Status and progress of Icotinib in treatment of EGFR-mutant non-small cell lung carcinoma

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Systematic Review

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Abstract

Lung cancer has a high incidence and mortality worldwide. Among them, non-small cell lung cancer (NSCLC) accounts for the majority. In terms of treatment, targeted therapy is a more effective option for NSCLC patients with genetic mutations when compared with chemotherapy. Currently, there are a number of targeted drugs targeting different mutations in NSCLC on the market, among which, icotinib (Conmona®) is an oral small molecule epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI). It's approved as first-line treatment for locally advanced or metastatic NSCLC patients with EGFR-mutant, for monotherapy to treat locally advanced or metastatic non-small cell lung cancer (NSCLC) after the failure of at least one prior chemotherapy regimen (primarily platinum-based combination chemotherapy) and approved as postoperative adjuvent therapy for stage □-□A NSCLC with EGFR-mutant in China. What's more, there are many other usages and further clinical trials are underway. Here, we review the status and progress of icotinib in the treatment of EGFR-mutant NSCLC.

Introduction

Lung cancer, one of the most common malignancies, among nearly 100 known malignancies, its morbidity and mortality are among the best (Siegel et al. 2020). According to the pathological type, it is divided into small cell lung cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC). NSCLC accounts for about 80–85% of lung cancer, mainly includes lung adenocarcinoma, lung squamous cell carcinoma, large cell lung cancer, etc. In terms of treatment, comprehensive treatment based on surgery is usually selected, and follow-up treatment is performed according to the parameters such as pathology and stage. Chemotherapy, targeted therapy, immunotherapy, radiotherapy and other means may be considered for advanced cases that are inoperable at the time of discovery. For patients with pathological type of lung adenocarcinoma, driver gene detection (EGFR, ALK, ROS1, BRAF, RET, MET, etc.) can be carried out first after diagnosis. According to the results, corresponding targeted therapy is feasible for patients with positive driver gene.

In the past, treatment was scarce and chemotherapy was the first choice for advanced patients. With the progress of science and technology, the emergence of new therapeutic methods such as targeted therapy, immunotherapy, etc, treatment options tend to be diverse. IPASS, WJTOG3405, CONVINCE, OPTIMAL, NEJ002, ENSURE, LUXLUNG6 (Fukuoka et al. 2011; Mitsudomi et al. 2010; Shi et al. 2017; Zhou et al. 2011; Inoue et al. 2013; Wu et al. 2015; Wu et al. 2014) all confirm to varying degrees that compared with traditional chemotherapy, epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) treatment of EGFR-mutant advanced NSCLC patients can significantly prolong progression-free survival (PFS). The adverse reactions were mild which patients can tolerate well and the quality of life can be significantly improved (Shi et al. 2016).

Among all mutated genes, EGFR mutations are more common in Asian population, as shown in Fig. 1 (Seo et al. 2012). Currently, there are four generations of EGFR-TKIs on the market, among which the first generation includes gefitinib, erlotinib and icotinib. Icotinib, BPI-2009H (Conmona®), developed by

Zhejiang Beta Pharmaceutical Co., Ltd., is the first self-developed EGFR-TKI drug in China, which makes up for the vacancy in this field in China and is known as "domestic Iressa". This review focuses on the therapeutic efficacy and tolerability of icotinib in patients with NSCLC, and summarizes its pharmacological properties.

Brief Introduction Of Mechanism Of Action And Pharmacological Activity

EGFR HER1 / erbB-1 is a transmembrane receptor protein, locates on neoplastic cells originating from epithelial cells. After binding to the ligand, it activates the intracellular tyrosine kinase domain and leading to its phosphorylation. EGFR regulates cell proliferation, differentiation and apoptosis by regulating gene transcription. EGFR-mediated signal is closely related to multiple functions, including tumor metastasis, vascular proliferation, and drug resistance, etc. EGFR-TKIs block EGFR signal transduction by binding to tyrosine kinase domain, it has therapeutic effect to tumor and has less adverse effects than chemotherapy (Wells et al. 1999; Cappuzzo et al. 2005; Janmaat et al. 2003; Paez et al. 2004).

Icotinib hydrochloride, chemical structure (Fig. 2) (Zhao et al. 2011), chemical formula: C22H21N3O4 HCL(similar to gefitinib and erlotinib), is an effective and reversible oral EGFR-TKI. Its 50% maximum inhibitory concentration [IC50] is 5nmol/L. Its pharmacological mechanism is to block EGFR-mediated intracellular tyrosine phosphorylation in epidermoid carcinoma A431 cells (IC50 = 45 nM) and inhibit tumor cell proliferation. It has strong antitumor activity both in vitro and in vivo. It inhibites the growth of human tumor cell lines (IC50 1mol/ L for A431 cell) and human epithelial carcinoma A431 in nude mouse xenograft model (inhibition rate is 60.1% at 60 mg/kg) with high EGFR expressing. In a preclinical kinase application study, icotinib showed high specificity and selectivity for its target EGFR: Among 85 kinases screened, only EGFR and its three mutants were strongly and selectively inhibited, the other 80 kinases were not significantly inhibited (Tan et al. 2012).

Application Status Of Icotinib Monotherapy

Phase I and phase Ⅱ clinical trials of icotinib monotherapy

Before icotinib came into the market, several phase I / Ⅱ clinical trials (Zhao et al. 2011; Liu et al. 2009; Zhang et al. 2009; Ruan et al. 2012; Ren. 2011; Zhou. 2010) have fully investigated its tolerability, safety, human pharmacokinetics, usage and dose exploration and optimization for advanced NSCLC, efficacy and safety, etc. In a phase I clinical trial exploring the safety and tolerability of a single oral dose of icotinib in healthy volunteers, none of the 75 healthy subjects had test drug-related adverse events (AEs), all AEs were below grade Ⅱ and abnormal indicators returned to normal during the observation period. In a single-center, open, three crossover phase I clinical trial exploring the pharmacokinetics of icotinib tablets in healthy volunteers, after 10 days of treatment, only 3 of 12 healthy volunteers had 4 mild, transient AEs. According to the test results, the peak time is about 1–3 hours and the half-life period is about 6

hours, it showed good linear absorption characterization and tolerability between 100mg and 600 mg. In a two-phase, cross, randomized, open stage I clinical trial observing the pharmacokinetic effects of dietary intake on icotinib in healthy volunteers, plasma samples were collected and analyzed after drug administration in fasting and postprandial states respectively, the results showed that postprandial medication can significantly increase absorption, decrease clearance rate, but had no significant effect on peak time, and had good tolerance.

Another included two independent phase I/ a clinical trial of safety, tolerability, pharmacokinetic characteristics and preliminary efficacy of icotinib administered repeatedly at two centers in patients with advanced lung cancer (Ren. 2011; Zhou. 2010), a total of 109 patients were enrolled in phase I and clinical trials. After initial confirmation of the safe and effective dose in phase I, the number of participants in this dose group was expanded and the efficacy and safety were observed. The results showed that, icotinib was safe, and its AEs did not exceed grade , only 3 patients had rash of grade or above, and a few patients had transient transaminase increase, which no need for drug withdrawal or clinical treatment. Treatment-related adverse reactions occurred about 1 week after medication, which were transient and lasted about 2–3 weeks. In the known safe and effective dose group, the disease control rate (DCR) was 78.1%, the objective response rate (ORR) was 29.2%, and three patients achieved complete response (CR). Thus, it was shown that icotinib appeared to be safer and more effective than other EGFR-TKIs. The usage of 125 mg, three times daily is recommended for the later clinical trials.

Phase clinical trials and second / third-line treatment

In view of the above phase I / clinical trials, a randomized, double-blind phase , non-inferiority clinical trial ICOGEN (Shi et al. 2013) led by Professor Shi Yuankai was conducted in 27 hospitals nationwide, gefitinib was used as positive control in this trial. A total of 400 patients aged 18–75 years with advanced NSCLC who had previously failed one or more platinum-based chemotherapy were enrolled between February 26, 2009 and November 13, 2009, they were treated with icotinib or gefitinib respectively. The results showed that the PFS of icotinib group is not lower than that of gefitinib group, with a median PFS of 4.6 months versus 3.4 months, p = 0.13. There was no significant difference in median time to progression(TTP) between the two treatments (5.2 months [95% CI 3.6–6.6] in icotinib group vs 3.7 months [2.5-5.0] in gefitinib group, p = 0.065). By December, 2011, 324 patients had died, 56 (28%) in the icotinib group and 70 (36%) in the gefitinib group with progression had received subsequent therapies. Overall survival (OS) was similar for icotinib and gefitinib (166 [83.4%] patients died in the icotinib group vs 158 [80.6%] patients in the gefitinib group). Median OS was 13.3 months (95% CI 11.1–16.2) in the icotinib group versus 13.9 months (11.4–17.3) in the gefitinib group, p = 0.57. Rash and diarrhea were the most common adverse events, with 41%, 22% in the icotinib group and 49%, 29% in the gefitinib group, AEs was lower in icotinib group than gefitinib group (61% vs 70%, P = 0.046). In conclusion, icotinib is not inferior to gefitinib and can be used in the second / third line treatment of advanced NSCLC. EGFR mutants were more likely to benefit than non-mutants. Thus, the China Food and Drug Administration approved it for the second-line or later treatment of locally advanced / metastatic NSCLC in which at least one chemotherapy regimen had failed.

After this, Hu Xingsheng et al (Hu et al. 2015) conducted a study designed to evaluate the efficacy and safety of icotinib in the treatment of patients with advanced NSCLC who previously received platinum-based chemotherapy. A total of 128 patients were enrolled from 15 centers nationwide and received 125mg icotinib three times a day. The primary endpoints of the study is PFS, the secondary endpoints are OS, TTP, ORR, safety, etc. The median PFS and TTP was 5.0 months and 5.4 months, the ORR was 25.8%, the DCR was 67.7% and the median OS was over 17.6 months (95%CI 14.2m-NA). The most common treatment-related AEs were rashes (26%), diarrhea (12.6%) and elevated transaminase (15.7%). This study further verifies the safety and effectiveness of icotinib in second / third line treatment for advanced NSCLC with previous chemotherapy failure (Hu et al. 2015), and compared with ICOGEN (Shi et al. 2013), the security is better.

Phase Ⅳ clinical trials and first-line treatment in advanced NSCLC

In view of the previous efficacy and safety validation, a phase Ⅳ clinical trial ISAFE (Hu et al. 2014) for safety monitoring was conducted after the marketing of icotinib, it aims to evaluate the safety and efficacy of icotinib in a wide range of patients with advanced NSCLC. A retrospective study of 6087 advanced NSCLC patients who were inoperable and/or relapsed treated with icotinib. The primary endpoint is safety, the secondary endpoints are ORR and DCR, EGFR mutations and elderly patients were stratified. The results showed that, a total of 5549 patients were evaluated for safety and efficacy, with a median age of 63 years, 28.3% of whom were over 70 years old, and most of them were stage Ⅳ adenocarcinoma without smoking history. The overall incidence of AEs was 31.5%, rash (17.4%) and diarrhea (8.5%) were the most common AEs, and interstitial lung disease occurred in 3 patients. The ORR and DCR of first-line, second-line and third-line, multiline subpopulations were 33.4% and 81.2%, 30.3% and 80.3%, 30.4% and 89.3%, respectively. For all evaluable patients, the ORR and DCR were 49.2% and 92.3%. In addition to extend the experience of applying icotinib to more representative subpopulations, this large phase Ⅳ study of more than 6000 patients also confirmed the acceptable safety and favorable efficacy of icotinib in a broad NSCLC population, further confirmed the results of ICOGEN.

Another phase Ⅲ clinical study CONVINCE(Shi et al. 2017), enrolled 296 patients with EGFR mutation stage Ⅲ/Ⅳ lung adenocarcinoma, the patients were randomly divided into icotinib group (148 cases) and chemotherapy group (137 cases). The treatment regimen was either oral icotinib or cisplatin combined with pemetrexed 3-week chemotherapy for a maximum of 4 cycles, pemetrexed was maintained for patients without progression until disease progression or toxicity intolerance. The primary endpoint is PFS. Results showed that PFS was significantly longer in the icotinib group (11.2 vs 7.9, P = 0.006), there was no significant difference in OS between the total population and EGFR mutation subgroup. The most common grade 3/4 AEs in the icotinib group were rash and diarrhea, the chemotherapy group were nausea, vomiting and blood decline. AEs and treatment-related AEs in the icotinib group were significantly lower than chemotherapy group: 79.1% vs 94.2%, P < 0. 001 and 54.1% vs 90.5%, P < 0.001. This study confirmed that, for patients with EGFR mutation advanced lung adenocarcinoma, icotinib has better efficacy and less side-effects than cisplatin/ pemetrexed plus pemetrexed maintained first-line

chemotherapy. Icotinib can be the standard first-line treatment regimen. Thus, icotinib was approved for the first-line treatment of advanced NSCLC with EGFR mutation.

A multicenter randomized controlled trial of the first-line treatment for brain metastasis patients BRAIN (Yang et al. 2017) enrolled 176 patients with EGFR-mutated advanced NSCLC with initial treatment/second-line brain metastases. Patients were divided into icotinib monotherapy group or whole brain radiotherapy (WBRT) combined with synchronous/sequential chemotherapy group, with 85 patients and 91 patients respectively. Stratified according to EGFR status, number of treatment lines, craniocerebral metastasis status and presence of cranial hypertension symptoms. The primary endpoint was intracranial progression-free survival (iPFS), the median follow-up time was 16.5 months. The results showed that, the iPFS of icotinib group and WBRT group were 10 months vs 4.8 months, respectively. Grade 3 and above AEs in icotinib group were significantly less than WBRT group (8% vs 38%). The mortality rate was 49% in icotinib group and 51% in WBRT group, one patient in WBRT group died of chemotherapy-related thrombosis. It shows that, compared with WBRT combines with chemotherapy, icotinib significantly prolonged iPFS and PFS, improved ORR and DCR in NSCLC patients with EGFR-mutant with multiple brain metastases, it can be considered a better first-line choice.

Postoperative adjuvant trerapy

With the publication of research results such as ADJUVANT and EVAN (Zhong et al. 2017; Yue et al. 2018), postoperative adjuvant targeted therapy has gradually been recognized. But it still faces some confusion, such as the order of medication, the time of medication, the timing of medication, etc. The five postoperative adjuvant targeted therapy trials of icotinib are fully covered, and these confusions will be answered in the future.

Exploration of the adjuvant treatment of icotinib monotherapy

A study named EVIDENCE(He et al. 2021) led by Professor Zhou Caicun is aiming to evaluate the efficacy and safety of icotinib in adjuvant treatment of EGFR-mutated NSCLC. A total of 322 patients who were all stage □-□A postoperative were enrolled, they were randomly assigned to the icotinib treatment group for 2 years or the control group for 4 cycles standard adjuvant chemotherapy until recurrence, intolerance or death, and the control group crossed over to the icotinib group after recurrence. The primary end point is disease free survival (DFS), the secondary end points are OS and safety. The interim analysis of the study shows 40 (26%) of 151 patients in the icotinib group and 58 (44%) of 132 patients in the chemotherapy group had disease relapse or death. Median DFS was 47.0 months (95% CI 36.4-not reached) in the icotinib group and 22.1 months (16.8–30.4) in the chemotherapy group (stratified hazard ratio [HR] 0.36 [95% CI 0.24–0.55]; p < 0·0001). 3-year DFS was 63.9% (95% CI 51.8–73.7) in the icotinib group and 32.5% (21.3–44.2) in the chemotherapy group. OS data are immature with 14 (9%) deaths in the icotinib group and 14 (11%) deaths in the chemotherapy (HR 0.91 [95% CI 0.42–1.94] in the full analysis set). Treatment-related serious AEs occurred in two (1%) of 156 patients in the icotinib group and 19 (14%) of

139 patients in the chemotherapy group. The interim analysis results suggest that compared with chemotherapy, icotinib significantly improves DFS and has a better tolerability profile in patients with EGFR-mutant stage □-□A NSCLC after complete tumour resection. Based on this, the new indication for post-operative adjuvant therapy of icotinib was approved.

Exploration of sequential adjuvant treatment mode between icoctinib and chemotherapy

An ongoing phase □ clinical trial ICWIP (BD-IC-IV59, NCT02125240) recruited 124 EGFR-mutant stage □-□A lung adenocarcinoma patients aged 18–75 years who had previously received complete surgical resection and standard platinum-based dual chemotherapy from June 3, 2014 to November 15, 2018, they received icotinib or placebo for 36 months and were observed for 3 years, the primary endpoint is DFS and the secondary endpoints are 3-year DFS and safety, etc.

Another multicenter, randomized, prospective, open phase □ clinical study ICTAN (GASTO1002, NCT01996098) initiated by Sun Yat-sen University, was conducted in patients with stage □A-□A EGFR-mutated NSCLC who completed adjuvant chemotherapy (4 cycles platinum-based) after complete resectionis. At present, 318 patients were recruited and randomly divided into two groups in which patients were given icotinib (125mg three times a day) orally for 6 months or 12 months, respectively. DFS, OS, safety and tolerability were observed, the trial is still in progress now, and the results are remarkable.

Exploration of duration of icotinib adjuvant treatment

A multicenter, randomized, controlled, phase II trial BD-IC-IV50 (NCT01929200) conducted by Professor Yang Yue and Professor Lv Chao's team from Peking University Cancer Hospital is about postoperative adjuvant therapy with icotinib for EGFR-mutant NSCLC for 2 years versus 1 year. A total of 120 stage □-□A patients after resection were enrolled, the primary end point is PFS and the secondary end point is OS. The first patient was enrolled in September 2013. At present, the enrollment of this study is nearly completed, and more than half of the patients have completed experimental medication and entered the follow-up period.

Study on the safety of icotinib in adjuvant therapy

ICAPE (BD-IC-IV57, NCT02044328), a clinical study to explore the efficacy and safety of icotinib in postoperative adjuvant treatment of stage □-□A EGFR-mutant lung adenocarcinoma. Ten units in North China are involved and 80 patients have been enrolled so far. The experimental group: postoperative adjuvant treatment with icotinib for 18 months. The primary endpoint was DFS. Currently, the study enrollment has been completed, and follow-up results are in progress.

The above five studies will answer the difficult questions of adjuvant targeted therapy at the present stage, and the results are expected to be announced!

Neoadjuvant therapy

Effective targeted therapy can regain surgical resection opportunities for some patients with advanced lung cancer. In addition, surgery can provide complete pathological tissue and lay a comprehensive and accurate foundation for subsequent treatment. Targeted neoadjuvant therapy has high feasibility and low cost, and the comprehensive treatment model of combination of the two treatment can increase the chance of curing advanced lung cancer.

A phase Ⅱ clinical study EMERGING-CTONG1103 (Zhong et al. 2019), comparing the efficacy of erlotinib and gemcitabine combined with cisplatin in the neoadjuvant treatment of untreated EGFR-mutant ⅢA-N2 NSCLC, confirmed the feasibility and potential efficacy of neoadjuvant TKI.

In addition, clinical trials related to EGFR-TkIs including icotinib as neoadjuvant therapy are under way, and the results still need to be awaited. Study BD-IC-IV82 (NCT03749213), designed to evaluate the efficacy and safety of icotinib neoadjuvant treatment in patients with EGFR-mutant, radical surgical resection stage ⅢA-N2 NSCLC, 36 patients are expected to be enrolled, with preoperative icotinib for 8 weeks as neoadjuvant therapy and continue receiving icotinib as postoperative adjuvant therapy for 2 years, or disease progression, intolerant toxic side effects. The main observation index is ORR, the secondary indicators are DCR, OS, treatment-related AEs, etc. Another clinical trial BD-IC-IV81 (NCT03349203) designed to evaluate the ORR of lung and metastatic lesions after preoperative treatment with icotinib for EGFR-mutant stage ⅢB or oligometastatic NSCLC. Patients who are likely to undergo radical surgery were given oral icotinib 125mg, 3 times daily for 8 weeks as neoadjuvant therapy, and postoperative adjuvant therapy of icotinib was continued for 2 years. 60 patients are expected to be enrolled, the primary endpoint is ORR and the secondary endpoints are DCR, TTP, treatment-related AEs, etc. There is also an open, multicenter, single-arm phase Ⅱ trial RIPOT1606 (NCT02820116), designed to evaluate the efficacy and safety of icotinib neoadjuvant therapy for EGFR-mutant stage ⅢA-ⅢB NSCLC. A total of 67 resectable patients will be included and preoperative oral icotinib for 8 weeks, postoperative oral icotib for 2 years, or disease progression and toxicity was intolerable. The main observation indicator is complete resection rate, and the secondary indexes are ORR, OS, AEs, etc. The three trials above are ongoing and the results are very promising, they are expected to add new treatment indications.

Consolidate / maintenance therapy

For patients with stage Ⅲ NSCLC, if the efficacy of first-line chemotherapy is complete remission (CR), partial remission (PR) or stable disease (SD), the maintenance treatment can be followed. The INFORM study (Zhang et al. 2012) and the SATURN study (Cappuzzo et al. 2010) established the status of gefitinib and erlotinib as maintenance therapy for advanced NSCLC. A clinical trial of icotinib as consolidation therapy CH-L-069(NCT03396185) is currently underway, the objective of this study is to evaluate the relapse free survival (RFS) of patients with EGFR-mutant stage ⅢA-ⅢB NSCLC who are given icotinib as consolidation therapy after either concurrent or continuous radiotherapy and chemotherapy. 30 patients with unresectable EGFR-mutant stage ⅢA-ⅢB lung adenocarcinoma will be enrolled and treated with icotinib as consolidation therapy after synchronous/ sequential radiotherapy and chemotherapy. The primary endpoint is RFS, the secondary endpoints are OS, treatment-related AEs. The results are also

worth looking forward to. It will confirm that advanced NSCLC with EGFR-mutant controlled by first-line chemotherapy may be treated with icotinib as consolidation therapy.

High-dose treatment

According to CONVINCE, LUX-Lung6, ICOGEN (Zhou et al. 2011; Wu et al. 2014; Shi et al. 2013) et al study, median PFS in NSCLC patients with EGFR 19DEL mutation was longer than that in the 21L858R group. A phase clinical trial INCREASE(Li et al. 2020) aimed to explore safety and efficacy of high-dose icotinib in comparison with routine-dose icotinib in patients with NSCLC harboring 21-L858R mutation. A total of 269 patients with treatment-naive, EGFR-mutant (21-L858R or 19 DEL) NSCLC were enrolled, 186 patients with 21-L858R mutation were randomized to receive routine-dose icotinib (125 mg, thrice daily; L858R-RD) or high-dose icotinib (250 mg, thrice daily; L858R-HD), including 86 in L858R-RD group and 90 in L858R-HD group, whereas 77 patients with exon 19 deletion received only routine-dose icotinib (19-Del-RD) until progression, death, or unacceptable toxicity. The primary endpoint was median PFS (mPFS). The mPFS in L858R-HD group was similar to that in 19-Del-RD group (12.9 months and 12.5 months) and was significantly longer than that in L858R-RD group (12.9 months vs 9.2 months, HR: 0.75; 95% CI 0.53–1.05). A longer but statistically nonsignificant mPFS was observed between 19-Del-RD and L858R-RD groups (12.5 months vs. 9.2 months, HR: 0.80; 95% CI, 0.57–1.13). A higher ORR was observed in L858R-HD group compared with L858R-RD group (73% vs. 48%), also between 19-Del-RD and L858R-RD groups (75% vs. 48%). Similar incidences of grade 3/4 toxicities were observed among the three treatment groups. Conclusions: High-dose icotinib improved mPFS and ORR in patients with NSCLC harboring 21-L858R mutation with acceptable tolerability, which could be a new therapeutic option for this patient population.

Application Status Of Icotinib Combination Therapy

In addition to monotherapy, combination therapy of icotinib also exerts amazing advantages.

Icotinib Combined with chemotherapy

A prospective study(Xu LS et al. 2019) aimed to explore the efficacy and safety of icotinib combined with chemotherapy in treatment of advanced lung adenocarcinoma with EGFR-mutant. Advanced lung adenocarcinoma patients with untreated EGFR-mutant were recruited from 10 general hospitals in Shandong Province, they were randomly divided into icotinib combined with pemetrexed plus carboplatin group and icotinib monotherapy group. The primary endpoint was PFS. Results: Among 179 patients with evaluable efficacy, PFS was significantly longer in the combination group than in the monotherapy group (16.0 months vs. 10.0 months,P = 0.003). The ORR and DCR in combination group were higher than those in single-drug group (77. 8% vs 64.0%,χ^2 = 4.094, P = 0.043; 91.1% vs.79.8%,χ^2 = 4.632, P = 0.031), the overall survival was 36.0 months vs. 34.0 months, HR = 0.81, 95% CI 0.54–1.22, P = 0.309. The incidence of leukopenia grade 3–4 liver function damage in the combination group was significantly higher than that in the monotherapy group (12.2% vs 0%,χ^2 = 11.086, P = 0.001; 12.2% vs 3.5%,χ^2 = 4.488, P = 0.034).

Compared with monotherapy, icotinib combined with chemotherapy for first-line treatment significantly improved PFS, ORR and DCR in advanced lung adenocarcinoma patients with EGFR-mutant. Although AEs increased, they could be cured and were tolerable.

Another ongoing study QLHX-0531 (NCT02031601), aimed to compare the efficacy and safety of chemotherapy combined with insertional EGFR-TKI with TKI monotherapy for first-line treatment in stage □B/□ NSCLC. The study is expected to enroll 250 people, they will be divided into combination therapy and monotherapy. Combination group: docetaxel or pemetrexed plus platinum chemotherapy for d1, TKI treatment for d2-15, 3 weeks per cycle, 4 cycles in total. Monotherapy: EGFR-TKI oral daily. All patients continued TKI treatment until progression, toxicity or death. The primary endpoint is PFS, the secondary endpoints include ORR, OS, duration of response (DOR), etc. Expected results: PFS in combination group extended to 19 months and 10 months in the monotherapy group. OS in combination group extended to 36 months and 26 months in the monotherapy group. Presupposition: Platinum-based chemotherapy combined with insertional TKI for first-line treatment will prolong PFS and OS in patients with NSCLC.

Icotinib combined with anti-angiogenic drugs

With the conducting of study NEJ026, RELAY(Saito et al. 2019; Nakagawa et al. 2019) et al. The "A + T" therapy model of targeted therapy combined with anti-angiogenesis showed good benefits. A prospective, single-arm, multicenter clinical study ALTER-L004 (NCT03736837) (Ding et al. 2021) led by Tianjin Cancer Hospital, aimed to explore the efficacy and safety of icotinib combined with anlotinib in first-line treatment of EGFR-mutant NSCLC. The experiment is currently ongoing, as of September 2021, 60 patients with locally advanced and/or metastatic stage □B-□ non-squamous NSCLC with previously untreated EGFR-mutant were enrolled. They were treated with 125 mg of icotinib (po, tid) in combination with 12 mg of anlotinib (po, qd, d1-14, q3w), 56 of whom underwent at least one tumor evaluation. The median PFS was 15.1 months (95%CI 11.3–18.9), ORR was 67.9% and DCR was 98.2%. 58.9% of patients had 30% tumor reduction at first response assessment (defined as early tumor regression, ETS). Median PFS was 15.6 months (95%CI 10.4–20.8) in patients with co-mutations and 14.9 months (95%CI 9.1–20.7) in patients with pathogenic co-mutations. 23 patients are still receiving treatment. The incidence of grade 3/4 AEs was 40%. The most common AEs were hypertriglyceridemia and diarrhea. The most common grade 3/4 AEs were hypertension and diarrhea, one patient developed drug-related severe AE(acute coronary syndrome). 26.7% of patients required dose adjustment. Current results suggest that the combination of the two drugs in first-ine treatment has potential efficacy and is safe and tolerable for advanced NSCLC with EGFR-mutant. The combination is an improvement over traditional "A + T" because anlotinib is an oral preparation, which is more convenient than the three-week intravenous regimen.

Icotinib combined with radiotherapy

A study conducted by Li JR, et al (Li et al. 2016) aimed to explore the efficacy and safety of icotinib combined with WBRT in treatment of EGFR-mutant lung adenocarcinoma with brain metastatic (BMS). A total of 43 patients were included, all of whom received standard WBRT (3Gy per day, 5 times per week, 30Gy in total) with synchronous icotinib. After radiotherapy, patients continued oraling icotinib as

maintance therapy. The primary endpoint are iPFS and OS. Results: 4.7% of patients had CR and 46.5% had PR, the median iPFS and OS were 11.0 months and 15.0 months, respectively. The 1-year iPFS rate in the EGFR 19DEL group and 21L858R group was 40.0% vs 16.7% (P = 0.027). This clinical study demonstrates that icotinib combined with radiotherapy is more effective, safe and tolerable in EGFR-mutant lung adenocarcinoma with BMS, iPFS in 19 DEL group was significantly longer than that in 21L858R group, but it needs to be further verified.

Another retrospective study (Fan Y et al. 2017) included 152 patients and excluded 58 patients, in the remaining 97 patients, 56 patients received prophase radiotherapy including WBRT or stereotactic radiotherapy followed by icotinib, the other 41 patients received icotinib monotherapy. Intracranial PFS improved in the group treated with icotinib after radiotherapy compared with the icotinib monotherapy group (22.4 months vs 13.9 months, P = 0.043). In the entire cohort, the median OS for patients with confirmed BMS was 27.0 months (95% CI 23.9–30.1). There was no significant difference in OS between the icotinib added group and the icotinib monotherapy group (31.9 months vs 27.9 months, P = 0.237), and similar results were found in the stereotactic radiotherapy subgroup (35.5 months vs 27.9 months, P = 0.12). Patients with EGFR Del19 mutation had longer OS than those with 21L858R mutation (32.7 months vs. 27.4 months, P = 0.037). This study demonstrated that icotinib has good efficacy in treatment of EGFR-mutant lung adenocarcinoma with BMS. Icotinib combined with local radiotherapy had a longer duration of intracranial control compared with monotherapy. However, there was no significant difference in OS between the two groups, and further study is needed to determine the best time for local radiotherapy.

Icotinib combined with traditional Chinese medicine treatment

A multicenter, randomized, double-blind, placebo-controlled trial LH126 (NCT01745302) (Jiao et al. 2019) aimed to explore the efficacy, safety and the ability to activate EGFR mutations of Chinese herbal medicine combined with EGFR-TKI in advanced lung adenocarcinoma. A total of 354 patients were included, they were randomly divided into the experimental group (n = 185) of EGFR-TKI (erlotinib, gefitinib or icotinib) combined with traditional Chinese medicine or the control group (n = 169) of EGFR-TKI plus placebo. The results showed that, the median PFS in experimental group (13.50 months, 95%CI 11.20-16.46) was significantly longer than that in the control group (10.94 months, 95%CI 8.97–12.45), P = 0.0064. Subgroup analysis showed that TKI combined with Chinese medicine in first-line treatment (15.97 months vs 10.97 months, P = 0.0447) was superior to second-line treatment (11.43 months vs 9.23 months, P = 0.0530). PFS in EGFR 19del group was significantly longer than 21L858R group. EGFR-TKIs combined with traditional Chinese medicine significantly improved the ORR (64.32% vs 52.66%, P = 0.026) and the quality of life. The incidence of grade 1–2 AEs was lower in the combined group. This study provides the first conclusive evidence that EGFR-TKI combined with traditional Chinese medicine has better efficacy and safety in treatment of advanced EGFR-mutant NSCLC than EGFR-TKI monotherapy.

Another clinical study conducted by Tang M et al (Tang et al. 2019) aimed at exploring the efficacy and safety of combined traditional Chinese medicine with EGFR-TKIs in treatment of patients with advanced EGFR-mutant NSCLC. 153 patients were enrolled and randomly divided into EGFR-TKI combined with Chinese medicine group (n = 92) and EGFR-TKI monotherapy group (n = 61). Subgroup analysis was performed on 19DEL and 21L858R mutation patients. The results showed there was no significant improvement in DCR in Chinese medicine combined with EGFR-TKI group compared with EGFR-TKI monotherapy group (90.11% vs 83.33%, P > 0.05). The median PFS in the combination group was significantly longer than that in the monotherapy group (13 months vs 8.8, p = 0.001). For 19DEL mutant NSCLC, the median PFS was significantly longer in the combination group than in the monotherapy group (11 months vs 8.5, p = 0.007), and in 21L858R mutant NSCLC, the median PFS was also significantly longer in the combination group than in the monotherapy group (14 months vs 9.5, p = 0.015). The median PFS lengthened significantly in patients with 21L858R mutation. And there was no additional adverse effects in combination treatment group (p = 0.956). Conclusion: traditional Chinese medicine combined with EGFR-TKIs in treatment of EGFR-mutant advanced NSCLC can improve the efficacy and the adverse reactions are controllable.

Exploration Of Drug Resistance

Acquired drug resistance often occurs after EGFR-TKIs treatment for a period of time, and the mechanism is relatively complex. In addition to the known mutations such as EGFR T790M, PI3K, MET, many mechanisms of resistance remain unclear. EGFR T790M mutation accounts for about 50% of these patients, and osimertinib is feasible for subsequent treatment. For other patients, treatment after drug resistance remains to be further explored (Sequist et al. 2011).

A randomized controlled study CHEST006 (Chang et al. 2020), aimed to compare the efficacy of EGFR-TKI combined with concurrent chemotherapy with sequential chemotherapy in NSCLC patients with slow progression after first-line EGFR-TKI treatment. Slow progression patients with EGFR T790M negative were randomly divided into synchronous group (n = 49) and sequential group (n = 50). In the concurrent group, patients were treated with pemetrexed plus cisplatin combined with EGFR-TKI. In the sequential group, patients were given EGFR-TKI monotherapy and switched to two-drugs chemotherapy when disease progressed again. Results: Median PFS was 7.7 months in the concurrent group vs 5.7 months in the sequential group, p = 0.026. The median OS in the concurrent group was longer than the sequential group (20.0 months vs 14.7 months, p = 0.038). This study showed that, for NSCLC patients with slow progression and EGFR T790M negative after first-line EGFR-TKI treatment, the efficacy of concurrent EGFR-TKI combined with chemotherapy was better than EGFR-TKI sequential chemotherapy.

Another retrospective study conducted by Wang Y et al (Wang et al. 2018) aimed at evaluating the feasibility of continuing EGFR-TKI combined with concurrent radiotherapy in patients with EGFR-mutant locally advanced NSCLC after first-line EGFR-TKI theatment. 44 patients were enrolled and treated with EGFR-TKI for first-line, then combined with concurrent radiotherapy after local progression. TTP, PFS, tumor response rate and AEs were observed. Results: The median TTP and PFS of measurable lesions (n

= 31) were significantly prolonged after radiotherapy. The ORR and local tumor control rates for all lesions (n = 50) were 54.0% and 84.0, respectively. The median OS was 26.6 months. There was no serious AEs before and after radiotherapy. The study confirmed that, NSCLC patients treated with EGFR-TKI first-line and locally unsuccessful, combined EGFR-TKI with concurrent radiotherapy for the second-line treatment is feasible and effective.

EGFR-TKI combined with antiangiogenic-targeted drugs can kill tumor jointly after T790M resistant mutation (Thress et al. 2015; Planchard et al. 2015). A study of apatinib combined with EGFR-TKI aims to explore the efficacy of two-drug combination in acquired resistant cell lines, tumor transplantation and in patients with EGFR-TKI resistance. Results: PFS of drug-resistant patients reached 4.60 months after combination therapy, which was better than EGFR-TKI monotherapy, and both in vivo and in vitro. Another retrospective study of icotinib combined with apatinib aims to analyze the efficacy and safety of combination therapy for icotinib treatment failed advanced NSCLC. 27 patients were enrolled and treated with icotinib combined with apatinib until disease progression or toxicity intolerable. Results: The comprehensive treatment lasted 7.47 months, there were 8 deaths, the median PFS, ORR and DCR was 5.33 months, 11.1%, 81.5%, respectively. It is confirmed that, apatinib combined with icotinib for advanced NSCLC patients failed in first-line treatment of icotinib had definite efficacy and adverse effects can be tolerated (Wu et al. 2019).

Summary And Prospect

Icotinib, since its listing in 2011 till now, by unremitting research and exploration, three indications have been approved in China. There are still many relevant studies in progress, and the results are worthy of expectation. With the development of the times, all kinds of new drugs appear on the market constantly, and the original drugs also appear new permutations and combinations. Therefore, the clinical application of icotinib in the future is still very broad and worthy of exploration, we still need to continuously study its new usage and try to overcome its drug resistance.

Declarations

Ethics declarations

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Conflict of interest: Xingwen Zhou, Junhao Huang, and Tao Zhou report no conflicts of interest.

Ethics approval, Consent to participate, Consent for publication, Availability of data and material, Code availability Not applicable.

Authors' contributions All authors contributed to the study conception and design. Xingwen Zhou, Junhao Huang and Tao Zhou conceived and designed the analysis. Xingwen Zhou and Junhao Huang

performed the literature search. Junhao Huang and Tao Zhou undertook the revisions. Xingwen Zhou, Junhao Huang and Tao Zhou wrote the paper, approved the final version of the manuscript for submission, and agree to be accountable for the work.

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Figures

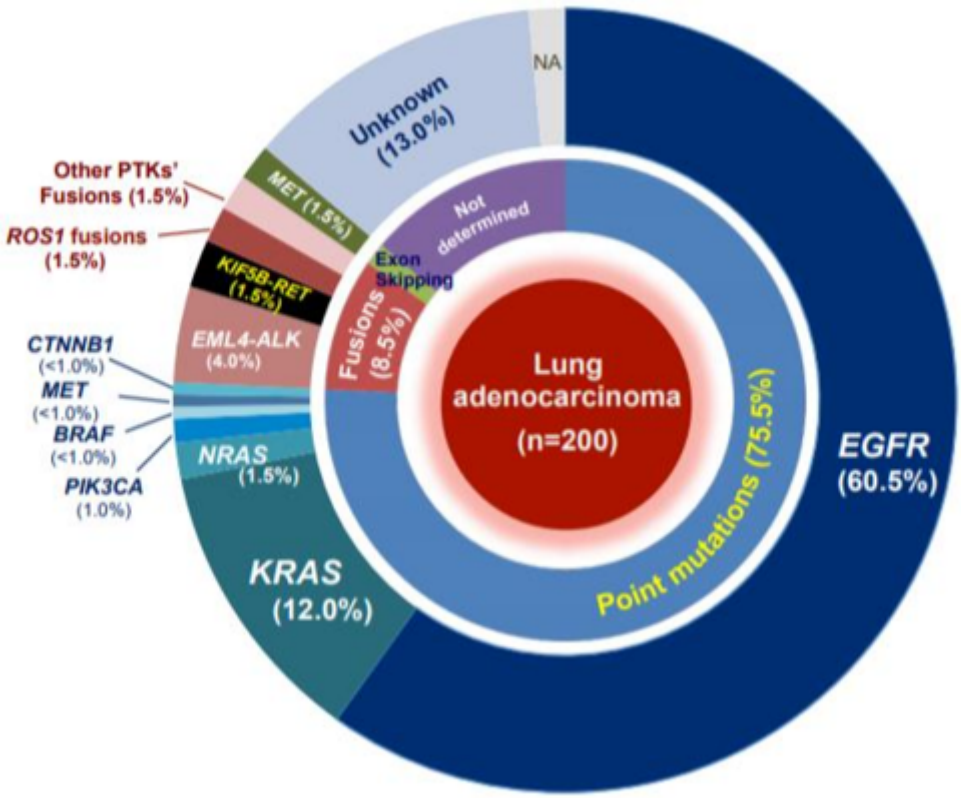

Figure 1

Driver gene profile of Asian lung adenocarcinoma (Seo et al. 2012)

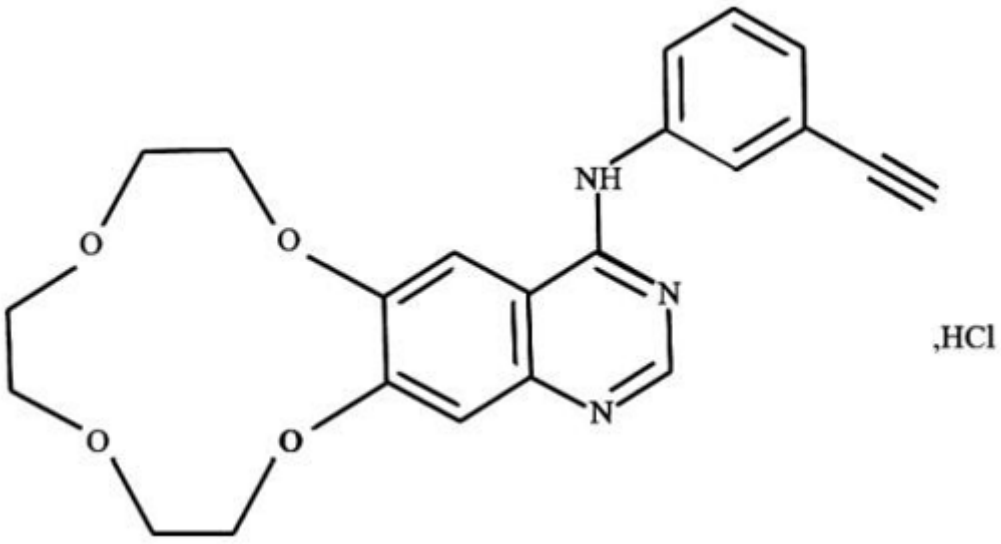

Figure 2

Chemical structure of icotinib (Zhao et al. 2011)