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REVIEW ARTICLE

Advances in the management of acquired resistance to EGFR-TKI in non-small cell lung cancer

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Abstract

Drugs that specifically target the tyrosine kinase domain of epidermal growth factor receptor (EGFR), such as erlotinib or gefitinib, have exhibited striking efficacy in non-small cell lung cancer (NSCLC) patients harboring activating EGFR mutations. However, acquired resistance inevitably develops and remains a serious barrier for the successful management of patients with this disease. Multiple mechanisms are reportedly involved in the process of acquired resistance, which provide new insights into the management of EGFR-tyrosine kinase inhibitor (EGFR-TKI) resistance. Here, we provide an overview of the emerging treatment approaches for patients with EGFR-TKI resistance.

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With the identification of epidermal growth factor receptor (EGFR) mutations that are correlated with the sensitivity to EGFR-targeted tyrosine kinase inhibitors (EGFR-TKIs) over the past decade [1–2], the development of targeted therapy for patients with these oncogenic driver mutations has tremendously improved the treatment of advanced non-small cell lung cancer (NSCLC). A series of randomized trials have successfully demonstrated that EGFR-TKIs can significantly improve the objective response rate (ORR), progression-free survival (PFS), and quality of life (QoL), with less toxicity than standard chemotherapy, in NSCLC patients harboring activating EGFR mutations [3–10]. Despite initially dramatic EGFR-TKI activity, most, if not all, patients inevitably develop disease progression after 6 to 12 months [3, 6], known as acquired resistance. Multiple mechanisms for acquired resistance have been identified that can be broadly divided into four categories: (1) secondary T790M mutation [11–12], the gatekeeper mutation in EGFR; (2) activation of bypass signaling (e.g., c-MET amplification [13–14], hepatocyte growth factor (HGF)-mediated MET activation [15], or HER2 amplification or mutation [16]; (3) activation of downstream signaling, including the PI3K-AKT-mTOR [17–18] and RAS-RAF-MEK-ERK pathways [19–20]; and (4) phenotypic alterations, including epithelial to mesenchymal transition (EMT) [21–22] and small cell lung cancer (SCLC) transformation [23–24].

Although cytotoxic chemotherapy remains the standard management when patients become resistant to EGFR-TKIs, the advances in knowledge of the mechanisms involved in acquired resistance provide new insights into the management of EGFR-TKI resistance and development of more effective treatment strategies to overcome EGFR-TKI resistance. Therefore, the present review mainly focuses on the emerging treatment approaches for patients with EGFR-TKI resistance.

Continued EGFR-TKI treatment beyond progression

In clinical practice, it is reasonable to discontinue chemotherapy when patients experience disease progression. However, a similar approach for EGFR-TKI treatment has not been clearly established. Indeed, withdrawal of EGFR-TKIs was associated with a clinically significant risk of accelerated disease progression (disease flare) in clinical practice [25]. The hypothesis that some clones remain sensitive to EGFR-TKIs at the time of disease progression may partly explain the benefits of continued EGFR-TKI treatment.

Currently, continued EGFR-TKI treatment options

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include local therapy plus EGFR-TKIs, conventional chemotherapy plus EGFR-TKIs, or continuation of only EGFR-TKI. Retrospective studies have found that continuing EGFR-TKIs is superior to switching to chemotherapy for patients who experience gradual progression [26]. However, switching to chemotherapy appeared to be the better option in patients with symptomatic or rapid radiographic progression [26]. Meanwhile, if local progression develops, continued EGFR-TKI treatment in addition to local therapy can be considered [26–28].

Results of the IMPRESS trial were recently released at the European Society of Medical Oncology (ESMO) conference in 2014. To the best of our knowledge, the IMPRESS trial was the first randomized trial to compare continued EGFR-TKIs (gefitinib) in addition to chemotherapy versus chemotherapy alone in patients harboring activating EGFR mutations after first-line treatment failure with gefitinib. However, there was no significant difference between combination therapy and chemotherapy alone in terms of PFS [5.4 vs. 5.4 months; hazard ratio (HR), 0.86; 95% confidence interval (CI), 0.65–1.13; P = 0.273] or ORR (31.6% vs. 34.1%; P = 0.760). Moreover, chemotherapy alone was better in terms of overall survival (OS) (14.8 vs. 17.2 months; HR, 1.62; 95% CI, 1.05–2.52; P = 0.029); however, the OS data were collected over a short period, and the post-study treatment tended to favor chemotherapy alone. Several prospective clinical trials are currently underway to assess the benefits of continued erlotinib, combined with chemotherapy, beyond disease progression in NSCLC patients with acquired resistance (NCT01928160, NCT02064491, and NCT02098954, www.clinicaltrials.gov). These trials aim to establish the role of continued erlotinib in addition to chemotherapy in this setting.

Targeting EGFR mutations at T790M

EGFR T790M mutations are the most common cause and account for more than 50% of cases of acquired resistance [11–12]. Second-generation irreversible EGFR inhibitors (e.g., afatinib, dacomitinib, and neratinib) can covalently bind the tyrosine kinase (TK) domains and inhibit EGFR, HER2, and HER4; thus, they are expected to overcome the acquired resistance imparted by T790M mutations. However, their role in acquired resistance remains unclear [29–30]. Intriguingly, the combination of afatinib and cetuximab (an EGFR monoclonal antibody) demonstrated remarkable clinical activity in NSCLC patients with failed erlotinib or gefitinib treatment in a recent study [31]. In this study, 11/35 patients with EGFR T790M mutations achieved confirmed partial response (PR). At present, the most promising strategy that overcomes the acquired resistance due to T790M mutations is the use of third-generation EGFR-TKIs.

CO-1686 is an oral, covalent TKI that targets both activating EGFR mutations and T790M. In a phase I/II study [32], CO-1686 exhibited good tolerability and efficacy against proven T790M EGFR mutant NSCLC. At a dose of 900 mg bid, 6 of 9 (67%) patients with T790M mutation with failed EGFR-TKI treatment achieved PR, and 2 (22%) achieved stable disease. The ORR was approximately 58%; although the median PFS has not yet been reached, the estimated PFS is currently more than 12 months. Hyperglycemia was the most concerning adverse effect of CO-1686 (22%, > grade 3), but it can be managed well with oral hypoglycemics and/or dose reduction.

AZD9291 is another oral, irreversible, third-generation inhibitor of both activating EGFR mutations and T790M. In a more recent phase I study [33], the ORR of AZD9291 in 89 patients with acquired resistance to EGFR-TKIs (centrally confirmed T790M mutations) was promising, as high as 64% (95% CI, 53%–74%) (confirmed and unconfirmed). Diarrhea (14%, any grade) and rash (24%, any grade) were the most common toxicities.

HM61713 is also an oral, irreversible inhibitor for both activating mutations and T790M, but not EGFR wild-type. The side effects of HM61713, including rash and diarrhea, were milder than first-generation TKIs. In a phase I trial [34], HM61713 was well tolerated and showed promising efficacy in patients with T790M mutations with prior failed EGFR-TKI treatment. Nevertheless, the overall response rate of HM61713 was 32%, appearing inferior to both CO-1686 and AZD9291.

Targeting bypass and downstream pathways

c-MET

Activation of MET receptor signaling is another mechanism of acquired resistance, and approximately 5%–22% patients with acquired resistance have MET amplification [14, 18]. In a phase II trial [35], erlotinib plus tivantinib [a selective, oral, small-molecule inhibitor of MET receptor TK (RTK)] failed to prolong PFS compared with erlotinib plus placebo in NSCLC patients who had been previously treated with a chemotherapy regimen but were naive to EGFR-TKIs (3.8 versus 2.3 months; HR, 0.81; 95% CI, 0.57–1.16). Notably, in another phase II trial [36], onartuzumab (MetMAb) plus erlotinib improved both PFS (HR, 0.53; P = 0.04) and OS (HR, 0.37; P = 0.002) in MET-positive patients who had previously received chemotherapy. However, the phase III METLung study showed that onartuzumab plus erlotinib failed to improve PFS (2.7 vs 2.6 months; HR, 0.99; P = 0.92), OS (6.8 vs 9.1 months; HR, 1.27; P = 0.068), or ORR (8.4% vs 9.6%; P = 0.63) compared with erlotinib alone [37]. It should be noted that the clinical trials described did not prospectively assess the

efficacy of combination treatment in a population with acquired resistance. Recently, several ongoing clinical trials that evaluated the efficacy of MET-TKIs in addition to EGFR-TKIs in this population showed promising results. In 35 patients with EGFR-mutant NSCLC who progressed with EGFR-TKIs, 4 patients achieved PR when treated with cabozantinib (an oral MET/VEGFR2/RET inhibitor) plus erlotinib (2 confirmed, 2 unconfirmed). In a single-arm phase Ib/II study, INC280 (an oral MET inhibitor) in combination with gefitinib was well tolerated in patients who progressed with EGFR-TKIs due to MET (MET amplification or MET overexpression) and exhibited promising results [PR observed in 6/41 (15%) evaluable patients; 5 confirmed, 1 unconfirmed]. A prospective clinical trial evaluating an anti-HGF-directed monoclonal antibody (rilotumumab) in this setting is also underway (NCT01233687).

HER2

HER2 is a member of the EGFR family of RTKs, which also includes EGFR (HER1), HER3, and HER4. EGFR-TKI resistance can also be induced by HER2 mutation, gene amplification, or protein overexpression [16, 38]. Several HER-2 targeted agents, including lapatinb, neratinib, and dacomitinib, showed modest benefits as monotherapy in NSCLC patients [29–30, 39]. Notably, combination treatment (afatinib and cetuximab) showed promising efficacy in NSCLC patients, as already discussed [31]. Several clinical trials are underway to assess the efficacy of HER-2 targeted agents in select populations [HER2 overexpression, HER2 fluorescence *in situ* hybridization (FISH) positive, or HER2 gene mutation] of NSCLC patients (NCT00004883, NCT00758134, and NCT01827267). However, the role of HER-2 targeted agents in acquired resistance needs to be further established.

PI3K-AKT-mTOR pathway

The PI3K-AKT-mTOR pathway is downstream of the RTKs (EGFR, MET, HER2) and plays an essential role in proliferation, survival, and apoptosis (Fig. 1). Therefore, the hypothesis that PI3K-AKT-mTOR pathway activation can lead to EGFR-TKI resistance is reasonable. Preclinical studies have already demonstrated that PIK3CA mutations and loss or reduced expression of PTEN can result in EGFR-TKI resistance [40–41].

Several prospective trials are ongoing to evaluate the efficacy of BKM120, an oral PI3K inhibitor, in combination with gefitinib (NCT01570296) or erlotinib (NCT01487265) in patients with NSCLC who progress with single-agent EGFR-TKIs and meet the clinical definition of EGFR-TKI resistance.

MK-2206 is an oral AKT inhibitor, and preclinical studies have found a synergistic effect in erlotinib-insensitive cell lines treated with MK-2206 and erlotinib [42]. In a phase II study including patients with progression following prior benefit from erlotinib, MK-2206 in combination with erlotinib showed modest activity [RR, 9% (4/46); median PFS, 4.4 months; 95% CI, 2.7–6.6 months] in EGFR-mutant patients. It is of note that the combination treatment also showed promising activity in EGFR wild-type patients (median PFS, 4.6 months; 95% CI, 2.9–8.5 months) [43]. Evaluation of the efficacy of MK-2206 combined with gefitinib is also underway in a phase I study (NCT01147211).

Everolimus is an oral, potent inhibitor of mTOR, and preclinical studies have exhibited promising efficacy of everolimus in EGFR-TKI resistant cell lines [44–45]. However, the efficacy of combined treatment was very limited in the presence of acquired resistance [46]. A phase I trial is underway to assess the efficacy of afatinib plus sirolimus in NSCLC patients harboring EGFR mutations and/or progressing with EGFR-TKIs (gefitinib or erlotinib) (NCT00993499).

RAS-RAF-MEK-ERK pathway

The RAS-RAF-MEK-ERK pathway is reportedly another critical downstream signal pathway of RTKs in addition to the PI3K-AKT-mTOR pathway (Fig. 1). Clear evidence has demonstrated that KRAS mutations are associated with primary resistance to EGFR-TKIs [20]. However, KRAS mutations and EGFR mutations are mutually exclusive in EGFR-mutant patients with acquired resistance [12, 17, 19]. Notably, a recent study found that 2 of 195 (1%) EGFR-mutant patients with acquired resistance had

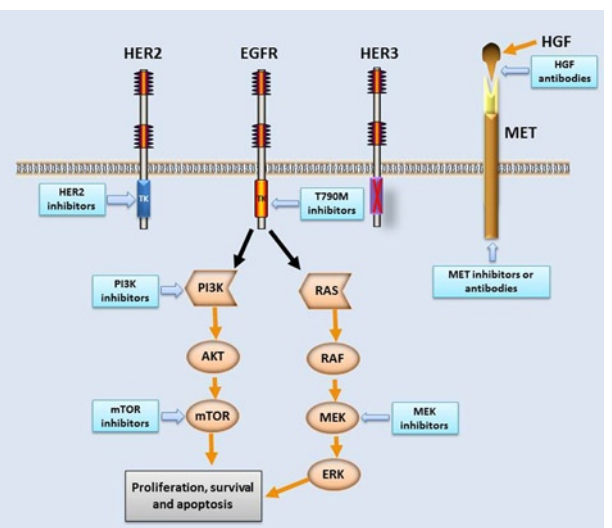

Fig. 1 Mechanisms of acquired resistance to epidermal growth factor receptor-targeted tyrosine kinase inhibitors (EGFR-TKIs), including activation of bypass signaling (c-MET, HGF, HER2, HER3 etc.) or downstream signaling (PI3K-AKT-mTOR pathway and RAS-RAF-MEK-ERK pathway). Targets for potential combined therapeutic strategies to overcome resistance are marked

mutations in BRAF (a member of the RAF kinase family). Selumetinib, an inhibitor of MEK1/MEK2, in combination with gefitinib is currently being evaluated in a phase I/II trial including EGFR-mutant NSCLC patients with acquired resistance to EGFR-TKIs (NCT02025114).

Immune therapy

Immune therapy that blocks the immune checkpoints, such as CTLA-4, programmed death-1 (PD-1), and programmed death-ligand 1/2 (PD-L1/2), is currently a hot topic in NSCLC treatment. Preclinical studies have demonstrated that chemotherapy and radiotherapy could actively cause immunogenic tumor cell death and, therefore, prime the immune system and create an environment better suited for T-cell activation [47]. Moreover, preclinical data showed that EGFR-driven tumors create a favorable microenvironment for proliferation of tumor cells by inducing PD-L1 expression, and blockade of the PD-1 pathway significantly increased overall survival of EGFR-mutant mice [48]. Blocking antibodies against PD-1 or PD-L1 as monotherapy has been encouraging in NSCLC patients [49–50]. Several clinical trials are underway to estimate the efficacy of nivolumab (BMS-936558, an anti-PD-1 monoclonal antibody) in combination with EGF816 (a covalent TKI that targets both activating EGFR mutations and T790M) in NSCLC patients with T790M mutations (NCT02323126) or erlotinib in EGFR-mutant NSCLC patients (NCT01454102). MPDL3280A (an anti-PD-L1 antibody) in combination with erlotinib is also being assessed in patients with NSCLC in a phase Ib trial. The results of these trials, together with other anti-PD-1/PD-L1 monoclonal antibodies [e.g., lambrolizumab (MK3475) and MEDI-4736] as part of various strategies (monotherapy or combination therapy) and in various settings (first- or second-line), will be released in the near future and may dramatically change the treatment paradigm of NSCLC patients.

Conclusions and perspectives

Despite the tremendous success of treatment with EGFR-TKIs (erlotinib and gefitinib) in NSCLC patients harboring activating EGFR mutations, the development of acquired resistance inevitably occurs and remains a serious barrier for the management of these patients. Multiple mechanisms have been demonstrated in the process of acquired resistance; however, it is still too early to celebrate the removal of this barrier because the prognosis of these patients is still very poor.

For patients with acquired resistance due to secondary T790M mutations, third-generation EGFR-TKIs (e.g., CO-1686, AZD9291, and HM61713) have the potential to dramatically change the treatment paradigm for patients who progress with treatment using first-generation EGFR-TKIs. It is of note that the new EGFR-TKIs could target both activating EGFR mutations and T790M; therefore, it remains unclear which is better for patients with activating EGFR mutations. We believe that the ongoing trials (TIGER 1: CO-1686 versus erlotinib in EGFR-mutant NSCLC patients, NCT02186301; FLAURA: AZD9292 versus erlotinib or gefitinib in EGFR-mutant NSCLC patients, NCT02296125) will definitively answer this question. For patients who develop acquired resistance due to activation of bypass signaling or downstream signaling, the corresponding antibodies or small molecular TKIs, in combination with EGFR-TKIs, are expected to be effective. For patients with an EGFR-mutant tumor that transforms from NSCLC into SCLC, standard SCLC treatment appears to be effective [17]. For patients who progress with EGFR-TKIs due to EMT, histone deacetylase (HDAC) inhibitors (entinostat) showed promising efficacy, but new drugs that target EMT more are still needed. Moreover, recently developed immune therapies that block immune checkpoints and heat shock protein 90 (Hsp90) inhibitors that block Hsp90 have also been encouraging for the management of acquired resistance.

Regardless, a "one fits all" approach to the treatment of NSCLC is no longer an option, and the complexity, heterogeneity, dynamic nature, and multiple mechanisms of acquired resistance emphasize the importance of re-biopsy with disease progression and changes in clinical behavior, which will help us more accurately manage NSCLC patients on an individualized basis.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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