Progress in target therapy of advanced non-small cell lung cancer

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***Abstract*—Lung cancer is one of the most common malignant tumors, and its morbidity and mortality are relatively high. Especially for small cell lung cancer (SCLC), the mortality rate is between 80-90%. Unfortunately, more than 50% of lung cancer patients are diagnosed at an advanced stage. The traditional treatment for advanced non-small cell lung cancer (NSCLC) is chemotherapy. In recent years, with the rapid development of molecular pathology, we have a deeper understanding of the underlying pathological mechanism and heterogeneity of lung cancer, especially NSCLC. Molecular targeted therapy is more accurate because of its anti-tumor effect, and the incidence of adverse drug reactions is low. Compared with chemotherapy in the traditional sense, the degree of damage to normal tissues is also significantly reduced. Therefore, it has become a research hotspot in recent years. This article reviews the research progress of various molecular targeted drugs for the treatment of lung cancer based on domestic and foreign research literature and related data.**

***Key words*—NSCLC, Target therapy, Targeted drugs, Mutant gene**

INTRODUCTION

There are three main types of lung cancer, non-small cell lung cancer, small cell lung cancer and lung carcinoids. Among newly diagnosed lung cancer patients, non-small cell lung cancer (NSCLC) accounts for approximately 85%, small cell lung cancer (SCLC) accounts for approximately 10% to 15%, and carcinoids account for less than 5% [1]. NSCLC is divided into different histological subtypes, including adenocarcinoma, large cell carcinoma and squamous cell carcinoma. Traditionally, the standard treatment for advanced non-small cell lung cancer is a platinum-based two-drug combination chemotherapy regimen. However, Scagliotti and Collagues [2] established the importance of histology in the treatment of non-small cell lung cancer, showing that the combination of pemetrexed and platinum drugs has advantages in the first-line treatment of NSCLC. At present, combined chemotherapy with Taxanes and platinum drugs is the first choice for the treatment of squamous cell carcinoma. Molecular targeted drug therapy has brought new directions for the clinical treatment of NSCLC. Similarly, as a predictive and prognostic indicator to guide treatment, the molecular characteristics of NSCLC have become more and more important.

EPIDERMAL GROWTH FACTOR RECEPTOR-TYROSINE KINASE INHIBITOR (EGFR-TKI)

EGFR is the expression product of the proto-oncogene C-ErbB, and is a regulatory factor for cell survival, growth, differentiation and cancer cell metastasis. EGFR mutations can cause abnormal activation of tyrosine kinase (TK), which can inhibit cell apoptosis, accelerate blood vessel formation, enhance cell adhesion, and ultimately lead to tumor cell proliferation. It is one of the most common driver genes in NSCLC [3].

The first generation of EGFR-TKI

EGFR-TKIS is the first NSCLC targeted therapy to achieve a huge breakthrough. Large-scale genetic testing data show that about 10-15% of NSCLC patients worldwide carry EGFR gene mutations [4], and the mutation rate in non-smokers of Asian women with lung adenocarcinoma is as high as 60%. Represented by Gefitinib, Erlotinib and Icotinib, the first generation of EGFR-TKI targeted drugs is mainly aimed at reversible inhibitors of exon 19 deletion and 21 exon mutation of tyrosine kinase site. In addition, clinical studies have confirmed that the first-generation EGFR-TKI is significantly superior to traditional platinum-based chemotherapy regimens in the first-line treatment of advanced NSCLC with EGFR mutations.

Gefitinib Gefitinib is a reversible tyrosine kinase inhibitor. It binds to the Mg-ATP site on the catalytic region of EGFR-TKIs to block the cell signal transduction pathway of EGFR, thereby inhibiting the growth, proliferation and migration of tumor cells. In 2004, the epidermal growth factor receptor (EGFR) mutation was the first molecular target to be discovered in a subgroup of patients with non-small cell lung cancer, and it had a significant response to oral tyrosine kinase inhibitor (TKI) Gefitinib [5].

In 2005, Gefitinib had two clinical trials in China. In the IPASS test (Gefitinib (experimental group) Vs. paclitaxel + carboplatin (control group)) [6], the 12-month progression-free survival (PFS) rate of the experimental group was significantly higher than that of the control group, which were 24.9% and 24.9% respectively. However, the latter trial First-SIGNAL did not show an improvement in outcome. Although the two studies failed to show a difference in overall survival (OS), patients with EGFR mutations had higher RRs and longer PFS when receiving targeted therapy.

Unfortunately, although EGFR-mutated NSCLC patients usually have a very good initial response to the first-generation TKI, most patients who respond to treatment will eventually develop disease progression after about 9 to 14 months of treatment [7].

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Erlotinib A study by Lim et al. [8] compared the efficacy of Erlotinib and Gefitinib in patients with stage IIIB/IV NSCLC who had relapsed or metastasized, and there was no statistically significant difference in the therapeutic effects of the two drugs. Although the above study finally got a negative result, a trial [9] proved that in the second-line treatment of lung squamous cell carcinoma, the survival time of patients in the Erlotinib group was longer than that in the Gefitinib group. It suggests that Erlotinib is better than Gefitinib for patients with advanced non-small cell lung squamous cell carcinoma.

Icotinib Icotinib is a small molecule EGFR targeted drug independently developed by China. In the CONVINCE study [10], 285 patients with stage IIIb/IV lung adenocarcinoma with EGFR exon 19 and/or 21 mutations were randomly selected. Comparing the therapeutic effects of Icotinib and the control group (pemetrexed combined with cisplatin), the objective response rate (ORR) of the Icotinib experimental group was significantly higher than that of the pemetrexed + cisplatin chemotherapy group. They were 64.8% and 33.8% respectively ($P < 0.001$). Moreover, the median PFS was 296 days and 219 days, respectively, and the Icotinib experimental group was also longer than the chemotherapy group.

The second generation of EGFR-TKI

The second generation of EGFR-TKIs mainly include Afatinib and Dacomitinib, which are irreversible covalent inhibitors of EGFR and other ErbB family members (HER2, ErbB3 and ErbB4).

Dacomitinib In 2017, a randomized phase III study (ARCHER 1050) reported [11] that Dacomitinib is superior to Gefitinib in the first-line treatment of EGFR-mutant NSCLC, and it can improve PFS (14.7 m Vs. 9.2 m) and hazard ratio (HR, 0.59, 95% CI: 0.47-0.74; $P < 0.001$). However, there were 2 treatment-related deaths in the Dacomitinib group and 1 in the Gefitinib group. The latest results show that Dacomitinib treatment of NSCLC can reduce the risk of disease progression by 41%, but it is similar to Gefitinib in alleviating the disease. In addition, Dacomitinib is more toxic and has more adverse drug reactions. We need to pay attention to it and ensure that the dosage of the drug is safe.

Afatinib A study from LUXLung 3 [12] compared the first-line treatment effect of Afatinib Vs. pemetrexed + cisplatin. The result was that the median PFS of patients with EGFR mutations was 13.6 months Vs. 6.9 months; ORR was 56% Vs. 23 %. This proves that Afatinib can be a reasonable choice for the first-line treatment of EGFR-mutant lung adenocarcinoma. In the overall study population, there was no difference in OS between Afatinib and chemotherapy. Based on data from the LUX-Lung 3 trial, the Food and Drug Administration (FDA) approved Afatinib for the treatment of patients with advanced NSCLC in July 2013.

In addition, Afatinib is also helpful for patients with squamous cell carcinoma who have failed chemotherapy. A phase III LUX-Lung 8 study [13] demonstrated the efficacy of second-line treatment in patients with advanced squamous cell carcinoma that progressed after at least one platinum-based chemotherapy. The experiment enrolled 795 patients between March 2012 and January 2014. The results of this study showed that the PFS of the Afatinib group was significantly better (2.4 m Vs. 1.9 m; $P = 0.0427$). The disease control rate of patients treated with Afatinib was better than that of the control group (45.7% Vs. 36.8%; $P = 0.020$). The results of the study suggest that Afatinib is more suitable than erlotinib as a second-line treatment for patients with advanced squamous cell carcinoma.

A 2016 study [14] showed that in patients with brain metastases, Afatinib tends to improve PFS compared with chemotherapy. Further combined analysis showed that the application of Afatinib Vs. pemetrexed + cisplatin combined chemotherapy in patients with lung cancer brain metastases showed a significant improvement in PFS (8.2 m Vs. 5.4 m; $P = 0.0297$). In 2017, Tamiya et al. [15] found that the median blood-brain barrier penetration rate of Afatinib was significantly higher than that of other TKI drugs, indicating that Afatinib may be effective for pial metastasis. Therefore, for the treatment of NSCLC patients with EGFR mutations, especially those with brain metastases, Afatinib can be the first choice based on the drug's ability to penetrate the blood-brain barrier.

The third generation EGFR-TKI

EGFR-TKIs can improve the survival rate of patients with advanced non-small cell lung cancer with sensitive mutations. Unfortunately, almost all of these patients will eventually progress, and about half of the patients will have the T790M mutation. In recent years, the third-generation EGFR-TKI has become a research hotspot and the main force of post-drug resistance treatment. The third-generation EGFR-TKI is an irreversible mutation-specific drug used for the treatment of T790M mutation resistance, which can effectively block EGFR-T790M, and also has an inhibitory effect on EGFR sensitive mutations [16].

Osimertinib has been shown to be very effective in lung cancer patients with T790M mutation and is the first choice for second-line treatment [17]. In 2017, the World Conference on Lung Cancer (WCLC) announced the data from the phase III clinical trial AURA3 of Osimertinib [18]. The effects of Osimertinib and platinum-containing dual-drug combination chemotherapy were compared in NSCLC with progression after first-line EGFR-TKI treatment. The results showed that the PFS of the Osimertinib group was better than the platinum-containing dual-drug chemotherapy group at 10.1 months and 4.4 months; ORR was also significantly better than the chemotherapy group at 71% and 31%, respectively. Moreover, the median duration of remission in the Osimertinib group was 9.7 months, while that in the chemotherapy group was only 4.1 months. After the EGFR-TKI treatment of EGFR-T790M-positive advanced NSCLC patients progressed, Osimertinib showed better clinical efficacy than pemetrexed + platinum, reducing the risk of disease progression by about 70%. The above studies have shown that Osimertinib is effective in the treatment of resistant patients with T790M mutation.

In 2018, Soria and Collegues [19] reported the good efficacy of Osimertinib compared to the first-generation TKIs (Erlotinib and Geftinib) as the first-line treatment for

untreated patients with EGFR mutations. Based on this, the FDA has approved Osimertinib for the first-line treatment of EGFR-mutant advanced non-small cell lung cancer. The Nazartinib developed by Novartis is the third-generation EGFR-TKIS and is currently in phase II clinical trials. The interim results of the clinical trial in 22 evaluable patients, ORR was 54.5%, disease control rate (DCR) was 86.4%, which has a certain effect on EGFR-positive metastatic NSCLC.

The fourth generation EGFR-TKI

The fourth-generation EGFR-TKIS drug Brigatinib developed by Ariad/Takeda was approved for marketing by the FDA in April 2017. The indications are ALK-positive metastatic NSCLC (approved) and EGFR C797S-positive metastatic NSCLC (in research) that are progressing or intolerant to Crizotinib. The ORR of Brigatinib for ALK-positive second-line treatment of NSCLC is 45%~54%, the median duration of response is 11.1~13.8 months, and the PFS of the first-line treatment of ALK-positive lung cancer is 34.2 months. It is currently the only targeted drug that can target the EGFR and ALK targets of NSCLC, and is effective against the C797S/ T790M/ EGFR mutation that is resistant to Osimertinib.

AZD-3759 developed by AstraZeneca is the world's first TKIS drug specifically designed to penetrate the blood-brain barrier and treat brain metastases. It is currently in phase I/II clinical trials. The results of phase I clinical trials have an ORR of 65% and a disease control rate (DCR) of 90%. For the treatment of meningeal metastases, the ORR was 28%, and the DCR was 78%. It is a very promising drug for the treatment of EGFR-positive NSCLC brain metastases and pial metastases.

EAI045 represents a new type of selective inhibitor that can overcome C797S and T790M resistance mutations [20]. EAI045 binds to allosteric sites in the tyrosine kinase molecule, causing changes in its molecular spatial structure, thereby hindering the occurrence of enzymatic reactions and inhibiting tumor cell proliferation. Since EGFR dimerization is a prerequisite for tyrosine kinase activation [21-23], EAI045 cannot completely inhibit dimerization-mediated signal activation. In the tumor-bearing mouse model of lung cancer, there was no response when EAI045 was used alone to treat mice. However, EAI045 combined with cetuximab can block EGFR dimerization [20] and can significantly slow down tumor growth [24]. Compared with EGFR wild type, EAI045 is 1000 times more sensitive to mutant EGFR. It is because L858R can expand the allosteric domain of tyrosine kinase, and it is easy for EAI045 to bind to tyrosine kinase, but it has no obvious inhibitory effect on 19del/T790M. At present, the research on EAL045 is only limited to the laboratory, and whether it has clinical value remains to be further researched and explored. The C797S mutation of EGFR gene leads to clinical resistance of third-generation TKIs (AZD9291 and HM61713, etc.). This may be an acquired phase III mutation for all three generations of EGFR-TKIs, which is still a major challenge in the treatment of lung cancer.

ANAPLASTIC LYMPHOMA KINASE GENE REARRANGEMENTS

The ALK gene and EML4 gene combine to form the EML4-ALK gene, which leads to abnormal activation of the combined ALK tyrosine kinase, thereby stimulating cell growth and proliferation leading to tumorigenesis. Wild-type EGFR and KRAS are clinical features of NSCLC patients with positive EML4-ALK fusion gene. It is reported that 3-5% of patients with NSCLC have ALK gene rearrangement, and the use of EGFR-TKIs is not sensitive to treatment. Therefore, targeted therapy for EML4-ALK fusion gene is very important.

The first generation ALK inhibitors

In phase I and phase II clinical trials (PROFILE 1001 and 1005), the first-generation ALK-TKIs Crizotinib was used to treat chemotherapy-resistant ALK-rearranged NSCLC patients, and the results of the study showed that the ORR was 50-61% [25]. Based on this, the FDA approved Crizotinib for the treatment of such patients in 2011. Subsequent phase III studies have shown that for patients who are newly treated with ALK-TKIs, Crizotinib is significantly better than chemotherapy in terms of several lines of treatment [26]. In the first-line treatment (PROFILE 1014), compared with chemotherapy, Crizotinib significantly prolonged PFS (7.0 m Vs. 10.9 m) and ORR (45% Vs. 74%) [26]. Crizotinib has been established as the first-line treatment of ALK rearrangement of NSCLC.

Despite the remarkable efficacy, most patients relapse within 1 year after Crizotinib treatment. The analysis of Crizotinib-resistant clinical specimens revealed that the acquired mutation in the ALK tyrosine kinase domain was about 20%, and the ALK amplification was about 8%. In addition, other off-target mechanisms have also been discovered, such as the activation of EGFR and other bypasses, epithelial-mesenchymal transition, and small cell lung cancer transformation [27]. In addition to the classic bypass such as EGFR and Src [28], the bypass signaling pathway of IGF1R or other members of the HER family was also found in NSCLC patients with ALK rearrangement [29]. The research results of preclinical models prove that it is reasonable to overcome off-target drug resistance through the combination therapy of targeting ALK and the alternative signaling pathway [30].

The second generation ALK inhibitors.

The second-generation AIK-TKIs (Ceritinib, Aletinib and Brigatinib) are approved for the treatment of NSCLC patients with Crizotinib refractory ALK rearrangement [31-32]. Among the patients after Crizotinib treatment progressed, about 50% of patients were sensitive to the second-generation ALK-TKIs treatment, and most of the remaining patients were in stable condition. It was confirmed that the NSCLC patients with ALK rearrangement experienced recurrence and progression in the first-generation ALK inhibitor treatment. After that, they are still sensitive to the ALK signal pathway.

Interestingly, the structural differences between the second-generation ALK-TKIs led to different resistance mechanisms. Therefore, about 50% of the tumors that progressed after the second-generation ALK-TKls treatment had ALK fusion gene resistance mutations. Moreover, the resistance mechanism of each TKI is not exactly the same. The most common resistance mutation is ALK G1202R, which is highly refractory and resistant to a variety of second-generation TKIs. Regarding the application of second-generation ALK-TKIs in first-line

treatment, the ASCEND-4 study showed that the median PFS of first-line treatment with Ceritinib was significantly better than chemotherapy (16.6 m Vs. 8.1 m). However, the chemotherapy regimen used in the control group in this study was not the standard first-line treatment, and the incidence of side effects was high. During the course of treatment, more than two-thirds of patients had gastrointestinal side effects, which limited the use of Ceritinib in the first-line treatment [33]. In a recent phase III clinical trial, the efficacy of Aletinib Vs. Crizotinib as a first-line treatment was compared. The results of the study showed that the median PFS of Aletinib was significantly better than that of Crizotinib (34.8 m Vs. 10.9 m) [34]. Therefore, Aletinib is approved as the preferred drug for first-line treatment.

The third generation ALK inhibitors

Although the listing of second-generation ALK tyrosine kinase inhibitors (TKIs) has benefited the majority of patients, patients with ALK gene-positive NSCLC continue to develop drug resistance and develop central nervous system metastases, leading to disease progression. Loratinib is a third-generation ALK-TKI with strong brain penetration characteristics. It shows strong clinical activity in ALK mutation-positive NSCLC patients, especially for patients with central nervous system metastasis. Studies [35] suggest that the objective remission rate of Lauratinib in Crizotinib-resistant ALK-positive patients is 69%, and the intracranial objective remission rate is 68%; Treatment of ALK-positive patients who have previously received non-Crizotinib ALK inhibitor treatment has an objective response rate of 33%, and an intracranial objective response rate of 42%; Treatment of ALK-positive patients who have previously received 2 or 3 ALK inhibitor treatments (with or without chemotherapy) has an objective response rate of 39%, and an intracranial objective response rate of 48%.

ROS1 REARRANGEMENT

As a unique oncogenic sequence, ROS1 gene was first discovered in avian sarcoma virus. The gene-encoded ROS1 protein is a transmembrane tyrosine kinase of the insulin receptor family. Abnormal activity of ROS1 protein kinase can activate multiple downstream signal pathways, leading to tumor formation. ROS1 has 49% homology with ALK kinase domain. The incidence of ROS1 rearrangement in NSCLC patients is 1-2%, and the most common fusion partner is CD74 (40%-45%). The clinical feature is that young, non-smokers with Asian adenocarcinoma are prone to ROS1 rearrangement. Crizotinib, as a multi-target TKI, can effectively inhibit ROS1. The results of the phase I clinical trial study showed that the ORR was 72%, and the median PFS was 19.2 months [36]. Based on this, it was approved by the FDA as the only drug to treat patients with ROS1 rearrangement of NSCLC. Subsequent phase II clinical studies also further confirmed that Crizotinib has a significant therapeutic effect and a long-lasting drug effect.

Nevertheless, most patients will relapse within 2 years, and 53% of NSCLC patients with ROS1 rearrangement who are resistant to Crizotinib will have ROS1 gene mutations. The most common resistance mutation is G2032R, which is similar to the ALK G1202R mutation. Cabozantinib has shown preclinical activity for the treatment of Crizotinib-resistant mutations including G2032R and D2033N [37]. However, Cabozantinib is poorly tolerated, which limits its clinical application. Loratinib is also an effective inhibitor of ROSl. In a phase I study of 12 NSCLC patients with ROS1 rearrangement, 6 patients achieved partial remission, and 2 of them had been treated with Crizotinib. Preclinical studies on the effectiveness of Loratinib against G2032R resistant mutations have shown that the concentration required for Loratinib to inhibit G2032R is more than 100 times the concentration required to inhibit non-ROS1 mutations [38]. TPX-0005 is an ALK/ROS1/TRK inhibitor for overcoming the ROS1 G2032R resistance mutation and is currently in clinical trials [39].

BRAF MUTATION

BRAF mutations are present in a variety of tumor types such as melanoma, NSCLC, and colorectal cancer. Braf mutation V600E accounts for about 50% of NSCLC and often occurs within penetr 15. The main BRAF inhibitor drugs are vemurafenib (developed by vemurafenib, Genentech and Plexxikon) and dabrafenib (developed by dabrafenib, Novartis). Blocking BRAF alone or in combination with other downstream inhibitors (MEK) has a very good effect on patients with BRAF V600E mutations. On June 22, 2017, the FDA approved trametinib (MEK1/2 inhibitor) combined with dabrafenib to be used for BRAF V600E mutation-positive NSCLC patients. The approval is based on phase II clinical trial data. Among them, 93 patients received a combination of two targeted drugs. The ORR of the newly treated patients was 61%, and 57 patients had received chemotherapy. The ORR of patients who had received chemotherapy was 63%, and the median duration of remission reached 12.6 months.

NTRK FUSION

NTRK fusion is a genetic abnormality, which accounts for 0.5-1% of common tumors. However, it accounts for more than 90% of some rare tumors, such as salivary gland cancer. The Larotrectinib developed by Loxo/Bayer is a selective inhibitor targeting NTRK fusion protein. It is a highly selective TRK inhibitor against the presence of NTRK1, 2, 3 gene fusion. Recently, Larotrectinib has been used in lung cancer patients with NTRK gene fusion [40].

RET GENE FUSION

RET gene fusion usually occurs in 2% of NSCLC patients. The selective RET inhibitor LOXO-292 developed by Loxo/Array is in phase I clinical trials. The latest research data shows that the ORR of evaluable patients treated with LOXO-292 is 69%. Among them, the ORR of NSCLC patients reached 65%, including 3 patients with brain metastases. The ORR of patients with papillary thyroid cancer reached 83%. This indicates that LOXO-292 is well tolerated and has obvious anti-tumor activity against cancer patients with RET fusion mutations, including patients who are resistant to previous multikinase inhibitors (MKI) and have brain metastases.

SUMMARY

The diagnosis and treatment of lung cancer has entered an era of precision. Targeted therapy has undergone more

than ten years of exploration, and its remarkable clinical efficacy and low toxicity and side effects have been widely favored by researchers. Molecular targeted therapy is gradually replacing traditional chemotherapy. Although the current targeted therapies for advanced NSCLC are developing rapidly, there are still many problems. For example, the survival time of patients with advanced NSCLC is still very limited, molecular targeted therapies cannot escape the problem of drug resistance, and the efficacy and safety of many new target drugs remain to be considered.

We need to have a deep understanding of the molecular basis of targeting, improve the accuracy of biomarker detection, screen suitable clinical treatment populations, and find the best combination of targeting and chemotherapy regimens for patients. It is believed that with in-depth research and exploration of the signaling pathway mechanism and targets of lung cancer, more patients will benefit from precise target therapy, which will provide broader prospects for the diagnosis and treatment of lung cancer. In addition, the combination of molecularly targeted drugs and radiotherapy in the treatment of locally advanced non-small cell lung cancer is also a focus of current research. But there is no definite conclusion yet. It is hoped that with the deepening of research, the combination of precision radiotherapy and precision target drug therapy will bring new gospel to lung cancer patients.

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