

Review Article

Progress of EGFR-TKI and ALK/ROS1 inhibitors in advanced non-small cell lung cancer

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Abstract: To discuss the mechanism and clinical application of EGFR-TKI and ALK/ROS1 inhibitors in non-small cell lung cancer (NSCLC), we reviewed recent available data mainly from PubMed. We found that chemotherapy, progression-free survival (PFS), objective response rate (ORR), and quality of life of patients with advanced NSCLC can be greatly improved in these drugs medication compared with conventional chemotherapy. Though many questions like resistance to EGFR-TKI and ALK/ROS1 inhibitors exist, molecular targeted therapy is an important therapeutic method for the management of NSCLC. The role of molecule targeted therapy in the initiation and development of NSCLC deserves further study.

Keywords: EGFR-TKI inhibitors, ALK/ROS1 inhibitors, non-small cell lung cancer

Introduction

Lung cancer is one of the most common malignant tumors, the survival rate is only 41.5% for one year, 15% for the five years, and among them about 85% is Non-small cell lung cancer. Patients are always in the advanced stages when they get final diagnosed and lost opportunities for the operation [1]. Currently, platinum-based double chemotherapy is the mainstream treatment for advanced NSCLC. Nevertheless, the severe adverse drug effects limit the clinical practices [2]. Afterward, molecule targeted-therapy thrived in this field because of good sound effects, friendly administration methods and mild adverse effects. At present, EGFR-TKIs and ALK/ROS1 inhibitors have widely used in clinical practices. In this article, we will review the mechanism, clinical practices and recent news of EGFR-TKI, ALK/ROS1 inhibitors in NSCLC.

Progress in the treatment of epidermal growth factor receptor

EGFR family is tyrosine transmembrane glycoprotein which encoded by proto-oncogenes, including HEB/erB-1, HEB/erB-2, HEB/erB-3, HEB/erB-4. EGFR can affect the tumor cell pro-

liferation, differentiation, migration, adhesion, transformation, survival and apoptosis [3]. It is reported that 43%-89% of NSCLC patients over-expressed EGFR in tissue samples, and these patients harboring high expression of EGFR are not sensitive to radiation and chemotherapy, therefore, EGFR became a prospective therapy target [4].

At present, the role of EGFR targeted drugs mainly has two kinds: one kind is small molecule tyrosine kinase inhibitor (TKI) which inhibiting EGFR tyrosine kinase activity of intracellular area; and another kind is artificial synthesis of EGFR monoclonal antibodies, by blocking outside the cell membrane and inhibiting activation of EGFR ligand binding domain.

Clinical pathological features of EGFR mutation

It is now well accepted that Asians, non-smokers and females are more likely to have tumors with EGFR mutations. For example, EGFR mutations have been shown to exist in approximately 30% of unselected patients in China. Adenocarcinoma tends to have a higher EGFR mutation rate than squamous carcinoma (42.5% vs. 9.5%), whereas in adenosquamous carcinoma,

the EGFR mutation rate ranges from 24.0% to 38.2% [5-7].

The epidermal growth factor receptor-tyrosine kinases inhibitors

EGFR mutations have mainly focus on exon 18 to 21. The lack of exon 19 LREA, exon 21 L856R mutations which means sensitive to EGFR-TKI, while exon 20 mutations is generally the signal insensitive to EGFR-TKI treatment [8, 9]. A large number of clinical studies confirmed that patients with EGFR mutations can benefit from the EGFR-TKI treatment, and EGFR-TKI drugs have been used clinically for a relatively long amount of time and are recommend by NCCN and EMSO guidelines for the treatment of advanced NSCLC [10, 11].

Gefitinib

Gefitinib is the first small molecule drug for NSCLC patients. It works through binding the intra membrane domain of EGFR tyrosine kinase against ATP. In 2009, IPASS, a multi-center Phase III clinical trial, aimed at comparing gefitinib with paclitaxel/carboplatin in the none or slighter smoker lung adenocarcinoma patient in the first line therapy. The conclusion was that gefitinib prolonged progression-free survival (PFS), elevated Objective Response Rate (ORR) and caused minor adverse reactions than paclitaxel/carboplatin. Furthermore, in the subgroup analysis, gefitinib performed better than paclitaxel/carboplatin in EGFR mutation group (PFS 9.8 m vs. 6.4 m respectively, $P<0.001$) [12]. Later studies WJTOG3405 and NEJ002 conducted in EGFR mutation patients compared gefitinib with docetaxel/cisplatin or paclitaxel/carboplatin respectively, and revealed that gefitinib had a longer PFS than conventional chemotherapy. The adverse reactions of gefitinib were light, and the most common side effects were rash, diarrhea and dysfunction of liver, which would not lead to drug withdrawal in general cases. Grade 3 or above adverse reactions occurred 2%-10% in different clinical researches, however interstitial pneumonia was rare and fatal, occurring about 1%, which should arouse physician attention [13, 14].

Erlotinib

To our knowledge, erlotinib has the same mechanism of action as gefitinib. A phase II trial revealed that the 1- and 2-year survival rates

for patients with stage IIIB/IV NSCLC who underwent erlotinib treatment were 46% and 19%, respectively [15]. An earlier study, BR21, showed that almost all subgroups of NSCLC patients can benefit from erlotinib treatment. According to the results of the BR21 study, erlotinib may be a good treatment option for male smokers with non-adenocarcinoma [16], but erlotinib does not seem to have an advantage over gefitinib. A Taiwanese retrospective study of 440 cases treated with gefitinib and 276 cases treated with erlotinib indicated that the PFS and ORR were not significantly different between these two treatments, regardless of whether they were given as first- or second-line therapies [17]. Another 1:1 matched retrospective study found no significant differences in ORR or PFS between erlotinib and gefitinib treatments (ORR 90.0% vs. 76.7% $P=.431$, median PFS 14.5 m vs. 11.7 m $P=0.507$) [18]. Because gefitinib and erlotinib are extensively applied in clinical practice, more prospective studies and economic analyses should be performed to determine any differences between these drugs.

Icotinib

Icotinib is a first-generation EGFR-TKI that was developed independently by Chinese researchers and was later approved by the state food and drug administration. ICOGEN, a multi-center phase III study, compared the efficacy and safety of icotinib to those of erlotinib in unselected, previously treated NSCLC patients. The results suggested that the PFS of icotinib was slightly longer than that of erlotinib, but this difference was not statistically significant (4.6 m vs. 3.4 m $P=0.13$); furthermore, adverse drug effects occurred in 61% of patients treated with icotinib and in less than 70% of patients treated with erlotinib ($P=.045$) [19]. Moreover, in the phase I trials of icotinib that were performed to determine the common dose, the maximum tolerant dose that would achieve much more favorable outcomes without causing severe side effects was not reached during dose escalation [20, 21]. Nevertheless, some cases that were treated with icotinib at the recommended or higher dosage after erlotinib failure were shown to have a strong response [22]. Overall, icotinib is not inferior to erlotinib when it is used as a second-line therapy, and it is safer than erlotinib; moreover, icotinib has potential as a first-line therapy and as a therapy after the development of EGFR-TKI resistance.

Afatinib

Other than gefitinib or erlotinib, afatinib is an irreversible blocker of ErbB family like EGFR, HER2, HER3, exerting anti-tumor effects [23]. LUX-lung, a series of clinic trials designed to illuminate afatinib in NSCLC, have produced several satisfying and encouraging results. LUX-lung 3 and LUX-lung 6 indicated that, in the first line therapy of EGFR mutation patients, afatinib exceeded traditional chemotherapy in PFS [23-25]. Based on that, FDA had approved afatinib as the new first line option for the EGFR mutation NSCLC patients. On another aspect, LUX-lung 1 trial suggested that, compared with placebo, afatinib prolonged PFS and increased the ORR in spite of indistinctive OS due to post treatments after gefitinib or erlotinib failure [26]. Combining with afatinib peculiar mechanism, this implies a promising outlook for those one failing the first generation EGFR-TKIs. However, Afatinib show much more common and severe adverse effects. Rash and diarrhea are still the most common adverse effects. Rate of rash was 14.6% to 91.9%, rate of diarrhea was 5.4% to 91.9%, and severe adverse effects like interstitial pneumonia or exfoliate dermatitis were observed according to the LUX-lung trials [24-26].

EGFR monoclonal antibody

Cetuximab is a sort of IgG1 monoclonal antibody that suppresses EGFR through bonding to its extracellular domain directly. Beyond that, ADCC brought out by cetuximab-EGFR complex can also induce tumor cell death. FLEX, focusing on the EGFR expressed, untreated NSCLC patients, assigned patients to receive gemcitabine/cisplatin combined with cetuximab or not randomly, then the results indicated these receiving cetuximab had a longer OS (11.3 m vs. 10.1 m $P=0.04$), however, almost 40% of experimental objects had level 4 leukopenia [27]. In this case, some experts are still wondering clinical benefits would fade because of severe adverse effects. Necitumumab, a new humanized monoclonal antibody, is up and coming in ASCO 2014, the preliminary results showed that Necitumumab combined with gemcitabine/cisplatin prolonged the OS than gemcitabine/cisplatin in the advanced squamous NSCLC (11.5 m vs. 9.9 m $P=0.012$) [28]. This agent may open up a novel way in the targeted therapy of squamous lung cancer.

EGFR-TKI clinical treatment

A meta-analysis including 23 studies that compared EGFR-TKIs and chemotherapies or placebo in advanced NSCLC (13 for first line, 3 for maintenance, 7 for second line), showed us that, regardless of first line, maintenance or second line, the present of EGFR mutation was the biomarker of PFS benefits from EGFR-TKIs [29]. For this reason, mutation status of EGFR should be identified before the patients are prescribed to EGFR-TKIs. For non-squamous NSCLC, EGFR mutation detection is recommended as category 1A by NCCN guideline, in case of large possibility for mutation-positive and sufficient clinical evidence. Identically, usually for mixed history or never-smoker squamous NSCLC patients, EGFR mutation tests are recommended [10].

First line

For EGFR mutant advanced NSCLC, WJTOG-3045 [13], NEJ002 [14], EURTAC [30], OPTIMAL [31], LUX-lung 3 [24] research compared EGFR-TKIs with platinum based doublet chemotherapy, and all results demonstrated EGFR-TKIs lengthened the PFS significantly, and had relatively mild adverse effects against chemotherapy. Noticeably, a subgroup data from OPTIMAL trials conducted by CTONG showed that EGFR mutant in advanced NSCLC patients only receiving chemotherapy (21 cases) had a short OS for 11.7 m, receiving erlotinib only (33 cases) had OS for 20.6 m, while receiving both treatments (94 cases) had OS for 30.4 m, which hints EGFR-TKIs and chemotherapy have overlying effects [31]. FASTACT-2 discussed the intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer. Merely for the EGFR mutant patients, the PFS was prolonged significantly than the control arm. The PFS was 16.8 m for the combined drugs usage, while the PFS for the control was 6.9 m ($P<0.001$), and OS was prolonged as well (31.4 m vs. 20.6 m $P=0.0092$), meanwhile, combined medication had a close severe adverse effects occurrence rate [32]. CALGB 30406 also observed approximate phenomena in erlotinib combined with Paclitaxel/carboplatin controlled by single erlotinib [33].

As for advanced squamous lung cancer, clinical trials are relatively few, due to the low EGFR mutant frequency, erlotinib was proven effective

tive in EGFR mutant squamous NSCLC patients, and the median PFS was 12 m, but the trials was small sample, and lack of control arm [34]. Much more clinical evidences are needed to probe the EGFR-TKIs in treatments of squamous lung cancer, especially for those whose EGFR mutation is positive.

Second line

In 2012, TITAN suggested that erlotinib showed an equivalent effect to docetaxel or pemetrexed, but had better tolerance [35]. KCSG-LU-0801 determined the efficacy of gefitinib or pemetrexed in the second line treatments for the never smoker, adenocarcinoma Asians. The PFS for gefitinib was 9.0 m and pemetrexed for 3.0 m ($P=0.0006$), and subgroup analysis showed a larger gap for the EGFR mutant patients (PFS 15.7 m vs. 2.9 m respectively $P=0.005$) [36], on the other side, TAILOR, DELTA and CTONG0806 indicated that the PFS and ORR of EGFR-TKIs for those EGFR mutant negative, were inferior to common chemotherapy in second line therapy [37-39]. Therefore, EGFR-TKIs are recommended to EGFR mutant positive ones as a second line choose.

Maintenance

SATURN detected effects of erlotinib in maintenance period, PFS was 12.3 w in EGFR mutation positive patients against 11.1 w of placebo ($P<0.0001$) [40], gefitinib also prolonged the PFS in the INFORM research (4.8 m vs. 2.6 m for the placebo, $P<0.0001$), and conspicuous difference was observed in EGFR mutation positive ones (16.6 m vs. 2.8 m $P<0.0001$) [41]. Based on these, erlotinib or gefinib are recommended to maintenance therapy after 4-6 cycles chemotherapy.

The resistant of EGFR mutations

Advanced NSCLC patients can benefit from EGFR-TKIs, but ineluctably, in less than 1 year, drug resistance turns up. The mechanisms for drug resistance mainly include primary resistance, secondary resistance, EGFR modifications, activation of other pathways, historical transformation [42]. A retrospective research conducted by Yang classified drug resistance by disease control time (DCT), tumor burden and clinical manifestations into 3 models: rapid progression (DCT>3 m, rapid development of tumor burden), slow progression (DCT>6 m,

slight development of tumor burden), local progression (DCT>3 m, solitary extra or intra cranial lesion progression). The PFS were 9.3 m, 12.9 m and 9.2 m, respectively ($P<0.0001$), and OS were 17.1 m, 39.4 m and 23.1 m, respectively ($P<0.0001$). In the rapid progression model, the OS of patients taking continuous EGFR-TKIs was shorter than those changing into chemotherapy; therefore, turning into chemotherapy seasonably is a reasonable recommendation. In the slow progression model, the OS for continuing EGFR-TKI and changing into chemotherapy are 39.4 m and 17.8 m respectively ($P=0.02$), so sustaining EGFR-TKIs is recommended. While in the local progression model, OS for both were approximate, but taking the quality of life and locally progression into consideration, local treatments are to be added up to EGFR-TKIs [43].

Chong CR reviewed the mechanisms of EGFR-TKIs resistance and the treatment strategies about it. He concluded that new generations of EGFR-TKIs can be used after gefitinib or erlotinib resistance [42]. LUX-lung 1 indicated afatinib had effects after the first generation EGFR-TKIs resistance [26], but probably owing to its irreversible binding to EGFR in other sites of human, the effective drug concentration is hard to reach, and more adverse effects are induced [44]. EGFR-T790M point mutant is the universally accepted mechanism to acquired drug resistance, accounting for the 60% of all drug resistance. The third generation EGFR-TKIs were proven to work in the group harboring both EGFR mutation and T790M mutation, like AZD9291, in-vitro study found out that AZD9291 can inhibit growth of EGFR mutant and T790M mutant cell lines [45], in the meantime, they have a low affinity for the wild type EGFR hence, they show better performances and less adverse effects over their predecessors [46].

With ALK fusion gene and ROS1 as targets for treatment

ALK rearrangement

ALK was identified in a subtype of anaplastic large cell lymphoma, and considered as the driver gene [47]. Later, Soda and Rikova [48, 49] detected ALK in NSCLC separately. ALK is activated through fusion protein, ALK overexpression, or ALK point mutation. EML4-ALK

fusion is the most common way of ALK activation in NSCLC [50]. The frequency of ALK fusion is about 5% [51]. It still makes sense partly because the incidence of NSCLC is rather higher, and more importantly, ALK fusion takes 25% of the population EGFR, KRAS, HER2 or TP53 mutant negative [52].

Clinical pathological feature of ALK rearrangement

A research reported that the mutant rate was about 5.4% for the adenocarcinoma, and lower in squamous carcinoma, only 1.8% [52]. In adenocarcinoma, the solid or mucous adenocarcinoma rich of signet cell were more likely to have ALK rearrangement than other sorts [53]. The clinical features of ALK resemble the feature of EGFR mutation except for the tendency to be the young and the male gender [54].

ROS1 rearrangement

ROS1 rearrangement is firstly found in human glioblastoma [55], but to date, the physical function is still unclear. Rikova and his colleagues track ROS1 rearrangement in NSCLC cell line in 2007 [49]. ROS1 rearrangement is thought to be a driver gene in process of NSCLC, and detected in 1.7%-4.6% of NSCLC patients [56-61].

Clinical pathological features of ROS1 rearrangement

ROS1 rearrangement is inclined to take place in acinus or solid adenocarcinoma, generally, the well-differentiated ones. Female, non-smoker, young, or having an early T stage are the characteristics of ROS1 rearrangement [56-60].

ALK/ROS1 inhibitor treatment strategies

ALK rearrangement test should be performed ahead of ALK inhibitors medication. Once diagnosed with non-squamous lung cancer, ALK rearrangement detection is recommended in cooperation with EGFR mutation test [10]. While in squamous lung cancer, due to its low incidence, this test is proposed only for non-smoker or mixed histological type [62].

Crizotinib: Phase I trials suggested that the ORR was 60.8%, m PFS is 9.7 m for the ALK rearrangement positive NSCLC patients [63]. Following phase III trials compared crizotinib

with docetaxel or pemetrexed in ALK rearrangement positive advanced NSCLC patients who previously received chemotherapy. The results indicated the m PFS were 7.7 m and 3.0 m (HR=0.49 $P<0.001$), ORR were 65% and 20% ($P<0.001$) respectively, but significant different of OS was not found possibly because of crossover in the late phase of disease [64]. The adverse effects observed were visual impairment, edema, abnormal renal or liver function, etc. but lethal drug related pneumonia occurred occasionally [63, 65].

Crizotinib inhibit ROS1 rearrangement as well, 2013 ASCO scholars reported the efficacy of crizotinib in ROS1 arrangement positive patients. ORR for measurable 25 cases is 56%, DCR (disease control rate) for 8 weeks and 16 weeks were 76% and 60% respectively. Crizotinib targeting ROS1 rearrangement and CMET amplification is under further clinical studies [66].

Treatment after crizotinib resistance: Although ALK rearrangement positive patients benefit from crizotinib, drug resistance takes place in about 1 year [67]. A research shows that acquired resistance, ALK copy number increase, and alternative activated pathways play roles in the resistance process, for instance, L1196M and C1156Y, are slightly similar to T790M in EGFR mutation, but not that contributable and estimated less than 30% [68]. Alectinib is a novel generation of ALK inhibitors, phase I and II suggested alectinib was effective and safe for patients after crizotinib resistance. In 47 patients, one got completely response, 14 got confirmed partial response. Ceritinib is also a new ALK inhibitor, and can suppress L1196M, G1269A, I1171T, S1206Y etc. [69]. A recent clinical trial demonstrated the ORR for ceritinib after crizotinib resistance was 56% [70], which offered evidence for treatments after crizotinib resistance.

Questions and prospects

Abundant clinical evidences had proven targeted therapy and unique status in treatments of advanced NSCLC. EGFR-TKIs and ALK/ROS1 inhibitors these two medications are applied to clinical practice maturely. However, arguments and questions merged with their clinical usage, and more problems and blind areas are waiting to be set. After reviewing the processes and

updates of EGFR-TKIs and ALK/ROS1 inhibitors in NSCLC, we brought these questions and prospects forward: first, drugs targeting to other driver genes are still in their infancies, some are on the further preclinical studies, or some are lack of solid clinical trials. Second, the key to targeted therapy is to find effective targets. Progressions were made in checking out the non-squamous lung cancer, but sluggish in squamous lung cancer. Last but not least, the tactics and algorithm have not been formed after EGFR-TKIs or crizotinib resistance. Much more high-ranking clinical evidences are needed to support novel drugs, new strategies.

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