Original Article

Review of treatment management for patients with Epidermal growth factor receptor (EGFR) mutated non-small cell lung cancer

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ABSTRACT

Introduction: Nowadays, lung cancer is the most popular cause of cancer-related deaths all around the world. However, the new progressions in determining specific oncogenes with driver mutations, such as the Epidermal Growth Factor Receptor (EGFR) gene has ameliorated the prognosis of non-small-cell lung cancer formation. Studies on these bio-markers have targeted the pathways in which drugs act as specific inhibitors to cancer progression. Tyrosine Kinase Inhibitors (TKIs) against EGFR, such as Erlotinib and Gefitinib, have been able to provide considerable progression free survival (PFS) for patients by stopping these tumour boosting properties in non-small-cell lung cancers. Unfortunately, persistent resistance mechanisms have made these agents ineffective in their treatment. To overcome resistance, new multiple agents were developed, but the treat of resistance still looms over each new advance in EGFR inhibition based targeted therapy. This article reviews the 1st and 2nd Generation EGFR inhibition, common resistance mechanisms, 3rd Generation EGFR inhibitor and subsequent treatment option.

Keywords: EGFR, Disease management, Non-small cell lung cancer.

Introduction

Overview of Lung Cancer Management with EFGR inhibitors

By far, lung cancer has been considered as the single most common cause of cancer-related mortality with nearly 1.8 million (nearly 20%) new cases worldwide in 2012 [1].

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Although, surgery is considered as the most optimal treatment for lung carcinoma, the emergence of molecular receptor targeted therapy has brought major breakthroughs in patient survival, particularly for the more common (~80%) non-small cell lung cancer (NSCLC). Hence, it has now become a pre-requisite for NSCLC patient to undergo tumor screening for known biomarkers that predict sensitivity and prognosis to targeted therapy prognosis respectively [2]. In the last decades, most of the research studies have examined the epidermal growth factor receptor gene (EGFR) mutations which have been prevented successfully by EGFR tyrosine kinase inhibitors (TKI). EGFR expression has emerged as one of the most likely target to inhibit cancer progression and is widely reported in NSCLC patients of Asian

heritage. Subsequently, these patients produce very encouraging responses when treated with the corresponding TKI agent. Unfortunately, the resistance to these TKI agents occur quite frequently leading to a complex management plan for these patients. In this review, the 1st, 2nd and 3rd generations of EGFR inhibitors, the resistance mechanisms that inhibit their use, and finally, the remaining options when all the TKI agents have been exhausted, have been reviewed.

EGFR Inhibitors- 1st and 2nd Generations

EGFR belongs to a family of receptor tyrosine kinases that can trigger a vast array of signaling pathways leading to cell growth, proliferation and survival. Such flow-on pathways include the RAS-RAF-MEK-ERK or MAPK pathway and the PI3K-AKT-mTOR pathways. For EGFR activation, there exist three major mechanisms which include: enhancing the expression of EGFR on malignant cells; increasing ligand production by malignant cells; and initiating the mutations of EGFR within malignant cells [3, 4]. Although it was initially thought that the overexpression of EGFR was the main therapeutic target for NSCLC, it was eventually discovered that the real modifier of cancer progression in EGFR positive patients was the activating mutations in the tumors. The most common activating mutations occur at Exon 19 (particularly E746-A750del) and amino acid substitution in exon 21 (leucine to arginine at codon 858 (L858R) offering significant target for cancer suppression. Inhibiting these pathways halts disease progression and improves recovery in EGFR mutated NSCLC patients [5, 6]. Thus, molecular translational research has developed agents that are capable of deactivating these mutations. These inhibitors became known as EGFR TKI's.

Gefitinib and Erlotinib were the first generation of EGFR TKIs which were developed, and both are reversible competitive inhibitors of ATP for the tyrosine kinase domain of EGFR resulting in blockade of downstream pathways. EGFR TKI's were earlier used in all EGFR positive patients to explore efficacy and safety in NSCLC management. As trials matured, characteristics that correlated with optimal response such as adenocarcinoma histology, Asian ethnicity and minimal smoking history were identified [7-9]. This benefitted the medical fraternity as guidelines showing which population benefited most from EGFR TKI'S. Subsequently, the first-generation of EGFR TKI's (gefitinib and erlotinib) became the standard for first-line management of the patients with advanced *EGFR*-mutated NSCLC. Unfortunately, there was a major obstacle in EGFR TKI management. Although these agents improve progression-free survival, the resistance usually develops within 12 months of therapy [10]. There were 2 kinds of resistance observed in clinical trials which included primary and acquired resistance. Along with other gene mutation in the downstream of EGFR signaling pathway, such as the KRAS mutation, the primary resistance usually occurred in EGFR wild-type patients. The resulted mutation is mostly due to the mutation in exon 20 after continued treatment, that is recognized as the replacement of threonine at position of 790 by methionine (T790M) in the tyrosine kinase functional domain of EGFR. The T790M mutation placed in the ATP-/drug-binding cleft can activate the resistance by blocking the binding of Gefitinib and kinase domain [11, 12]. This prevents TKI from inhibiting EGFR thus allowing disease progression. Along with T790M, other kinds of resulted mutations, like c-MET amplification, D761Y, L747S, and T854A, were also recognized in Gefitinib-resistant patients. All these acquired resistance mechanisms will render EGFR inhibitors ineffective in the battle for survival.

To overcome resistance, 2nd generation of EGFR Inhibitors like Afatinib were developed to offer options for EGFR mutated NSCLC patients. Afatinib forms covalent irreversible bonds with their target that intensifies their efficiency by inhibiting EGFR signaling more effectively. Afatinib which is considered as the only ascertained drug indicating an intensified overall survival (OS) can treat patients with an exon 19 deletion compared to chemotherapy, i.e. 31.7 (95% confidence interval (CI) of 28.1–35.1) vs. 20.7 (95% CI of 16.3–25.6) months, respectively [13, 14]. However, for the patients with a L858R mutation, OS can be achieved by afatinib and chemotherapy treatment with OS 22.1 months for afatinib; 95% CI of 19.6–25.4 vs. 26.9 months for chemotherapy with 95% CI of 23.2–31.7 [15]. Unfortunately, afatinib was not spared from resistance mechanisms as well. Most resistance mechanisms for afatinib are similar to 1st generation EGFR inhibitors whereby both T790M and MET gene amplification were potent resistance mechanisms that rendered minimal benefits of patients. Multiple other mechanisms such as phosphorylation of Src family kinase (SFK) [16] and autocrine signaling of the JAK/STAT 3 pathway [17] were also contributory to afatinib resistance, but are quite rare among patients.

3rd Generation EGFR Inhibitor

The emergence of resistance mechanism in both 1st and 2nd Generation of EGFR TKI'S has led to the development of third-generation TKIs targeting the most common resistance mechanism, T790M mutation. EGFR-TKIs with the capacity to bind T790M mutated receptor and inactivating it, were synthesized and successfully tested in patients with respective acquired resistance. Additionally, third-generation TKIs have shown high tolerability because of their higher ability to spare EGFR wild-type counterpart [18]. Therefore, 3rd Generation TKIs have brought fewer side effects and better quality of life for the patients. This was demonstrated in a study in which EGFR resistant patients with T790M mutations were treated by osimertinib, a third generation egfr inhibitor, that showed to have superior OS and better tolerability to standard platinum–pemetrexed chemotherapy [19, 20]. The high effectiveness of osimertinib in patients with T790M-mediated AR led to its increased approval by the FDA in November 2015 [21]. Lately, the findings of the confirmatory phase III examination of osimertinib versus platinum-based chemotherapy were presented. The effectiveness of osimertinib as a standard treatment for T790M-positive NSCLC patients after disease progression on a first- or second-generation EGFR TKI was clearly demonstrated by the obtained findings [22-24].

Along with the three EGFR TKIs advocated in the frontline setting, the EGFR-mutant NSCLC paradigm was changed in the late 2017 with the phase 3 FLAURA outcomes at the 2017 European Society of Medical Oncology (ESMO) Congress. The findings showed that osimertinib should not be reserved for EGFR patients who had therapy resistance to 1st and 2nd generation EGFR TKI's. Instead, it should be used as the first line treatment for all EGFR positive patients [25, 26]. The outcomes of FLAURA indicated that frontline osiemrtinib reduced 54 percent of the risk of progression or death comparing to the standard therapy, which included Tarceva or Iressa. In addition, the duration for standard therapy for median progression-free survival (PFS) was 10.2 months, and while it was 18.9 months for Tagrisso. The median duration of response was doubled with Tagrisso versus standard therapy at 17.2 and 8.5 months, respectively [27]. This represented a very big step forward for EGFR mutated NSCLC patients who had renewed hope on battling the cancer.

Unfortunately, tertiary EGFR resistant mutations have also been reported for osimertinib as well, whereby a mutation at exon 20 sounds like a common escape mechanism. P.C797S happened in EGFR exon 20 shaping the replacement of a cysteine with a serine in the position 797. The amino-acid cysteine located at the position 797 represented the site used by all third-generation EGFR-TKIs for the covalent binding to the receptor, that is needed to contrast the intensified affinity for ATP determined by p. T790M [28, 29]. Subsequently, this change caused an inability in the TKI to disrupt EGFR activity and cancer progression resumes.

Several authors have recognized the appearance of p.C797S in preclinical setting as an EGFR resistance mechanism. [30] conducted a research on evaluating EGFR mutations resistant to osimertinib, rociletinib or WZ4002, by applying mutagenesis. They declared that C797s is one of the most widespread resistance mechanism to 3rd-generation TKI's. It was interesting that, based on their models, T790M-negative cells with p.C797S could prolong sensitivity to quinazoline-based EGFR inhibitors, such as gefitinib or afatinib. In a similar way, [31, 32] examined the cell lines treated with increasing doses of WZ4002, and found out that resistant cells expressed C797S point mutation, in cis with p. T790M in 85% of cases. They noticed that cells with mutations in Trans could be sensitive to a mixed therapy with first- and third-generation TKIs, while those with mutations in cis are resistant to any EGFR-TKI both alone and combined. This offered a treatment option which can be used to treat patients' resistant to osimertinib.

Apart from that, there are also cases where the selective pressure determined by third-generation TKI treatment could result in disappearance of the resistance mechanism reverting the tumor status to pre-T790M state [33]. Two various resistance pathways were identified by their study which include: one with intensifying the plasmatic levels of p. T790M and activating mutation, indicating the appearance of a resistant clone still carrying p. T790M and probably with newly gained mechanisms; the other with plasmatic T790M disappearance, suggesting the prevalence of T790M-negative clones unresponsive to drug inhibition. This showed that new mechanisms of resistance unrelated to T790m could occur as well as such CMet amplification and HER amplification as a result of osimertinib resistance. In particular, amplification of these genes could lead to an innate resistance to third-generation TKIs and justify a combination therapy. [33] also noticed that gene amplifications are popular form of resistance for EGFR target sites especially if targeted

therapy is given at suboptimal levels that does not hinder cancer progression adequately [33]. They hypothesized that more drug concentrations or a more powerful TKI-agent could not be vulnerable to this resistance mechanism.

Conclusion

In conclusion, EGFR mutated NSCLC has found vast progress in disease management with the introduction of EGFR TKI's. However, resistance mechanism has continued stubbornly to develop until impacting even the third-generation EGFR-TKIs. As indicated in this review, escape mechanisms EGFR-dependent or -independent are likely to emerge, highlighting the importance of repeated tumor biopsies and/or to collect plasma circulating tumor DNA (ctDNA) at the time of disease progression. Combination therapy looks likely to be the next step in EGFR mutated NSCLC management.

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