Review Article

The latest therapeutic strategies after resistance to first generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) in patients with non-small cell lung cancer (NSCLC)

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Abstract: First-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs), gefitinib and erlotinib, produce reliable responses and survival benefits in selected patients with advanced non-small cell lung cancer (NSCLC). Unfortunately, most patients who initially respond to first-line therapy with EGFR TKIs will experience disease progression in 1-2 years. To overcome the resistance of EGFR TKIs, the potent resistance mechanisms and novel therapeutic strategies have been developed. T790M mutation and activation of bypass signaling pathway are identified the predominant mechanisms of acquired resistance to TKIs. Several approaches have shown promise, such as next-generation EGFR TKIs, immunotherapy, and combinational therapies. And the limited clinical data suggest that all drugs are acceptable safe. Additionally, this review will also focus on the increasingly importance of re-biopsy at the time of disease progression, and the matching effective therapies is related to the identification of specific molecular types of tumors.

Keywords: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) resistance; non-small cell lung cancer (NSCLC); therapeutic strategies

Submitted Mar 07, 2015. Accepted for publication Mar 09, 2015.
doi: 10.3978/j.issn.2305-5839.2015.03.60
View this article at: http://dx.doi.org/10.3978/j.issn.2305-5839.2015.03.60

Introduction

Primary lung cancer is currently the leading cause of cancer-related mortality worldwide. With the rising incidence of lung cancer, the researches related to lung cancer attract more and more attentions. Non-small cell lung cancer (NSCLC) accounts for a high proportion in lung cancer. During the past decades, great progress has been made in research on the treatment of NSCLC including surgical resection, radiotherapy, chemotherapy, molecular-targeted therapy, immune therapy. In fact, due to lack of effective means for early detection of the disease, the majority of NSCLC patients are diagnosed with advanced stage, the surgical resection for the advanced disease are impossible, most patients need systematic therapies such as chemotherapy, molecular-targeted therapy. In the last decade, the emergence of targeted drug epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) for the treatment of NSCLC was a great advance. At present, many large studies have validated the superiority of EGFR TKIs over chemotherapy as first-line therapy for EGFR mutation-positive NSCLC patients (1-4). In these trials, the NSCLC patients with EGFR-activating mutations achieved marked objective responses rate and long median progression-free survival (PFS) by EGFR TKIs.

Although the results of EGFR TKIs for NSCLC have been effective, with the progression of disease, it ultimately may lead to drug resistance. So, how to carry on the subsequent treatment? In this review article, the authors

would like to put forward perspective treatment strategies according to the different types of resistance for NSCLC patients on treatment with TKIs, which is expected to overcome resistance to EGFR TKIs, and prolong survival in patients with a tolerated adverse effect.

Less than 5% patients with EGFR mutations in NSCLC who received TKIs exist the primary resistance (5). However, it is very common for acquired (or secondary) resistance. People who received TKIs with a great initial efficacy, inevitably experience acquired resistance within 1 or 2 years (1-4,6). The possible mechanisms have been investigated in several studies which displayed that the coexistent genetic alterations of cancer-related genes that could explain primary resistance in a small proportion of patients including PIK3CA mutation, EGFR 20 exons insertional mutagenesis, BIM deletion, and 60% unknown factors (5,7-10). Additionally, the EGFR T790M gatekeeper mutation, mesenchymal-epithelial transition (Met) amplification, and ALK fusion were also identified in the treatment-naïve samples (5,11). The acquired resistance to EGFR TKIs may be due to three mechanisms. The first is associated with the development of genetic alterations of the target, the secondary mutation. T790M mutation which prevents drug binding to the domain through steric hindrance, but the combination of ATP and tyrosine kinase was not affected, facilitates continued signal transduction (12,13). The second involves activation of additional signaling pathways, including Met amplification, HER2 amplification, CRKL amplification, AXL overexpression, KRAS mutation, BRAF mutation (13-16). The third is transformation into small-cell lung cancer (17). And there is also 18-30% unknown factors related to the acquired resistance.

Treatments for overcoming first generation EGFR TKIs resistance

The new therapeutic strategies are underlying the mechanisms of TKI resistance. There are many promising treatments are being studied in clinical trials. For many patients (50%), the occurrence of EGFR TKIs resistance is mainly due to an acquired mutation in T790M, and it has been the dominant resistance mechanism in the clinic (18,19). In addition, the emergence of Met overexpression/amplification, HER2 amplification, and transformation to a small-cell carcinoma have also been the significant barrier for the treatment with EGFR TKIs.

Next-generation TKIs

New strategies are developed to overcome the resistance of the first generation EGFR TKIs. The second-generation inhibitors afatinib in the phase 2b/3 randomized controlled trial assessed its efficacy in patients with advanced lung adenocarcinoma with previous treatment failure on chemotherapy and EGFR TKI. The trial identified 390 patients to afatinib, and 195 patients to placebo suggested that although afatinib was failed to show a difference in overall survival (OS) (median OS was 10.8 *vs.* 12 months), the benefit in terms of response rate (RR) and PFS compared with afatinib and placebo was modest significant (RR 7% *vs.* 1% and median PFS 3.3 *vs.* 1.1 months, respectively) (20,21).

Dacomitinib is an irreversible pan ErbB family TKIs of HER1/EGFR, HER2, and HER4. In a phase II trial (22), the overall RR were seen in 5% patients with NSCLC who had disease progressed on treatment with chemotherapy and erlotinib, but no responses were seen in patients with EGFR T790M. Generally, the second generation irreversible EGFR TKIs haven't routinely induced impressive responses.

Recently, the new promising finding, the third-generation EGFR inhibitors, has a breakthrough efficacy for NSCLC patients with acquired resistance to the first generation EGFR TKIs, especially for the T790M positive mutation resistance. AZD9291, in this global phase I trial exhibited a significant result in patients who had failed from the EGFR TKIs. The overall response rate (ORR) was 53%, there were no difference in ORR between different races. In patients acquired resistance to EGFR TKIs with centrally confirmed T790M positive mutation ORR =64%, the disease control rate was 96%. The patients confirmed negative T790M mutation ORR =23%, the patients with T790M positive mutation has longer PFS and better prognosis than that in T790M negative mutation. AZD9291 demonstrated no dose-limiting toxicities and no maximum-tolerated dose were defined. According to the phase I study, the 80 mg once daily dose has been selected for the ongoing phase II study (23). Based on these persuasive results, the FDA will give priority to review AZD9291 for research in patients with metastatic NSCLC who acquired EGFR T790M positive mutation following the disease progression on TKI treatment, and speed up the AZD9291 listing process.

CO-1686, an oral EGFR TKI, is a highly selective and irreversible inhibitor of both sensitizing EGFR active

mutation and the T790M resistance mutation. According to an ongoing phase I/II trial presented at the 2014 American Society of Clinical Oncology (ASCO) Annual Meeting, the ORR was 58% with patients who were acquired T790M resistance mutation from TKIs. And the patients with brain metastases can be benefit as well. At present the median PFS has been more than 12 months, and most patients still alive, we haven't reached the OS. However, the EGFR related adverse events (AEs) in the trial were infrequent and obvious, with the most alarming were hyperglycemia and long QT interval. About 22% hyperglycemia and 7% long QT interval were reached grade 3. Although the CO-1686 has certain toxicity, the limitation can't cover the encouraging results (24).

HM61713 is a novel, oral, mutant-selective inhibitor of EGFR and T790M, but not for EGFR wild-type. This open label phase I trial was showed the patients with T790M mutation-positive the RR was 29.2%, with a disease control rate of 75%. The primary side effects were nausea, headache, and rash (25). HM61713 caused mild side effects and can be controlled easily. The efficacy of HM61713 is not better than the other two—AZD9291 and CO-1686. However, because it is still in the exploration process, along with the subsequent trial is ongoing, find the right dose, we believe its curative effect will be better.

The emergence of three novel drugs will bring a breakthrough for the treatment of NSCLC patients. The three trials are carried out for the patients with advanced NSCLC who acquired T790M mutation resistance after the treatment of the first generation EGFR TKIs. The three drugs were showed favorable benefit and tolerability for the EGFR-mutant patients who had disease progression following the treatment of EGFR TKIs. The patients with T790M positive mutation have an apparent higher RR than the patients without T790M mutation. The adverse effects of AZD9291 and HM61713 were related to the toxicity of EGFR, CO-1686 had a lower extend of EGFR related-toxicity, but there is a tendency for hyperglycemia and prolongation of the QT interval, the mechanisms of the adverse reaction of CO-1686 is unclear, needs to be further confirmed.

Met inhibition

c-Met is one kind of the receptor tyrosine kinase. A large number of reports have shown that the aberrant activation of the c-Met pathway can play an important role in the development of lung cancer (26). Met gene alterations including overexpression, amplification, and mutation are the potential biomarkers targeted for Met inhibits. Many studies indicated Met amplification was closely associated with patients who had acquired resistance with gefitinib/erlotinib (27-29). Met amplification occurs in approximately 3-7% of untreated NSCLC, and this type of resistance termed primary resistance, 21% in previously treated with EGFR TKIs related to acquired resistance (28,29). It's suggested Met amplification and overexpression were an important resistance mechanism of EGFR TKIs. We can overcome the acquired resistance of EGFR TKIs through inhibiting Met, antagonizing the combination with hepatocyte growth factor (HGF), and Met monoclonal antibody. Trials of the HGF binding antagonists (Ficlatuzumab) (30) and Met monoclonal antibody (Onartuzumab) (31) didn't confer any benefit on OS and PFS with Met positive NSCLC patients and finally stopped in failure. However, currently evidence suggests that Met inhibits are effective and safe for the treatment in NSCLC patients with EGFR-mutant, Met-positive who have progressed after EGFR TKIs treatment. For the primary c-Met resistant patients, Met inhibits may be active of this problem. Crizotinib is an orally bioavailable, small-molecule inhibitor of c-Met, the ongoing trials exhibit 33% patients reached partial response (PR), and all the patients showed intermediate and high level Met status (32). The treatment-related AEs include diarrhea, nausea, vomiting, peripheral edema and visual impairment. Most AEs were not severity. So, crizotinib may be a good solution for the NSCLC patients with intermediate and high level Met resistance. INC280 is an oral, highly selective c-Met receptor tyrosine kinase inhibitor for the treatment of solid tumors with activation of the c-Met pathway. The phase I is a dose escalation study evaluated INC280 in patients with Met dependent advanced solid tumors. Recommended drug dose to achieve the best curative effect for 400 and 600 mg bid (33). For the acquired c-Met resistant patients, oral INC280 in combination with the first generation EGFR TKIs showed a good antitumoral activity and well tolerated toxicity in Met-positive patients who had acquired resistance to EGFR TKIs (34). The preliminary reported results support further study for the patients with Met-positive NSCLC.

T790M mutation and Met amplification are two major causes of EGFR TKIs drug resistance, to address these resistance problems, several novel third generation TKIs and Met inhibits are being developed, and the results are found very satisfying. However, we haven't found a solution

for the patients with acquired T790M mutation and Met overexpression resistance at the same time. The ongoing studies indicated that combined treatment with EGFR TKIs and Met inhibits can't achieve clinical benefit for acquired resistance with T790M mutation and Met overexpression together. Further studies are necessary for us to explore the mechanism and new therapeutic strategies.

Immunotherapy

The world authoritative magazine—*Science*, have chosen cancer immunotherapy as one of the Breakthrough of the Year for 2013. Thus began the crazy immunotherapy wave, and bring a totally new dimension of thinking pattern to attacking a cancer cell. It's a novel treatment strategy, and completely different with the conventional radiotherapy, chemotherapy, operation. It focused the immune microenvironment, not the tumor itself. At present the cancer immunotherapy mainly through blocking immune checkpoints to restore immune surveillance and achieve antitumor effect. The checkpoints are Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and programmed cell death protein 1 (PD1), programmed death-ligand 1 (PD-L1) (35-37). CTLA-4 is expressed on the surface of T cell, competitively binding with B7 to decrease the effect of T cell and maintain the steady of immune system. The combination of a CTLA-4 monoclonal antibody—ipilimumab, can reverse this inhibitory effect, reconstruction the immune response of anti-tumor (35,38). A phase II study combined paclitaxel and carboplatin chemotherapy with concurrent or phased ipilimumab and placebo treatments. The median immune-related progression-free survival (irPFS) was 5.7 months for the phased ipilimumab arm *vs.* 4.6 months for chemotherapy and placebo [hazard ratio (HR) =0.72; P=0.05] and 5.5 months for the concurrent ipilimumab arm *vs.* 4.6 months for chemotherapy and placebo arm (HR =0.81; P=0.13). And the median OS for phased, concurrent ipilimumab, and control treatments were 12.2, 9.7, and 8.3 months. The main AEs were associated with the autoimmune diseases caused by excessive activation of T cell (38).

PD-1is an inhibitory receptor expressed on T cells, PD-L1 is expressed on antigen presenting cells (APCs) and tumor cells. Activated T cells secreted inflammatory factor interferon-γ (IFN-γ), which continued to induce the expression of PD-L1 on the surface of tumor cells that limited the activity of T cells through binding to PD-1 (32,33). It suggested that tumor cells used the programmed death 1 (PD-1) pathway to evade immune detection. Thus, PD-1 and PD-L1 inhibitors can block the combination of PD-1 with its ligands, PD-L1 and PD-L2, and released its anti-tumor activity. In an ongoing phase I study reported in 2014, the ASCO annual meeting, Gettinger *et al*. found that treatment with the PD-1 inhibitor nivolumab produced a high RR in NSCLC patients. The objective RR was 30%, median PFS was 47.2 weeks in patients with non-squamous tumors and 15.1 weeks in those with squamous tumors (39). Another ongoing study demonstrated that nivolumab plus erlotinib may provide durable responses and tolerability with relapsed or refractory EGFR mutation advanced NSCLC patients who had previously treated with EGFR TKIs, objective RR was 19% (4/21 patients) and PFS rate at 24 weeks was 47%, median PFS was 29.4 weeks, and OS was not yet reached. The common AEs included rash, diarrhea, increased aspartate amino transferase (AST) or alanine amino transferase (ALT). Only 24% treatment-related AEs were grade 3-4 (40). The study suggested that nivolumab combined with erlotinib may bring durable clinical benefit in chemotherapy-naive and EGFR mutant NSCLC patients who had disease progression on treatment with EGFR TKIs. Our oncologists are currently at a corner of cancer treatment. However, these promising results of immunotherapy have raised hope to many suffers, and give new options for EGFR TKIs resistant patients in the future. Immunotherapy could become an important part of the treatment of patients with NSCLC in the future.

TKIs continuation with chemotherapy

Now the connotation of individualized treatment becomes more and more abundant. Most of the above novel drugs and methods mentioned haven't yet been used routinely in the clinical practice, and at the moment, chemotherapy is still the cornerstone of the cancer therapy, and platinum-based chemotherapy remains the 'standard' therapy beyond progression. Nevertheless, it is still a controversial issue whether EGFR TKIs should be continued with other approaches after the emergence of TKIs resistance. The recently reported trial indicated that the median survival time was longer for TKI continuation beyond disease progression than TKIs discontinuation. 40% patients continued to receive TKIs beyond RECIST based progressive disease and could be clinically stable at least 6 months. However, the rate of disease flare was only 1.3% (6 patients) less than the previous report (41,42).

In patients with isolated disease progression after TKIs resistance, continuation of targeted therapy combine with local surgery or radiotherapy seems to be the preferable option. In patients with disease flare after TKIs resistance, it is necessary to switch to cytotoxic chemotherapy. In patients with steady disease progression continue the TKIs plus chemotherapy, or directly switch to chemotherapy is hotly debated. For this argument, the two ongoing trials, LUX-Lung 5 and IMPRESS draw different conclusions (43,44). The recent study LUX-Lung 5 trial (43) compared efficacy and safety of afatinib plus paclitaxel *vs*. the investigator's choice chemotherapy in patients with NSCLC who had treated with erlotinib/gefitinib and afatinib previously. The trial demonstrated that the treatment with afatinib plus paclitaxel was superior to the single chemotherapy in terms of PFS and ORR (media PFS 5.6 *vs.* 2.8; HR =0.60; P=0.0031; and ORR 32% *vs.* 13%; OR =3.1; P=0.049). Afatinib plus paclitaxel had an acceptable safety profile. Compared with the monotherapy, the combination group had a higher incidence of diarrhea, rash, alopecia, and paronychia. LUX-Lung 5 is the first and largest prospective randomized study, indicating the benefit from continuous EGFR blockade with afatinib in patients with NSCLC who were previously treated with EGFR TKIs and acquired resistance. However, in the IMPRESS study (44), the results demonstrated no benefit for continuing the EGFR TKIs therapy plus chemotherapy compared with chemotherapy alone in patients with EGFR-mutated NSCLC who had acquired resistance with gefitinib. This study indicated that EGFR TKIs shouldn't be continued after disease progression by RECIST criteria. The standard treatment at progression remains platinum-based chemotherapy.

Conclusions

In summary, the diversity of resistance mechanisms in NSCLC decides the various therapeutic regimens. The medical model of immunotherapy combining with classic chemotherapy, targeted therapy, will be the main trend for the future development of global medicine. In addition, the oncogene owned by patients may influence the treatment options. Therefore, the role of re-biopsy at the time of disease progression on treatment with EGFR TKIs is of crucial importance for the subsequent treatment. Utilize re-biopsy to provide us the dynamic alteration of tumors to perform an analysis of the reasons of drug resistance. Finally, to ensure we can carry out the optimal specific therapy according to the changing molecular-typing of tumors.

Acknowledgements

Funding: This study was supported by Natural Science Foundation of China (No. 30971306), Jiangsu Province "333 High-Level Personnel Training Project"; Six Big Talent Peak in Jiangsu Province Project (the seventh batch No. 033), Nantong Social Development Project (No. S2009023; No. S2008017), and Nantong fourth period "226 High-Level Personnel Training Project" project and Rugao Science and Technology Development Project (No. 2013-72-68).
Disclosure: The authors declare no conflict of interest.

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Cite this article as: Xu M, Xie Y, Ni S, Liu H. The latest therapeutic strategies after resistance to first generation epidermal growth factor receptor tyrosine kinase inhibitors in patients with non-small cell lung cancer. Ann Transl Med 2015;3(7):96. doi: 10.3978/j.issn.2305-5839.2015.03.60

