Review Article

Evaluation of Three Small Molecular Drugs for Targeted Therapy to Treat Nonsmall Cell Lung Cancer

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Abstract

Objective: To guide the optimal selection among first-generation epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) in clinical practice. This review attempted to provide a thorough comparison among three first-generation EGFR-TKIs, namely icotinib, erlotinib, and gefitinib, with regard to their molecular structure, pharmacokinetic parameters, clinical data, adverse reactions, and contraindications.

Data Sources: An electronic literature search of the PubMed database and Google Scholar for all the available articles regarding gefitinib, icotinib, and erlotinib in the English language from January 2005 to December 2014 was used.

Study Selection: The search terms or keywords included but not limited to "lung cancer", "nonsmall cell lung cancer (NSCLC)", "epidemiology", "EGFR", "TKIs", and "optimal selection".

Results: As suggested by this review, even though the three first-generation EGFR-TKIs share the quinazoline structure, erlotinib had the strongest apoptosis induction activity because of its use of a different side-chain. The pharmacokinetic parameters indicated that both erlotinib and icotinib are affected by food. The therapeutic window of erlotinib is narrow, and the recommended dosage is close to the maximum tolerable dosage. Icotinib enjoys a wider therapeutic window, and its concentration in the blood is within a safe dosage range even if it is administered with food. Based on multiple large-scale clinical trials, erlotinib is universally applied as the first-line treatment. In marked contrast, icotinib is available only in China as the second- or third-line therapeutic approach for treating advanced lung cancer. In addition, it exhibits a similar efficacy but better safety profile than gefitinib.

Conclusions: Although there is a paucity of literature regarding whether icotinib is superior to erlotinib, its superior toxicity profile, noninferior efficacy, and lower cost indicate that it is a better alternative for Chinese patients living with advanced NSCLC.

Key words: Advanced Nonsmall Cell Lung Cancer; Epithelial Growth Factor Receptor; Optimal Selection; Tyrosine Kinase Inhibitors

Introduction

According to the American Cancer Society,[1] in the 21st century, lung cancer accounts for a substantial proportion of morbidity and mortality worldwide. The main types of lung cancer are small-cell lung carcinoma (SCLC) and nonsmall cell lung cancer (NSCLC). The majority (85%) of lung cancer diagnoses are NSCLC, whereas SCLC consists of 15% of the diagnoses. NSCLC mainly includes adenocarcinoma, squamous cell carcinoma, and large cell undifferentiated carcinoma. Although the progress in the diagnosis and treatments of early stage lung cancer has been remarkable, the remission rate remains low. Among those with advanced NSCLC and who are undergoing first-line platinum-based double-agent chemotherapy, the remission rate is approximately 30–40%. In addition, the median survival time was reported to be 31–40 weeks, and the 1-year survival rate is barely 30–40%. Therefore, a growing body of literature suggests an increasingly urgent need to understand the key issues regarding alternative therapeutic approaches for treating NSCLC.

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Rapid advances in tumor-driving genes indicate that targeted therapy is a better alternative for treating advanced NSCLC, with one of the most representatives such as tyrosine kinase inhibitor (TKI), which targets mutated epithelial growth factor receptors (EGFRs). In NSCLC, the frequency of EGFR mutations in adenocarcinomas ranges from 15% to 60% with higher percentages reported in Asian population than in their Western counterparts.[2,3] EGFR mutation is more commonly detected in individuals living with adenocarcinoma who have never smoked.[4] Currently, five major Phase III trials[5-9] have established the clinical efficacy of gefitinib, erlotinib, or icotinib in that molecularly selected population.

The selection among first-generation EGFR-TKIs in NSCLC treatment is recognized as a key issue in clinical practice. We attempted to thoroughly compare gefitinib, erlotinib, and icotinib with regards to their molecular structures, pharmaceutical kinetic parameters, clinical data, adverse reactions, and contraindications. We expected that the findings would provide a basis for establishing recommendations regarding optimal drug selection in clinical practice.

Epidermal Growth Factor Receptor-tyrosine Kinase Inhibitors

EGFR is a member of the *erb*B family of receptor tyrosine kinases, which is expressed on the cell surface and activated by binding to the ligands including HER1 (EGF/*erb*B1), HER1 (*ner*/*erb*B2), HER3 (*erb*B3), and HER4 (*erb*B4). Following activation,[10] the monomeric EGFR dimerizes, which further activates the intracellular kinase pathways and causes auto-phosphorylation of tyrosine to residue. The phosphorylated tyrosine recruits more proteins and consequently triggers intracellular signaling cascades, mainly through Ras-receptor accessory factor (RAF)-mitogen-activated protein kinase (MAPK)/phosphatidyl inositol 3-kinase (PI3K)-Akt/JAK-STAT pathways which are involved in the process of cellular proliferation, anti-apoptosis, angiogenesis activation, and cancer metastasis. EGFR protein is encoded by EGFR gene and is highly expressed in epidermoid carcinomas. The activation of EGFR triggers a signaling cascade through RAS/RAF/MET/MAPK and PI3K/AKT pathways which affect critical cell functions. Currently, more than one hundred different types of mutations have been identified in adenocarcinomas of lung cancer with the majority harboring one of the seven mutations. The four main types of activating mutations[11,12] include point mutations in Exon 18 such as G719X, G719S, and G719A, deletions in Exon 19, insertions in Exon 20, and point mutations in Exon 21 such as L858R and the less-frequent L861Q. Exon 19 deletions and leucine to arginine mutations at codon 858 in Exon 21 are considered the most frequent mutations, and they account for 85–90% of all EGFR mutations.

The intracellular binding domain of the catalytic site of tyrosine kinase is highly conserved. It has been demonstrated that binding of 4-anilinoquinazoline to the intracellular catalytic site of tyrosine kinase inhibits tyrosine kinase activity and blocks the cellular proliferation signals.[13,14] The first-generation EGFR-TKIs compete with adenosine triphosphate (ATP) at the ATP-binding site in the intracellular domain of EGFR. Once taken up by cancer cells, they reversibly inhibit ATP-binding to the phosphate binding loop,[15] which in turn blocks auto-phosphorylation and activation of downstream signaling pathways and leads to inhibition of cell proliferation and induction of apoptosis in tumor cells.[16]

Two of the first-generation EGFR-TKIs, gefitinib and erlotinib, were introduced into the Chinese market in 2011 and exhibited an encouraging clinical response. In June 2011, icotinib hydrochloride, which is another first-generation EGFR-TKI, was approved by the China Food and Drugs Administration (CFDA) as the first homegrown anticancer drug for treatment in patients with locally advanced or metastatic NSCLC and who failed to respond to at least one previous chemotherapy regimen.

Comparisons of the Three First-generation Epidermal Growth Factor Receptor-tyrosine Kinase Inhibitors

Molecular structure

Gefitinib, whose chemical name is N-(3-chloro-4-fluoro-phenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy) quinazolin-4-amine and whose commercial name is Iressa, was first introduced to Japan in 2002, and it was approved in 2003 as the third-line drug for NSCLC in the USA and Australia. Gefitinib inhibits auto-phosphorylation with an IC_{50} of 0.029–0.079 μmol/L.[17]

Erlotinib, whose chemical name is N-(3-ethynylphenyl)-6,7-bis (2-methoxyethoxy) 4-quinazolinamine and whose commercial name is Tarceva, was approved in 2004 by the US Food and Drug Administration (FDA) as a treatment for patients living with advanced NSCLC whose cancer has spread after receiving first-line chemotherapy. Erlotinib has a high plasma concentration and inhibits auto-phosphorylation with an IC_{50} of 2 nmol/L.

Icotinib was approved by CFDA as the second- or third-line treatment for advanced NSCLC in June 2011.[18] The structure of icotinib is similar to that of erlotinib; however, the side-chain of the icotinib forms a closed ring structure which could increase its hydrophobicity and fat solubility. As a result, icotinib can easily pass through the cell membrane and blood–brain barrier to reach cancer sites to mediate antitumor effects. Icotinib inhibits EGFR tyrosine kinase activity with an IC_{50} of 5 nmol/L. Among all the 88 tested kinases [Table 1], icotinib[18] inhibits only a few mutants, including deletions in Exon 19 and point mutations in Exon 21 such as L858R and the less-frequent L861Q, which indicates a high selectivity.

All the first-generation EGFR-TKIs share the quinazoline structure. The core structure of icotinib exhibits greater similarity with erlotinib, except for the closed-ring part. Such structures permit icotinib to be more soluble in fat, thus resulting in an easier ability to pass through the cell membrane and the blood–brain barrier. In addition, icotinib has a lower molecular weight, which increases the likelihood of it reaching the tumor site. The literature suggests that the binding activities and inhibitory capacities are mainly determined by IC_{50}. Because erlotinib has the lowest IC_{50}, it also has the strongest apoptosis induction activity. In general, a comparison of their molecular structures indicates that erlotinib has the highest anti-tumor activities. The activity of icotinib is similar to that of erlotinib,

Table 1: Activities of 88 kinases in the presence of icotinib (0.5 nmol/L)

Kinase	Activity (%)
Abl (h)	91
Abl (T315I) (h)	86
ALK (h)	103
ARK5 (h)	102
Aurora-A (h)	106
Axl (h)	103
Blk (m)	87
Bmx (h)	105
BRK (h)	109
CDK1/cyclinB (h)	92
CDK2/cyclinA (h)	98
CDK5/p35 (h)	117
CHK1 (h)	102
CHK2 (h)	94
CK1-1 (h)	103
CK1-2 (h)	120
CK1-3 (h)	124
cKit (h)	114
cKit (D816H) (h)	82
cKit (V560G) (h)	95
CSK (h)	95
c-RAF (h)	100
cSRC (h)	89
DAPK1(h)	84
DDR2 (h)	95
DYRK2 (h)	105
EGFR (h)*	9
EGFR (L858R) (h)*	1
EGFR (L861Q) (h)*	4
EGFR (T790M) (h)*	39
EGFR (T790M, L858R) (h)*	39
EphA2 (h)	102
EphA7 (h)	91
EphB4 (h)	84
ErbB4 (h)	70
FAK (h)	101
Fer (h)	93
Fes (h)	101
FGFR1 (h)	88
FGFR2 (h)	108
FGFR3 (h)	111
FGFR4 (h)	117
Flt1 (h)	81
Flt3 (D835Y) (h)	96
Flt3 (h)	118
Flt4 (h)	92
Fms (h)	105
Hck (h)	108
HIPK2 (h)	102
HIPK3 (h)	109
IGF-1R (h)	110
IKK (h)	114
KDR (h)	94
PI 3-kinase α (h)	104
PI 3-kinase β (h)	100
PI 3-kinase γ (h)	98
LKB1 (h)	107
MAPK2 (h)	92
MEK1 (h)	109
MELK (h)	107
Mer (h)	90
Met (h)	115
MST3 (h)	97
p70S6K (h)	125
PAK4 (h)	98
PDGFR (h)	92
PDGFR (D842V) (h)	88
PDK1 (h)	109
Pim-1 (h)	96
PKBα (h)	101
PKCα (h)	111
PKCε (h)	93
PKCη (h)	112
PKCτ (h)	86
PKCμ (h)	94
PKCθ (h)	109
PKD2 (h)	103
Ret (h)	90
ROCK-I (h)	89
Ron (h)	104
Ros (h)	108
Snk (h)	105
TAK1 (h)	101
Tie2 (h)	107
TrkA (h)	95
Yes (h)	91
ZAP-70 (h)	115
ZIPK (h)	93

Among all the 88 tested kinases, when the plasma concentration of icotinib is 0.5 nmol/L, a few mutants are inhibited, including deletions in Exon 19 and point mutations in Exon 21 such as L858R and the less-frequent L861Q. *EGFR (h), EGFR (L858R) (h), EGFR (L861Q) (h), EGFR (T790 M) (h), and EGFR (T790M, L858R) (h) was inhibited byiconitib at 0.5 μmol/L with kinase activity inhibition of 91%, 99%, 96%, 61%, and 61%, respectively. h: Human; m: Mice; EGFR: Epidermal growth factor receptor.

and their activities are significantly higher than that of gefitinib [Table 2].

Pharmacodynamic data

Ranson *et al*.[19] found that the optimal clinical dose for gefinitib is 250 mg/d, and the therapeutic window is between 225 and 700 mg/d. Gefitinib is suitable for oral administration once daily among cancer patients. Its half-life is 48 h and its mean bioavailability is 60%. In addition, it is not significantly affected by food. Gefitinib[17] is mainly metabolized via cytochrome P_{450} in human body. Therefore, a substance that induces the activity of CYP3A4 is capable of increasing the gefitinib metabolism and consequently lowering its plasma concentration. In addition to CYP3A4, other enzymes are also involved in gefitinib metabolism. One clinical trial[20] confirmed that gefitinib binds to the substrate of CYP2D6 and increases the exposure rate of CYP2D6 by 35%, thus indicating that simultaneous administration of gefitinib, and drugs metabolized by CYP2D6 can increase the blood concentration of the latter. Gefinitib has three biotransformation pathways such as metabolism of the N-propyl morpholine group, demethylation of the quinazoline methoxy substituents, and oxidative defluorination of the halogenated phenyl group classes.

Yamamoto *et al*.[21] found that the recommended oral dose of erlotinib is 150 mg daily, and the therapeutic window is between 100 mg/d and 150 mg/d. Approximately 60% of the orally administered erlotinib is absorbed within 4 h to achieve amaximum plasma concentration. Food can significantly increase its bioavailability, with the peak plasma concentration increased by 57% and the exposure rate increased by 91%. Therefore, the manufacturer recommends administration on an empty stomach and waiting at least 1 or 2 h before ingestion of food. Erlotinib is mainly metabolized via CYP3A4 and CYP3A5 in the liver and small intestine within the human body but also via CYP1A2, CYP2C8, pulmonary CYP1A1 in extra-hepatic tissue, and CYP1B1 in tumor tissues. Because CYP3A4 is the main enzyme, combined application of its inducer/inhibitor and erlotinib should be conducted with caution. Earlier experiments[22] confirmed that smoking could induce CYP1A2, which resulted in an increased clearance rate of approximately 24%, causing a reduced blood concentration of this drug. Therefore, smoking cessation is always recommended for those being administered erlotinib.

Wang *et al*.[23] found that the recommended dose for icotinib is 125 mg every 8 h, and the therapeutic window is between 300 mg/d (100 mg, tid) and 1875 mg/d (625 mg, tid). Pharmacokinetic results from a single-dose study[24] indicated that there is a linear relationship between dose administration (100–600 mg with a half-life of 6–8 h) and availability and metabolism. It was also demonstrated that food that was rich in calories[25] could significantly increase its absorption among healthy volunteers, with increases of the maximum plasma concentration by 59% and area under the curve by 79%. Therefore, manufacturers generally recommend oral administration on an empty stomach or after a low-calorie meal. The major organ of icotinib metabolism is the liver, with the primarily enzymes being CYP2C19 and CYPA4 from the cytochrome P450 monooxygenase system,[26] whereas only one enzyme was identified for the other two drugs. Studies[25] confirmed that CYP2C19 exists as a polymorphism. Patients with heterozygous genotype (CYP2C19*1*2/CYP2C19*1*3) experienced a clearance rate 1.55 times lower and an exposure rate 1.44–1.56 times higher than those with the normal genotype (CYP2C19*1*1). Icotinib has 29 metabolites[24] with 75% passing in feces and 5% in urine. The metabolic sites of icotinib are similar to those of erlotinib. The side-chain of the 4-hydroxy-quinoline ring is opened and further oxidized, followed by hydroxylation of carbon 15 and oxidation of acetylene at carbon 14.

Comparisons with regards to the therapeutic window and pharmacodynamics of all three drugs indicated that gefitinib does not require administration on an empty stomach or smoking cessation. Therefore, it is more convenient in clinical practice, whereas both erlotinib and icotinib are affected by food. The therapeutic window for erlotinib is narrow, and the recommended dosage is close to the maximum tolerable dosage, leading to an increased probability of dose-limiting toxicity. In marked contrast, icotinib features a wide therapeutic window, and its concentration in blood is within a safe dosage range even if it is administered with food; therefore, it is significantly safer than erlotinib.

Because all three of these drugs are primarily metabolized via CYP3A4 of the liver cytochrome P_{450} monooxygenase system, patients with a liver disorder require a modified dosage. If the drugs are administered with CYP3A4

Table 2: Differences in anti-tumor activities among the three drugs

Categories	Gefitinib	Erlotinib	Icotinib
Molecular level (IC_{50}) (nmol/L)	27.0	2.5	5.0
Cellular level (IC_{50}) (nmol/L)	80.0–90.0	20.0	50.0
Cell growth (IC_{50}) (μmol/L)	8.8	1.0	1.0

IC_{50}: A certain concentration of a drug-induced apoptosis of tumor cells by 50%, which is known as the 50% inhibitory concentration or half inhibition rate. IC_{50} values can be used to measure the ability of drug-induced apoptosis, that is, the stronger ability to induce, the lower value. Molecular level: *In vitro* trials targeted the EGFR kinase protein, when concentration of gefitnib is 27.0 nmol/L, 50% of EGFR kinase protein in molecular level is inhibited; when concentration of erlotinib is 2.5 nmol/L, 50% of EGFR kinase protein is inhibited; when concentration of icotinib is 5.0 nmol/L, 50% of EGFR kinase protein is inhibited. Cellular level: *In vitro* trials targeted the tumor cells, when concentration of gefitnib is 80.0–90.0 nmol/L, 50% of intracellular EGFR kinase protein is inhibited; when concentration of erlotinib is 20.0 nmol/L, 50% of intracellular EGFR kinase protein is inhibited; when concentration of icotinib is 50.0 nmol/L, 50% of intracellular EGFR kinase protein is inhibited. Cell growth: *In vitro* trials targeted tumor cells, when concentration of gefitnib is 8.8 μmol/L, 50% of cell growth is inhibited; when concentration of erlotinib is 1.0 μmol/L, 50% of cell growth is inhibited; when concentration of icotinib is 1.0 μmol/L, 50% of cell growth is inhibited. EGFR: Epidermal growth factor receptor.

inducers (e.g., rifampin, phenytoin, carbamazepine, and barbiturates) or inhibitors (e.g., itraconazole, ketoconazole, and clotrimazole), their dosages need to be adjusted. Because a small amount of erlotinib is metabolized via CYP1A1 and smoking is a CYP1A1 inducer, patients on erlotinib need to quit smoking. Patients with heterozygous CYP2C19 have lower clearance rates and higher drug concentrations in their blood because a proportion of icotinib is metabolized via CYP2C19. In addition, they require clinical examination to guide the administration dosage and avoid severe toxic/side effects.

Clinical data

Comparisons with clinical data from phase I–II

Two randomized, double-blinded clinical trials[27,28] (IDEALI and IDEALII) demonstrated that gefitinib had definitive efficacy against NSCLC, which had developed resistance to chemotherapy with an effective rate ranging from 8.8% to 19% and a remission rate between 35% and 43%. In a randomized, placebo-controlled trial,[29] the Canadian Cancer Institute applied erlotinib and its best supportive care to patients living with advanced NSCLC and who had failed previous chemotherapy. The result indicated that among the nonselective population (EGFR mutations were not defined), erlotinib had an effective rate of 8.9%, whereas the placebo had an effective range of < 1%. The median survival time among patients on erlotinib was 2 months longer than those on the placebo ($P < 0.001$), and the 1-year survival rate was 45% greater ($P < 0.001$). A sub-group analysis also demonstrated that erlotinib was beneficial to those without an EGFR mutation. An open-label, multicenter, phase I/II clinical trial with the purpose of examining the overall efficacy of icotinib for treating advanced NSCLC[30] demonstrated that the objective response rate (ORR) and disease control rate (DCR) were 27% (27/100) and 76% (76/100), respectively. The median progression-free survival (PFS) was 4.97 months. The subgroup analysis demonstrated that among the selected population, namely females, nonsmokers, and those with adenocarcinoma, an ORR of 34.9% and a DCR of 79.1% occurred.

Comparison with data from the phase III clinical trial

Iressa NSCLC Trial Evaluating Response and Survival against Taxotere[5] is a standardized, head to head, global phase III clinical study that aims to evaluate the survival rates of patients living with NSCLC undergoing either EGFR-TKI or conventional second-line treatment. The results demonstrated that the overall survival (OS) rates with gefitinib and docetaxel were 7.6 and 8.0 months, and the 1-year survival rates were 32% and 34% (hazard ratio [*HR*] = 1.020, 95% confidence interval [*CI*]: 0.905–1.150), respectively. The predefined criterion with *HR* <1.154 was satisfied, which for the first time demonstrated that among nonselective advanced NSCLC patients, EGFR-TKI and docetaxel had similar treatment outcomes. In addition, gefitinib was more advantageous because it was safe and featured a guaranteed quality of life.

A phase IV clinical trial[31] analysis of a total of 3224 patients who received second-line erlotinib treatment[32] demonstrated that the complete response, partial response, and number of the patients with a stable disease were 25 (< 1%), 368 (14%), and 1444 (54%), respectively. The overall DCR was 68%. The median PFS and OS were 13.6 weeks and 8.6 months, respectively. The 1-year survival was 39%.

A randomized, double-blind, multicenter, parallel-controlled, head to head phase III clinical study (ICOGEN),[9] which used gefitinib as the positive control, found that among the nonselective population, icotinib was noninferior to gefitinib in terms of PFS, with a median PFS of 4.6 months (gefitinib: 3.4 months). The median OS was 13.3 months for icotinib and 13.9 months for gefitinib. The trial demonstrated no significant variation between icotinib and gefitinib when administered as the second- or third-line therapy. Retrospective genetic testing found that 43% of the patients in icotinib group and 59% in gefitinib group had EGFR mutations. There was no significant difference between icotinib and gefitinib in either of the EGFR mutation groups.

Stratified analysis to compare the responses to the three drugs among patients with different epidermal growth factor receptor mutations

Among the 1217 patients enrolled in the IRESSA Pan-Asia Study (IPASS),[6] a total of 437 (35.9%) were identified as harboring an EGFR mutation, including 261 (59.7%) with one mutation type and 11 (2.5%) with more than two mutation types. Among the mutated population, 140 (53.5%) had Exon 19 deletions, 111 (42.5%) had the L858R mutation, 11 (4.2%) had a T790M mutation at Exon 20, and 10 (3.8%) had other types of mutations. In gefitinib group, 64 had Exon 19 deletions and 64 had Exon 21 (L858R) substitution mutations; in contrast, in carboplatin-paclitaxel group, the corresponding numbers were 74 and 47, respectively. A subgroup analysis of the patients with EGFR mutations demonstrated that the efficacy was slightly better among those with an Exon 19 deletion than those with an Exon 21 point mutation. *HR*s of PFS were 0.38 for Exon 19 deletions and 0.55 for Exon 21 point mutations, respectively. Because the number of cases was small, a hypothesis test was not performed. ORR values of gefitinib and chemotherapy among the patients with Exon 19 deletions were 84.8% and 43.2%, respectively whereas, among the patients with the L858R mutation, ORRs were 60.9% and 53.2%, respectively. Patients with Exon 19 deletions reported a better clinical response than those with Exon 21 point mutations.

OPTIMAL study[7] analyzed the biomarkers and found that two major EGFR mutations were the Exon 19 deletion and the Exon 21 point mutation (L858R substitution mutations), which benefited significantly more from erlotinib than chemotherapy (Exon 19 deletion, *HR* = 0.13; Exon 21 point mutation, *HR* = 0.26). The median PFS among the patients with Exon19 deletions was slightly longer than that of the patients with Exon 21 point mutations (L858R substitution

mutations) (15.3 months vs. 12.5 months) after erlotinib treatment. However, the differences were not statistically significant.

Research regarding the efficacy of icotinib is still in progress, and relevant information has not yet been released.

Comparison of the first-line treatment data

IPASS study[6] suggested gefitinib as a new option for the first-line treatment of NSCLC patients who carry EGFR mutation. A total of 1217 patients recruited for the study were nonsmokers or light smokers. They were randomized into a gefitinib group (250 mg/d) or a standard doublet chemotherapy (carboplatin-paclitaxel) group. The results demonstrated that gefitinib was better than chemotherapy as the first-line treatment for advanced lung cancer (the 1-year PFS was 24.9% vs. 6.7%). Among the patients with EGFR mutations, the effective rate of gefitib was high (71.2% vs. 47.3%); however, among patients without mutations, the effective rate was low (1.1% vs. 23.5%). IPASS indicated that the treatment outcomes among the patients with EGFR mutations were better than those without mutations. In particular, Asian female nonsmokers with mutations benefited the most. In 2009,[33] gefitinib was approved by the European Medicines Agency for treating metastatic NSCLC as the first- and second-line therapy in patients harboring EGFR mutations.

A head to head phase III prospective study (OPTIMAL)[7] compared the efficacy of erlotinib and platinum doublet chemotherapy among NSCLC patients with EGFR mutations. The findings demonstrated that PFS of erlotinib was significantly prolonged compared with that of chemotherapy (13.1 months vs. 4.5 months, $HR = 0.16$, $P < 0.0001$). In 2013, based on the results of the EURTAC trials,[8,34,35] the US FDA approved erlotinib for the first-line treatment of NSCLC in tumors with EGFR Exon 19 deletions or Exon 21 (L858R) mutations.

There is a paucity of literature regarding efficacy reports on icotinib as the first-line treatment for advanced NSCLC.

Comparison of the efficacy for brain metastasis

Brain metastasis (BM) is a leading cause of NSCLC death. Ceresoli *et al*.[36] presented findings of a prospective study regarding gefitinib treatment (250 mg/d) among NSCLS patients with BM. A total of 41 patients were recruited, and the results indicated that the overall DCR was 27% (95% *CI*: 13–40%) and the median PFS was 3 months. However, erlotinib, which had fair tolerance, had a fair ORR if combined with whole-brain radiotherapy (WBRT). A 2013 study,[37] which recruited 40 patients with a mean follow-up of 28.5 months, indicated that the median OS was 11.8 months (95% *CI*: 7.4–19.1 months). Among the 17 patients with known EGFR genotypes, the median Oss among those with wild-type genotypes and those with mutant genotypes were 9.3 and 19.1 months, respectively. A phase I clinical trial[38] that combined icotinib and WBRT demonstrated that among the NSCLC patients with BM and mutated EGFR, simultaneous WBRT and icotinib treatment (125–375 mg every 8 h) followed by maintenance treatment was well tolerated. WBRT did not increase the penetration rate of icotinib; however, at a dose of 375 mg every 8 h, the icotinib concentration in cerebrospinal fluid and penetration rate were maximized.[37]

Drug-induced adverse reactions

EGFR-TKIs have different toxicity and side effects [Table 3] than other conventional cytotoxic agents. The major drug-related adverse reactions of the traditional cytotoxic agents include rash, diarrhea, severe bone marrow suppression, neuropathy, hair loss, and gastrointestinal reactions, with the most common adverse drug reactions being rash and diarrhea. A phase II study[31] that applied erlotinib alone for metastatic breast cancer treatment demonstrated that the degree of drug exposure was significantly correlated with the rash severity and time to onset. These results indicated that the occurrence rate and severity of rashes were significantly associated with the drug exposure rate.[39] Erlotinib caused the highest occurrence rate and rash severity. Because icotinib has a short half-life, it can be quickly metabolized and easily excreted without accumulation within the body. Consequently, the adverse reactions and severity related to icotinib are significantly less than those associated with the other two drugs.

Contraindications

Drugs are contraindicated in patients who are allergic to any of the ingredients. The inactive ingredients of these three drugs are different [Table 4]. Currently, large-scale clinical studies to demonstrate that patients who are severely allergic to one TKI drug can switch to another TKI drug have not been conducted. In 2011, Kijima *et al*.[40] found that an 83-year-old nonsmoking male patient living with advanced NSCLC (cT1N0M1, undefined EGFR genotype) was stabilized after oral gefitinib administration; however, 6 weeks later, drug-related grade 3 hepatotoxicity occurred, and the drug failed. Afterward, the patient was under erlotinib treatment for 28 weeks without any reported liver dysfunction. The three compounds have different side-chains, and the corresponding drugs have different inactive ingredients. Therefore, in clinical practice, if one TKI drug is effective but causes an allergic reaction, the other two drugs might be considered.

Conclusions

Globally, NSCLC affects millions of individuals. The approval of EGFR-TKIs over the past decade for the treatment of lung cancer has undoubtedly changed the way that health care professionals deliver therapeutic approaches to patients with lung cancer. Although the research into different cytotoxic combinations has reached a plateau, a large number of clinical trials suggested the use of routine icotinib administration, namely initial application as the second-line treatment in nonselected population, followed by the first-line therapy among those with EGFR-mutated tumors. EGFR-targeted therapy for lung cancer emphasizes the necessity of accurate subtyping as an adenocarcinoma

Table 3: Comparison of the most common toxicities between gefitinib, erlotinib, and icotinib in phase III clinical trials (%)

Adverse events	Gefitinib (n=1126), ISEL study[45]		Erlotinib (n = 485), BR.21 study[29]		Icotinib (n=417), ICOGEN study[9]	
	ALL	≥Grade 3+	ALL	≥Grade 3+	ALL	≥Grade 3+
Rash	37	2	76	9	41	1
Diarrhea	27	3	55	6	22	0
Anorexia	17	2	69	9	6	0
Nausea	17	1	40	3	4	1
Vomiting	14	1	25	3	5	0
Mucositis	–	–	19	1	5	0
Dry skin	11	0	7	4	–	–
Conjunctivitis, keratitis	–	–	28	1	–	–
Fatigue	13	3	79	19	–	–

ISEL study (gefitinib plus best supportive care in previously treated patients with refractory advanced nonsmall-cell lung cancer: Results from a randomised, placebo-controlled, multicentre study): This placebo-controlled phase III study investigated the effect on survival of gefitinib as second-line or third-line treatment for patients with locally advanced or metastatic nonsmall-cell lung cancer. BR.21 study (erlotinib in previously treated nonsmall-cell lung cancer): This is a randomized, placebo-controlled, double-blind trial to determine whether the epidermal growth factor receptor inhibitor erlotinib prolongs survival in nonsmall-cell lung cancer after the failure of firtst-line or second-line chemtherapy. ICOGEN study (icotinib versus gefitinib in previously treated advanced nonsmall-cell lung cancer): This is a randomized, double-blind phase III noninferiority trial to investigate whether icotinib is noninferior to gefitinib in patients with nonsmall-cell lung cancer. ISEL: Iressa Survival Evaluation in Lung Cancer.

Table 4: Active and inactive ingredients of gefitinib, erlotinib, and icotinib

Drug	Active ingredients*	Inactive ingredients
Gefitinib	N-(3-chloro-4-fluoro-phenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy) quinazolin-4-amine	Lactose, microcrystalline cellulose, hypromellose, povidone, sodium dodecyl sulfate†, magnesium stearate, hydroxypropyl methylcellulose†, polyethylene glycol†, titanium dioxide, red iron oxide†, and yellow iron oxide†
Erlotinib	N-(3-ethynylphenyl)-6,7-bis (2-methoxyethoxy) 4-quinazolinamine	Lactose, microcrystalline cellulose, hypromellose, magnesium stearate, sodium starch glycolate‡, sodium lauryl sulfate‡, carboxypropyl methyl cellulose, and titanium dioxide
Icotinib	4-[(3-ethynyl phenyl) amino]-6,7-benzo-12-crown-4-quinazoline	Lactose, microcrystalline cellulose, hypromellose, povidone, hydrophilic silica powder§, magnesium stearate, titanium dioxide, carboxypropyl methylcellulose, and artificial color§

*Gefitinib, erlotinib and icotinib share the quinazoline structure with is the core structure of active ingredients; †Some inactive ingredients only exist in geftinib; ‡Some inactive ingredients only exist in erlotinb; §Some inactive ingredients only exist in icotinib.

and the positivity of the EGFR molecular test and testing of other oncogenes.

Among patients with sensitive EGFR mutations, erlotinib, which has been approved by FDA, European Union, and CFDA, is universally applied as the first-line treatment. Across considerable amounts of researches[7,8] regarding advanced NSCLC with EGFR mutations, the median PFS was consistently longer for erlotinib than forgefitinib. A pooled analysis[41] demonstrated that erlotinib produced the longest PFS among patients with mutated EGFR. Meanwhile, erlotinib has a similar tolerability profile to gefitinib in EGFR-mutated NSCLC.[7,42,43]

Based on a randomized, double-blind, double-modulated, parallel-controlled, Phase III trial with single-agent icotinib in lung cancer patients after failure of chemotherapy,[9] icotinib is available only in China for second- or third-line treatment among patients with advanced lung cancer. ICOGEN[9] study demonstrated that icotinib has an efficacy similar to gefitinib when given to pretreated, unselected patients with stage IIIB or IV NSCLC. Because of the short half-life of icotinib, dosing of icotinib is relatively inconvenient compared with that of the other two drugs, which makes patient instruction challenging. Fortunately, because of its short half-life and wider therapeutic window, icotinib is associated with a decreased amount of drug-related adverse events compared with gefitinib or erlotinib.[2,9,44] Previous research has demonstrated that icotinib has a good efficacy and tolerability in Chinese patients with advanced NSCLC.

Because of its toxicity and efficacy profile and its sufficient equivalency, in Chinese patients with advanced NSCLC that harbor a sensitive EGFR mutation, icotinib appears to be a better option for a first-generation EGFR-TKI.

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Conflicts of interest

There are no conflicts of interest.

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