cancer (NSCLC). Crit Rev Oncol Hematol 2012;81:49–57.
[52] Johnson DH, Arteaga CL. Gefitinib in recurrent non-small-cell lung cancer: an IDEAL trial? J Clin Oncol 2003;21:2227–9.
[53] Giaccone G, Herbst RS, Manegold C, et al. Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial–INTACT 1. J Clin Oncol 2004;22:777–84.
[54] Herbst RS, Giaccone G, Schiller JH, et al. Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial–INTACT 2. J Clin Oncol 2004;22:785–94.
[55] Herbst RS, Prager D, Hermann R, et al. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2005;23:5892–9.
[56] Gatzemeier U, Pluzanska A, Szczesna A, et al. Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: the Tarceva lung cancer investigation trial. J Clin Oncol 2007;25:1545–52.
[57] 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.
[58] 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.
[59] 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.
[60] Cufer T, Vrdoljak E, Gaafar R, et al. Phase II, open-label, randomized study (SIGN) of single-agent gefitinib (IRESSA) or docetaxel as second-line therapy in patients with advanced (stage IIIb or IV) non-small-cell lung cancer. Anticancer Drugs 2006;17:401–9.
[61] Lee DH, Park K, Kim JH, et al. Randomized Phase III trial of gefitinib versus docetaxel in non-small cell lung cancer patients who have previously received platinum-based chemotherapy. Clin Cancer Res 2010;16:1307–14.
[62] Shepherd FA, Douillard JY, Fukuoka M, et al. Comparison of gefitinib and docetaxel in patients with pretreated advanced non-small cell lung cancer (NSCLC): meta-analysis from four clinical trials. In: 2009 ASCO Annual Meeting. 2009.
[63] Ciuleanu T, Stelmakh L, Cicenas S, et al. Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study. Lancet Oncol 2012;13:300–8.
[64] Vamvakas L, Agelaki S, Kentepozidis NK, et al. Pemetrexed (MTA) compared with erlotinib (ERL) in pretreated patients with advanced non-small cell lung cancer (NSCLC): results of a randomized phase III Hellenic oncology research group trial. In 2010 ASCO annual meeting. J Clin Oncol 2010;28:15s (suppl; abstr 7519).

[65] 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;29:2866–74.
[66] Han JY, Park K, Kim SW, et al. First-SIGNAL: first-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. J Clin Oncol 2012;30:1122–8.
[67] 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.
[68] 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.
[69] Ku GY, Haaland BA, de Lima Lopes Jr G. Gefitinib vs. chemotherapy as first-line therapy in advanced non-small cell lung cancer: meta-analysis of phase III trials. Lung Cancer 2011;74:469–73.
[70] Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011;12: 735–42.
[71] Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239–46.
[72] Lilenbaum R, Axelrod R, Thomas S, et al. Randomized phase II trial of erlotinib or standard chemotherapy in patients with advanced non-small-cell lung cancer and a performance status of 2. J Clin Oncol 2008;26:863–9.
[73] Lee DH, Kim SW, Suh C, et al. Phase II study of erlotinib for chemotherapy-naive patients with advanced or metastatic non-small cell lung cancer who are ineligible for platinum doublets. Cancer Chemother Pharmacol 2011;67:35–9.
[74] Reck M, Von Pawel J, Fischer R, Kortsik C, Bohnet S, von Eiff M, Koester W, Thomas M, Schnabel P, Deppermann KM. Erlotinib versus carboplatin/vinorelbine in elderly patients (age 70 or older) with advanced non-small cell lung carcinoma (NSCLC): A randomized phase II study of the German thoracic oncology working group. In 2010 ASCO Annual Meeting. Chicago: J Clin Oncol 2010:15s.
[75] Chen YM, Tsai CM, Fan WC, et al. Phase II randomized trial of erlotinib or vinorelbine in chemonaive, advanced, non-small cell lung cancer patients aged 70 years or older. J Thorac Oncol 2012;7:412–8.
[76] Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol 2010;11:521–9.
[77] Kabbinavar FF, Miller VA, Johnson BE, et al. Overall survival (OS) in ATLAS, a phase IIIb trial comparing bevacizumab (B) therapy with or without erlotinib (E) after completion of chemotherapy (chemo) with B for first-line treatment of locally advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC). In: 2010 ASCO Annual Meeting. 2010.
[78] Custodio A, de Castro J. Strategies for maintenance therapy in advanced non-small cell lung cancer: current status, unanswered questions and future directions. Crit Rev Oncol Hematol 2012;82:338–60.
[79] Zhang J, Zhang W, Huang S, et al. Maintenance erlotinib improves clinical outcomes of unresectable advanced non-small cell lung cancer: A meta-analysis of randomized controlled trials. Exp Ther Med 2012;4:849–58.
[80] Petrelli F, Borgonovo K, Cabiddu M, Barni S. Erlotinib as maintenance therapy in patients with advanced non-small cell lung cancer: a pooled analysis of three randomized trials. Anticancer Drugs 2011;22:1010–9.
[81] Zhang L, Ma S, Song X, et al. Gefitinib versus placebo as maintenance therapy in patients with locally advanced or metastatic non-small-cell lung cancer (INFORM; C-TONG 0804): a multicentre, double-blind randomised phase 3 trial. Lancet Oncol 2009;13:466–75.
[82] Chen X, Liu Y, Røe OD, et al. Gefitinib or erlotinib as maintenance therapy in patients with advanced stage non-small cell lung cancer: a systematic review. PLoS One 2013;8:e59314.
[83] Kim ST, Uhm JE, Lee J, et al. Randomized phase II study of gefitinib versus erlotinib in patients with advanced non-small cell lung cancer who failed previous chemotherapy. Lung Cancer 2012;75:82–8.
[84] Shao YY, Shau WY, Lin ZZ, et al. Comparison of gefitinib and erlotinib efficacies as third-line therapy for advanced non-small-cell lung cancer. Eur J Cancer 2013;49:106–14.
[85] Kim ST, Lee J, Kim JH, et al. Comparison of gefitinib versus erlotinib in patients with nonsmall cell lung cancer who failed previous chemotherapy. Cancer 2010;116:3025–33.
[86] Wu WS, Chen YM, Tsai CM, et al. Erlotinib has better efficacy than gefitinib in adenocarcinoma patients without EGFR-activating mutations, but similar efficacy in patients with EGFR-activating mutations. Exp Ther Med 2012;3:207–13.
[87] Wu JY, Wu SG, Yang CH, et al. Comparison of gefitinib and erlotinib in advanced NSCLC and the effect of EGFR mutations. Lung Cancer 2011;72:205–12.
[88] Sim SH, Han SW, Oh DY, et al. Erlotinib after Gefitinib failure in female never-smoker Asian patients with pulmonary adenocarcinoma. Lung Cancer 2009;65:204–7.
[89] Lee DH, Kim SW, Suh C, et al. Phase II study of erlotinib as a salvage treatment for non-small-cell lung cancer patients after failure of gefitinib treatment. Ann Oncol 2008;19:2039–42.
[90] Wong MK, Lo AI, Lam B, et al. Erlotinib as salvage treatment after failure to first-line gefitinib in non-small cell lung cancer. Cancer Chemother Pharmacol 2010;65:1023–8.
[91] Wong AS, Soong R, Seah SB, et al. 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;3:400–4.
[92] Cho BC, Im CK, Park MS, et al. Phase II study of erlotinib in advanced non-small-cell lung cancer after failure of gefitinib. J Clin Oncol 2007;25:2528–33.
[93] Costa DB, Nguyen KS, Cho BC, et al. Effects of erlotinib in EGFR mutated non-small cell lung cancers with resistance to gefitinib. Clin Cancer Res 2008;14:7060–7.
[94] Kaira K, Naito T, Takahashi T, et al. Pooled analysis of the reports of erlotinib after failure of gefitinib for non-small cell lung cancer. Lung Cancer 2010;68:99–104.
[95] Yokouchi H, Yamazaki K, Kinoshita I, et al. Clinical benefit of readministration of gefitinib for initial gefitinib-responders with non-small cell lung cancer. BMC Cancer 2007;7:51.
[96] Petrelli F, Borgonovo K, Cabiddu M, et al. Relationship between skin rash and outcome in non-small-cell lung cancer patients treated with anti-EGFR tyrosine kinase inhibitors: a literature-based meta-analysis of 24 trials. Lung Cancer 2012;78:8–15.