REVIEW

Treatment After First-Generation Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Resistance in Non-Small-Cell Lung Cancer

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Abstract

Systemic treatment is the basic treatment approach to advanced-stage non-small-cell lung cancer (NSCLC), and chemotherapy and targeted treatments are commonly employed in these patients. Recently, positive results achieved with immunotherapy have led to a growing number of treatment options and prolonged survival time. Today, specific tyrosine kinase inhibitors (TKIs), such as erlotinib, gefitinib, and afatinib, which target the epidermal growth factor receptor (EGFR), and the TKI crizotinib, which targets anaplastic lymphoma kinase gene rearrangement, have become the standard treatment among targeted therapies for patients with sensitive molecular anomalies. However, resistance develops against all these agents after a while. Numerous genetic mutations, T790M+ in particular, have been identified as resistance mechanisms against EGFR-TKIs, and researchers are developing specific inhibitors against them. Among those inhibitors, third-generation EGFR-TKIs such as osimertinib and rociletinib have gained prominence due to their high level of effectiveness and low toxicity profile. Besides, systemic chemotherapy and immunotherapy are proper alternatives. A second biopsy during the progression stage and better clarification of the mechanisms causing secondary resistance will enable more successful treatments in the future.

KEYWORDS: Epidermal growth factor receptor, tyrosine kinase inhibitors, resistance, non-small-cell lung cancer

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INTRODUCTION

Lung cancer is still the primary cause of cancer-related death for both sexes worldwide, causing approximately 1.4 million deaths every year [1]. Non-small-cell lung cancer (NSCLC) cases comprise approximately 80%-85% of all lung cancers. More than half of the NSCLC cases are advanced-stage at the time of diagnosis, and those patients are characterized by poor prognosis. Systemic chemotherapy has long been employed as the primary treatment approach for advanced-stage NSCLC. Despite a series of advances in chemotherapy and the application of histology-based approaches in the course of time, median survival time does not exceed 1 year [2]. On the other hand, recent discoveries of somatic mutations in NSCLC and the employment of specific inhibitors against them have led to significant changes in the treatment of advanced-stage NSCLC. Currently, there are two key oncogenic molecular anomalies reflected in routine practice: epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase gene rearrangement.

Epidermal growth factor receptor mutations are observed in approximately 10% of the whole patient group, whereas this rate may go up to 40% among Asians, non-smokers, and in patients who have adenocarcinoma histology. Deletion at exon 19 and point mutation at exon 21 (L858R) are the most common EGFR mutations [3]. The presence of these mutations indicates sensitivity to EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib, gefitinib, and afatinib. The use of erlotinib and gefitinib (first-generation TKIs) and afatinib (second-generation TKIs) in first-, second-, and third-line of treatment in patients with sensitive EGFR mutations has delivered significant survival advantages, and it has become a popular treatment option commonly preferred in routine daily practice (Table 1).

Although remarkable results have been achieved with first-/second-generation EGFR-TKIs, median progression-free survival (PFS) times do not exceed 10-12 months-that is, we encounter acquired resistance after a while [4]. Numerous genetic mutations have been identified as resistance mechanisms, and specific inhibitors are being developed against them. We aim to review resistance mechanisms against first-/second-generation EGFR-TKIs and evaluate potential approaches to overcome this resistance and next-generation EGFR-TKI agents.

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Table 1. EGFR-TKIs

First-generation (reversible) TKIs

  - Erlotinib, gefitinib

Second-generation (irreversible) TKIs

  - Afatinib, dacomitinib, neratinib

Third-generation TKIs

  - AZD9291 (osimertinib), CO-1686 (rociletinib), HM61713, EGF816X, ASP8273

EGFR: epidermal growth factor receptor; TKI: tyrosine kinase inhibitor

Table 2. Secondary resistance mechanisms to first/second-generation TKIs

Secondary mutations of the driver oncogene

  - T790M+ at exon 20

Activation of other signaling pathways

  - Activation of downstream signaling pathways

  • BRAF or PIK3CA mutation

  - Activation of parallel signaling pathways

  • MET, HER-2, and FGFR activation

  - Histological transformation

  • Epithelial-mesenchymal transition

  • As a recourse to the small-cell-type

  - Clonal heterogeneity

TKI: tyrosine kinase inhibitor

EGFR-TKI RESISTANCE AND APPROACHES TO OVERCOMING THE RESISTANCE

EGFR-TKI Resistance Mechanisms

Acquired resistance refers to disease progression after response to EGFR-TKI treatment [5,6]. It has been reported to occur mainly via two methods. The first includes secondary mutations of the driver oncogene, and the second is identified as the activation of bypass signal pathways other than the EGFR pathway [5,7,8]. The T790M gatekeeper point mutation at exon 20 is reported to be the most frequently observed (accounting for approximately 50%-60% of all causes) secondary mutation of the driver oncogene [8,9]. As for the activation of other signaling pathways that continue the carcinogenesis process by bypassing the EGFR pathway, identified primary resistance mechanisms include the activation of downstream signaling pathways such as BRAF (1%) or PIK3CA (2%) [10]; activation of parallel signaling pathways such as c-MET (5%), HER-2 (8%-13%), and FGFR [11,12]; epithelial-mesenchymal transition (6%) or histological transformation manifesting as a recourse to the small-cell type [13]; and clonal heterogeneity [5,7,14,15]. Since acquired resistance mechanisms present such a broad range, a re-biopsy during the progression stage is of key importance to reveal resistance mechanisms (Table 2) [5,16].

Approaches to Overcoming EGFR-TKI Resistance

While deciding on treatment options for a patient progressed during EGFR-TKI treatment, we need to identify the type of progression [5,7]. In this manner, two types of progression have been described: oligoprogression and systemic progression. In oligoprogression, the primary tumor is under control and the disease progresses slowly and includes few intracranial or extracranial asymptomatic metastases. Usually, lesions with limited progression are subjected to a stereotactic ablative radiotherapy and TKI treatment is maintained, which is considered a proper approach in such cases [7]. In systemic progression, however, other treatment alternatives, particularly systemic treatment, are recommended.

Transition to Chemotherapy

Chemotherapy is the most preferred method available today. As quite a large portion of EGFR mutations is observed in adenocarcinoma, pemetrexed is presented as a frequently used chemotherapeutic agent. A non-randomized retrospective study compared single-agent pemetrexed with platinum-based combination chemotherapy and reported that pemetrexed resulted in better PFS [17].

Continuation of EGFR-TKI

Clinical observations indicating that up to 23% of patients undergo rapid progression after the discontinuation of EGFR-TKIs have led to an approach that involves the continuation of TKI treatment [18]. In the ASPIRATION study (phase II) conducted on the EGFR-mutant Asian patients, it has been examined the effectiveness of continuing erlotinib therapy (used as a first-line treatment) after the progression. The study included a total of 207 patients; 81 of the 150 progressed patients continued to receive erlotinib, while the rest of the patients discontinued. The result showed better PFS with the continuation of erlotinib (9.3 months vs. 7.2 months) [19]. Although further randomized studies are required to better clarify this approach, it can be considered, especially for asymptomatic cases with slow progression [5].

Combining the EGFR-TKI with Other Agents

In this combined approach, EGFR-TKIs are combined with chemotherapy or other targeted agents. Among these, the combined-chemotherapy approach has been recommended based on the potential heterogeneity in EGFR-TKI resistance. As part of the combined-chemotherapy approach, patients continue to receive EGFR-TKIs to inhibit sensitive clones, and they are also administered chemotherapy to eliminate EGFR-TKI-resistant clones. The IMPRESS study (phase III) conducted in this article randomized patients progressed under the gefitinib treatment into cisplatin/pemetrexed or cisplatin/pemetrexed/gefitinib. Chemotherapy combined with gefitinib did not significantly contribute to survival (PFS: 5.4 months for both arms), concluding that platinum-based combined chemotherapy was the standard approach [20].

Combining the EGFR-TKI, which is administered as a first-line treatment, with other targeted agents after progression seems to be attractive as it has potentially advantages of the blocking of progression by two different ways. Cetuximab has been a prominent agent in this manner. After a preclinical study [21] showed that an afatinib/cetuximab combination overcame erlotinib resistance, a phase Ib study was conducted on this combination. This study, which included 126 cases that progressed under erlotinib/gefitinib, obtained a response rate and PFS of 29% and 4.7 months, respectively. Analysis

Table 3. Clinical studies conducted with third-generation TKIs

Study	TKI	Phase	ORR (%)			DCR (%)			PFS (months)		
			Total	T790M-	T790M+	Total	T790M-	T790M+	Total	T790M-	T790M+
AURA [28]	Osimertinib	I/II	51	21	61	84	61	95	8.2	2.8	9.6
AURA2 [29]	Osimertinib	II	64	NA	64	90	NA	NA	NA	NA	NA
Austrian Study [31]	Osimertinib	II	93	NA	93	100	NA	100	NA	NA	NA
AURA3 [32]	Osimertinib	III		71 vs. 31							10.1 vs. 4.4
TIGER-X [34]	Rociletinib	I/II	NA	29	59	NA	59	93	NA	5.6	13.1

TKI: tyrosine kinase inhibitor; ORR: objective response rate; DCR: disease control rate; PFS: progression-free survival; NA: not available

of patients as T790M+ or T790M- revealed similar results between the two groups [22]. On the other hand, another phase I/II study with a similar patient group reported no response with the erlotinib/cetuximab combination after erlotinib resistance [23]. Therefore, further studies are required to expand the cetuximab combination to all agents and to the whole patient group.

Second-Generation EGFR-TKIs
With resistance developed against first-generation EGFR-TKIs, second/third-generation TKIs have attracted all the attention. Afatinib, dacomitinib, and neratinib are the main second-generation TKIs, and they are able to bind irreversibly to EGFR with a high affinity. In addition, they block other members of the HER family, namely HER-2, HER-3, and HER-4. Relevant clinical studies have been conducted after preclinical studies demonstrated that those agents reversed first/second-generation EGFR-TKI resistance [24]. Regarding clinical studies conducted with afatinib, there is the LUX-Lung-1 study, which compared afatinib with placebo in patients progressed under EGFR-TKI treatment. Despite better PFS (3.3 vs. 1.1 months), the overall survival presented no significant difference (10.8 vs. 12.0 months) [25]. Although the LUX-Lung-1 and LUX-Lung-6 studies that examined the effectiveness of afatinib as a first-line treatment demonstrated its usefulness, the second-line treatment results fell short of expectations [26]. Likewise, studies on dacomitinib and neratinib could not present satisfactory results. This is considered to be associated with the high gastrointestinal and skin toxicities of this group of drugs, caused by their narrow therapeutic index. For instance, it has been reported that afatinib equally affected WT-EGFR and EGFR T790M+, and thus, the side effects limited T790M+ inhibition at therapeutic doses [27].

Third-Generation EGFR-TKIs
Primary, third-generation EGFR-TKIs include osimertinib (AZD9291), rociletinib (CD-1686), HM61713, EGF816, and ASP8273, which are mutant-selective, sparing the wild-type EGFR and targeting T790M in particular. Their most important characteristic is a quite low affinity to the wild-type EGFR. This eliminates the narrow therapeutic index problem related to toxicity, which is observed in first- and second-generation EGFR-TKIs.

Osimertinib (Tagrisso, AZD9291) is an irreversible EGFR-TKI that targets the cysteine-797 residue in the EGFR's ATP-binding site and binds to this site with a covalent bond. Following preclinical studies demonstrating its high effectiveness on

T790M mutation, in particular, clinical studies have been conducted with osimertinib. The first was a phase I study (AURA) that reported an overall response rate (ORR) of 51% and a disease control rate (DCR) of 84% with osimertinib in progressed patients with a history of EGFR-TKI treatment. With respect to T790M status, ORR, DCR, and PFS were found to be 61%, 95%, and 9.6 months in T790M+ patients and 21%, 61%, and 2.8 months in T790M- patients, respectively. Diarrhea (47% for all grades), rash (40%), and nausea (22%) were the most common side effects; however, dosage reduction due to side effects and treatment discontinuation rates were reported to be low (7% and 6%, respectively) [28]. AURA-2 is a phase II study that investigated the effectiveness of osimertinib on T790M+ patients progressed under EGFR-TKI treatment. The total response rate and DCR were 64% and 90%, respectively, PFS did not reach the median value, and side effects were reported as diarrhea (34% for all grades), rash (40%), and interstitial lung disease (1.9%), which were similar to those of previous studies [29]. Osimertinib has also been reported to be highly effective in central nervous system (CNS) metastases. A combined analysis of AURA and AURA-2 studies evaluated 39 metastatic patients and found the ORR as 56% and 64% in metastatic and non-metastatic patients, respectively [30]. Following these developments, osimertinib received an accelerated approval by the Food and Drug Administration (FDA). As part of another study based on real-life data, which was presented at the annual American Society of Clinical Oncology meeting in 2016, 30 T790M+ patients progressed after the first/second-line EGFR-TKI received osimertinib with 23% complete response, 70% partial response, and 7% stable disease response rates [31]. In the AURA-3 trial, osimertinib was compared with platinum + pemetrexed as second-line therapy in 410 patients with T790M+ who had progressed on EGFR-TKI treatment. Osimertinib showed superiority to chemotherapy in terms of response rate (71% vs. 31%) and PFS (10.1 months vs. 4.4 months) in whole group. This superiority has also been observed in patients with brain metastasis [32]. There are ongoing studies on osimertinib in the article of different lines, including adjuvant therapy (Table 3).

Rociletinib (CO-1686) is another third-generation EGFR-TKI. Rociletinib is EGFR-mutant-selective; it targets commonly monitored EGFR mutations, particularly T790M, and spares the WT-EGFR at the same time [33]. As part of a phase I/II study (TIGER-X), researchers carried out a dosage determination trial for 130 EGFR-mutant NSCLC patients who acquired resistance after EGFR-TKI treatment. This study employed a

re-biopsy to document secondary resistance. The T790M+ patient group presented an ORR and PFS of 59% and 13.1 months, which were reported as 29% and 5.6 months, respectively, for the T790M- patient group. Rociletinib also exhibits a reasonable toxicity profile with hyperglycemia (47% for all grades), nausea (35%), and fatigue (24%) as the most prevalent side effects (Table 3) [34]. The hyperglycemic side effect is suggested to be primarily associated with the metabolite M502, which causes hyperglycemia by blocking the insulin growth factor type-1 receptor and insulin receptor [33]. Rociletinib has also been demonstrated to be effective on CNS metastases. One hundred and seventy (42%) of 401 patients who received rociletinib were CNS-metastatic, and their response rate was reported as 41% [35]. After such developments, rociletinib was granted a "breakthrough therapy designation" by the FDA. There is an ongoing phase III study (TIGER-3), as part of which rociletinib is compared with a chemotherapy regimen preferred by the researcher for patients progressed after EGFR-TKI treatment or chemotherapy [36].

Other third-generation EGFR-TKIs, namely HM61713, EGF816, and ASP8273, are also irreversible TKIs; they are EGFR-mutant-selective, targeting commonly monitored EGFR mutations and T790M, in particular, and sparing the WT-EGFR. These agents are reported to show a 60-fold higher affinity to the mutant EGFR than does the WT-EGFR. Phase I studies conducted on these agents have reported similar response rates, survival rates, and toxicity characteristics to those observed with osimertinib and rociletinib [5,7].

Positive results obtained with all these agents both are promising for the resistant disease and show the importance of revealing resistance mechanisms by a re-biopsy in the case of progression and planning of treatment accordingly. Nevertheless, a re-biopsy sometimes becomes impossible due to the location of the primary tumor or refusal by the patient. In such cases, molecular analyses may be performed based on the circulating tumor cell DNA (ctDNA) through a liquid biopsy [37]. As the patients may potentially develop resistance to EGFR-TKIs after a while, it is useful to carry out repetitive tissue/liquid biopsies when progression takes place after each treatment.

Approaches to Other Pathways
C-MET activation is a significant cause of secondary resistance to EGFR-TKI treatment. This resistance mechanism, which frequently manifests as gene amplification, represents approximately 20% of all cases. As part of a phase II study conducted with capmatinib (INC280), a potent and selective c-MET inhibitor, c-MET-positive patients who progressed after EGFR-TKI treatment were administered capmatinib + gefitinib with 18% partial response rate, 62% stable disease rate, and 80% DCR [38]. There is an ongoing phase I/II study comparing capmatinib with chemotherapy [38].

Immunotherapy is an alternative treatment option when the patient develops resistance to first/second-generation EGFR-TKIs. Regarding immunotherapy, which has recently drawn a great deal of attention, a series of studies have been conducted with various immune checkpoint inhibitors in the advanced stage of the disease, and some of those agents have been included in treatment guides upon the FDA's approval [39,40]. Moreover, preclinical studies have demonstrated that the mutant EGFR directs the programmed death-ligand 1 expression, and the blocked PD-1 receptor increased survival in EGFR-mutant rats [7]. This is considered likely to take place through the stimulation of tumor cell death by EGFR-TKI treatment, followed by the stimulation of the immune system by a release of antigens [41]. Based on these findings, a limited number of patients were administered a combination of nivolumab (anti-PD-1 monoclonal antibody) and erlotinib, and the ORR was reported as 19% (three out of four patients with a response had progressed under erlotinib treatment) [42].

There are other approaches combining third-generation EGFR-TKIs with immune checkpoint inhibitors. Among them, a phase I study combining osimertinib and durvalumab reported a 57% partial response rate in a group of T790M+ patients [43]. Although the combination of these two groups of drugs offers theoretical and clinical advantages, it also brings about the risk of increased toxicity. Therefore, a clarification of the optimal dosage, scheme, and order of administration will reduce concerns in this regard.

In conclusion, first/second-generation EGFR-TKIs have long become the standard approach to the treatment of advanced-stage NSCLC patients with a sensitive EGFR mutation. Nevertheless, as secondary resistance-and hence, progression-becomes inevitable after a while, the principles of approach should be better established. Today, third-generation EGFR-TKIs are the most frequently employed approach in the transition to chemotherapy, and they are very promising thanks to their highly specific activity and low toxicity profiles. Besides, they also constitute alternative options in the transition to immunotherapy and in combination with other agents. Further clarification of the molecular patterns of secondary resistance will enable more specific treatments in the future.

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