From Mechanisms to Therapeutics: Tackling Resistance in EGFR, KRAS, and ALK in NSCLC

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Abstract. Apart from the genetic mutations in mutant EGFR and KRAS, and ALK fusion gene that characterize NSCLC, several other genetic mutations also distinguish NSCLC. The paper reviews the pathogenic mechanisms of these gene alterations and the principles generalized for new generations of agents against EGFR, KRAS, and ALK TKIs. Ways to future reduce resistance comprise new inhibitor designs and combinations, as well as approaches for early detection such as liquid biopsy. The focus is on those advances serving to increase the durability of targeted therapies and better patient outcomes in NSCLC.

Keywords: EGFR, KRAS, ALK, NSCLC, Resistance mechanisms, Targeted therapy, Therapeutic strategy.

1. Introduction

Lung cancer is next to the common and most fatal malignant tumour globally. New cases of lung cancer in the United States are on course to breach the 234,580 marks while the death from the disease is about to reach 125,070 by 2024 [1].

Among these, the majority were 85% of cases were of non-small cell lung cancer [2]. Comprehensive studies have been undertaken regarding the different oncogenic drivers associated with lung cancer, with a particular emphasis on potential therapeutic targets. Promising outcomes have been observed with tyrosine kinase inhibitors (TKIs), which have notably extended the time to recurrence and enhanced patient prognosis. Nevertheless, the emergence of drug resistance in TKI treatments poses a significant challenge in the management of lung cancer, thereby diminishing long-term effectiveness [3]. We summarized the resistance mechanisms of these targeted treatments in NSCLC, focusing on EGFR-TKIs, KRAS-TKIs, and ALK-TKIs. The discussion will delve into current therapeutic approaches, resistance mechanisms, and emerging strategies designed to overcome these challenges, offering insights into how precision medicine is reshaping the treatment landscape of lung cancer.

2. Resistance Mechanism

2.1. EGFR mutations

The receptor tyrosine kinases family involves a cytoplric protein tyrosine kinase domain with which the EGFR has been associated. EGFR have been identified to be expressed in various tissues where they play a very important role in growth, development and differentiation [4]. In cancer disease, either overexpression or mutation of EGFR results in abnormal activation of its pathways of which then does malignancy of the cells by causing proliferation, metastasis, and also resistance to apoptosis. The most common are the activating EGFR mutations 'deletion in exon 19' and 'L858R single-point substitution mutation in exon 21,' accounting for 80%-90% [5].

Modification in EGFR-TKIs, please divide to Primary Resistance and Acquired Resistance because of the distinct mechanisms and implications for clinical management [6]; Primary resistance defined traditionally as the patient failing to ever elicit a response to EGFR-TKI from the onset usually within the first few weeks to several months on therapy, where acquired resistance is a used

terminology in patient who after initial response to EGFR-TKI eventually progress disease due to the evolving resistance mechanisms.

Both first-generation (gefitinib, erlotinib, and icotinib) and second-generation (afatinib and dacomitinib) EGFR TKIs have demonstrated remarkable clinical benefits in patients with Ex19del and L858R mutations, advanced non-small cell lung cancer [7].

First-generation drugs like erlotinib and gefitinib are reversible inhibitors that bind to the tyrosine kinase domain of the EGFR protein in ATP-competitive manner binding to this domain with the drug reversibly inhibits its kinase activity and cause this way-inhibited activity to not activate the EGFR signaling pathway. Usually, the patients harboring EGFR- mutant tumors respond very well in the beginning to the first-generation TKIs; however, disease progression after 9-14 months is experienced by most of the patients [8, 9].

In contrast, inhibitors of the second generation, such as afatinib and dacomitinib, bind irreversibly to the tyrosine kinase domain of EGFR, thereby providing prolonged inhibition of EGFR activity. This mechanism effectively obstructs EGFR and its downstream signaling pathways, further augmenting the suppression of tumor cells. The extensive range of activity allows these inhibitors to more efficiently target a broader array of EGFR mutations, thus enhancing the inhibition of EGFR-dependent tumor proliferation in comparison to first-generation EGFR-TKIs [6]. However, the substitution of threonine with methionine at amino acid position 790 (T790M) in exon 20 of the EGFR gene results in resistance among patients receiving treatment with both first- and second-generation EGFR TKIs. It is believed that the T790M mutation confers resistance to reversible EGFR TKIs by introducing steric hindrance and increasing the affinity for ATP binding [9]. This mutation represents the most prevalent mechanism of resistance within this patient population, accounting for 50%-60% [7, 10, 11].

Third-generation tyrosine kinase inhibitors (TKIs), including Osimertinib, Rociletinib, and Abivertinib, were designed specifically to target the T790M mutation along with other resistance mutations associated with EGFR. Among these, Osimertinib has emerged as the preferred first-line therapy for non-small cell lung cancer (NSCLC) with EGFR mutations [6], owing to its effectiveness against both primary EGFR mutations and the T790M mutation. Nevertheless, resistance to Osimertinib frequently arises due to the occurrence of additional EGFR mutations, such as C797X, or the activation of alternative signaling pathways. The cysteine at position 797 (Cys797) acts as the covalent binding site for Osimertinib, regardless of the presence of T790M mutations. Mutations occurring at this site, referred to as C797X mutations, have become the predominant mechanism of resistance to Osimertinib [12].

To address bypass pathway activation, combination therapies are under exploration. For instance, combining EGFR-TKIs with MET or HER2 inhibitors has shown promising results in preclinical models. Osimertinib paired with MET inhibitors (such as Savolitinib) is currently in clinical trials to address MET-mediated resistance. Another potential target is the tumor microenvironment. Therapies being evaluated include those that target the components, such as immune cells and CA, along with other potential targets. Moreover, blocking immune checkpoint PD-1/PD-L1 with the combination of EGFR-TKIs is under investigation to increase efficacy and acquire resistance, cautiously trying this combination due to some added toxicity.

Fourth-generation TKIs in development that will target specifically resistance mutations such as C797S in EGFR not addressed by the current available TKIs. Developing these new agents will provide resources for treatments for patients who are resistant to osimertinib and other present therapies. In addition, pathway-specific bypass inhibitors (such as inhibitors for SHP2) are explored to minimize downstream signaling from a multitude of pathways and therefore further increase the potential for durable responses in EGFR-mutant NSCLC that have become resistant.

2.2. KRAS mutations

KRAS is a proto-oncogene with frequent mutation in lung cancer, occurring in about 31-35% of lung adenocarcinomas [13]. NSCLC has been associated with high incidence of KRAS mutation.

Mostly, these mutations are found with smoking-related lung cancers. It is also associated with very aggressive tumor behavior, more metastasis rates, and poorer overall survival. The sensitivity of KRAS-mutant tumors to conventional therapy, for example chemotherapy and targeted therapies against other signaling molecules, is low.

Most common RAS mutations in lung cancer occur in the KRAS gene and more particularly in exon 2 of the gene. They are especially frequent in NSCLC. Among the various mutations of KRAS, more than 80% of oncogenic alterations occur at codon 12 (specifically G12C, G12D, and G12V), with KRAS G12C being especially common in non-small cell lung cancer (NSCLC), representing approximately 44% of all cases with KRAS mutations [14]. When activated, RAS proteins trigger a cascade of downstream signaling pathways, which include the MAPK/ERK pathway, the PI3K/AKT pathway, and the Raf/MEK/ERK pathway, all of which play crucial roles in the regulation of cell growth and survival. Mutations in RAS can lead to the production of a constitutively active RAS protein, resulting in the persistent activation of downstream signaling pathways, even in the absence of activation from upstream receptors. This uncontrolled activation of RAS signaling is a major driver of tumorigenesis in a wide variety of cancers, including lung cancer [15].

The historical development of targeted therapies for KRAS mutations in lung cancer has presented significant challenges, primarily due to the shallow and smooth surface of the KRAS protein, which lacks distinct drug-binding pockets [16]. This characteristic complicates the effective binding of conventional small-molecule inhibitors. Nevertheless, the introduction of KRAS G12C inhibitors, including Sotorasib (AMG 510) and Adagrasib (MRTX849), has led to noteworthy progress in this area. Despite these advancements, the emergence of resistance to these inhibitors continues to pose a substantial clinical challenge.

Sotorasib takes advantage of the distinctive cysteine residue that is created by the G12C mutation. It specifically attaches to the KRAS G12C protein in its inactive, GDP-bound form through the formation of a covalent bond with the cysteine residue [17]. Accordingly, it is this binding which freezes KRAS in the GDP-bound state conformation, hence precluding it from transitioning back into the active GTP-bound form which is responsible for uncontrolled signaling in cancer cell proliferation. Since this molecule acts on the mutant protein, normal cells expressing wild-type KRAS are spared and, therefore, Sotorasib has low side effects. One such molecule is Adagrasib, which, as a highly specific small molecule inhibitor to the aforementioned mutant, activates covalent binding onto the inactive form of the protein that KRAS, thereby hindering its reactivation and thus, down-regulates all downstream pathways involved in tumoral growth [18]. It has already shown glorious efficacy in non-small cell lung cancer (NSCLC) and the very contemporary is about the blood to brain transmission, but there is resistance. Common mechanisms one can often observe are via subsequent secondary mutations in the very KRAS gene or essentially the activation pertaining to alternative pathways. To overcome resistance, combination therapies are being developed—for example, Adagrasib plus MEK inhibitors, SHP2 inhibitors, or immune checkpoint inhibitors—to increase efficacy and to block or slow resistance.

Resistance to therapies aimed at KRAS can be categorized into two main groups: primary (intrinsic) resistance, where patients fail to respond to therapy from the start, and acquired (secondary) resistance, which develops after an initial positive response to treatment but eventually leads to disease progression.

Primary resistance mechanisms are frequently attributed to co-mutations. A recent investigation indicated that the distribution of genetic co-mutations differed among various KRAS subtypes. The most commonly observed co-mutations included those in the tumor protein p53 gene (TP53) (39-42%), the serine/threonine kinase 11 gene (STK11) (20-29%), and the kelch-like ECH-associated protein 1 gene (KEAP1) (13-27%). Additionally, co-mutations were noted in the ataxia-telangiectasia mutated gene (ATM; 13%), the hepatocyte growth factor (MET) receptor (15.4%), and the Erb-B2 receptor tyrosine kinase 2 (ERBB2; 13.8%, exclusively in the G12C subtype); and some rare mutations such as EGFR (1.2%) and BRAF (1.2%) [13, 19, 20]. Certain studies indicate that specific co-mutations may hold both prognostic and therapeutic relevance in KRAS-mutant non-small cell

lung cancer (NSCLC) [21]. For instance, mutations in TP53 are present in more than 50% of NSCLC cases and generally emerge early during the development of lung cancer [22, 23]. Furthermore, an exploratory analysis revealed that adagrasib exhibited superior efficacy in patients harboring both $KRAS^{G12C}$ and STK11 co-mutations, in contrast to those with only the $KRAS^{G12C}$ mutation [24]. This observation underscores the potential necessity for more targeted treatment approaches for patients with co-mutations in KRAS-mutant NSCLC.

Although KRAS G12C inhibitors signify a notable advancement in the management of KRAS-mutant lung cancer, the challenge of resistance poses a significant obstacle to achieving sustained success. It is crucial to comprehend the mechanisms that contribute to both primary and acquired resistance in order to formulate innovative therapeutic strategies. Potential avenues for progress include combination therapies, next-generation inhibitors, and approaches based on synthetic lethality. As research progresses, the overarching objective remains to enhance the durability of KRAS-targeted therapies and to elevate survival rates for patients diagnosed with KRAS-mutant NSCLC.

A recent article reports that a degrader known as a bifunctional protein degrader (PROTAC) was developed to target and degrade various KRAS mutations. Beginning with non-covalent ligands for KRAS and the E3 ubiquitin ligase Von Hippel-Lindau (VHL), and utilizing crystal structures for refinement, they developed a small molecule that effectively degrades 13 out of the 17 prevalent KRAS mutations. Unlike inhibitors, KRAS degradation leads to deeper and more sustained pathway regulation, killing cancer cells without harming non-mutated models, offering a new therapeutic approach for KRAS-driven cancers [25].

2.3. ALK rearrangement

Changes in the ALK (anaplastic lymphoma kinase) gene are pivotal in the oncogenesis of non-small cell lung cancer (NSCLC), being identified in 4–6% of lung adenocarcinomas [26]. The primary mode of presentation involves gene rearrangements, notably the EML4-ALK fusion, which results in the aberrant and persistent activation of tyrosine kinase, facilitating uncontrolled cellular proliferation and tumor development. Tyrosine kinase inhibitors (TKIs) targeting ALK, such as crizotinib, alectinib, brigatinib, and lorlatinib, have shown significant effectiveness in the treatment of NSCLC characterized by ALK rearrangements. Nonetheless, despite initial positive responses, most patients develop resistance over time, leading to disease progression. The complexity of ALK resistance mechanisms has prompted ongoing research into overcoming this challenge. The factors contributing to resistance are complex and include additional modifications within the ALK gene itself, along with the activation of alternative signaling pathways by cancer cells to circumvent ALK inhibition.

In malignant tumors, abnormal activation of the ALK gene and its associated downstream signaling pathways is caused by point mutations or chromosomal rearrangements. Specifically, structural rearrangements of ALK entail the fusion of the kinase domain at the 3' end of the ALK gene with various partner genes at the 5' end, leading to the formation of a fusion protein that is constitutively active. Within non-small cell lung cancer (NSCLC), the predominant type of ALK fusion is Echinoderm microtubule-associated protein-like 4 (EML4)-ALK, which is present in approximately 85% of cases that are ALK-positive [27, 28].

The emergence of ALK fusion genes results in the heightened activation of pro-mitotic and anti-apoptotic signaling pathways, which encompass the RAS-MAPK [29], PI3K-AKT [30], and JAK-STAT cascades [31]. This sustained activation drives continuous cancer cell proliferation and survival, laying a foundational mechanism for the development and progression of various malignancies.

The mechanisms underlying resistance to ALK inhibitors in ALK-positive lung cancer are influenced by both ALK-dependent and ALK-independent factors. Resistance that is dependent on ALK often emerges due to mutations and gene amplification occurring within the ALK gene itself. These mutations alter the kinase's structural conformation, impairing the binding efficiency of TKIs. The first-generation ALK inhibitor, crizotinib binds in the ALK kinase domain. A function which stops the proliferation of cancer cells, for this reason, this first-generation ALK inhibitor is not very specific and therefore commonly leads to resistance. Two common mechanisms for the resistance are

ALK mutations to ALK^{L1196M} and ALK^{G1269A}, which bring conformational changes in the kinase making the binding of Crizotinib ineffective [32] or ALK amplification may allow over-expression of the ALK protein where its total increased expression overrides the inhibitory effect of Crizotinib. Bypass signaling through EGFR or MET allows this ALK independent mechanism to keep on proliferating.

Second-generation ALK inhibitors include Alectinib, Brigatinib, and Ensartinib, which can also affect Crizotinib–resistant ALK mutations or increase drug affinity for the ALK kinase domain. For example, Alectinib is effective against all the mutations leading to Crizotinib resistance with an added advantage that it crosses the blood-brain barrier; hence, it is effective in cases where the patient is suffering from metastasis in the brain. Alectinib has been reported to provide much better progression-free survival as compared to Crizotinib. The rate of 12-month progression-free survival is event-free 68.4% for Alectinib versus 48.7% in patients treated with Crizotinib (hazard ratio for disease progression or death, 0.47) [33]. Nonetheless, resistance might develop even against a second generation of the inhibitor due to additional mutations in ALK, including beyond G1202R, G1202del, D1203N, S1206Y, and S1206C, which further solvent-facing the ALK domain of the protein, not allowing the drug to bind due to steric hindrance [34]. Cancer cells may additionally activate bypass signaling pathways, such as MET [35] or HER2 and HER4 [36], to compensate for ALK inhibition, presenting new challenges in treatment and highlighting the need for third-generation inhibitors.

Lorlatinib, a third-generation ALK inhibitor, was created to overcome resistance encountered with both first- and second-generation ALK inhibitors [37, 38]. This particular inhibitor is engineered to effectively target a diverse array of ALK mutations, including compound mutations that provide resistance to Alectinib and Brigatinib. With its unique structure, Lorlatinib effectively inhibits ALK even in the presence of complex mutations like G1202R/L1198F and has excellent central nervous system penetration [39], which is beneficial for patients with brain metastases. However, additional resistance mutations often develop over time that alter the structure of protein, reducing Lorlatinib's binding affinity and leading to resistance [32]. Additionally, ALK gene amplification can result in increased protein expression, thereby overwhelming the inhibitory effects of the current TKI dosage. Given these challenges, current research is focusing on combination therapies and sequential treatment strategies to delay resistance and improve patient outcomes in ALK-positive NSCLC.

Just like in EGFR-mutated NSCLC, treatment options post-ALK TKI resistance are limited. Mechanisms frequently include secondary, tertiary or later mutations within the ALK, amplification of, or by-pass signally pathways which in either case allow the cancer cell to proliferate even with inhibition of the ALK pathway [40]. Besides, upon the development of resistance, some ALK-positive lung cancer cells make phenotypic changes, such as transformation into small-cell lung cancer (SCLC) or epithelial-mesenchymal transition. This raises their invasion and metastatic potential but also undermines therapies that had hitherto worked.

Therefore, in view of these resistance mechanisms, alternative strategies are a new focus for researchers to increase the clinical benefits of ALK-TKIs. Sequential treatment with different generations of ALK-TKIs, combination therapy of ALK-TKIs with EGFR or MET inhibitors, or immunotherapy has shown breakthroughs toward clinical outcomes. Moreover, new fourth-generation ALK-TKIs specifically designed against acquired resistance mutations are now being developed with a view to surmounting the limitations of the existing inhibitors. The better insight and development of adequate therapeutic measures for these resistance mechanisms will certainly make a positive impact on prolonging the life and quality of life of patients with ALK-positive lung cancer.

3. Future Perspectives

To address resistance and co-mutation problems, combination therapies are attempted by researchers. One such may be combining KRAS inhibition with EGFR TKIs, as one of the common mechanisms of tumor cells to escape growth inhibition at KRAS is via heightened EGFR signaling transduction. Simultaneous dual targeted therapy within these two arms may provide better results

than either pathway-inhibition monotherapy and prevent evasive tumor response. These combination therapies are just beginning to be explored in the many ongoing clinical trials. Also, available evidence supports the idea that EGFR-TKIs could also be contributing to combinations as they increase disease-free survival or adjuvant treatment for early resected NSCLC patients in the form of doublets [40, 41].

Certainly, not only the development of highly efficient new drugs directly, but other diagnostic methods can achieve early detection of tumors and detect drug resistance from the patient as well. An emerging non-invasive diagnostic technology, liquid biopsy, is showing promising potential for its application in the diagnosis and management of non-small cell lung cancer. Its primary goal is to analyze biomarkers related to tumors in body fluids, such as blood, among which are CTCs, ctDNA, and EVs. Generally, liquid biopsy may detect genetic mutations in ctDNA with high sensitivity and specificity for NSCLC, such as common EGFR and ALK mutations, which may provide assistance in the disease's early diagnosis [42]. ctDNA levels are related to the tumor burden, and changes in ctDNA levels can predict response weeks in advance of changes in imaging technologies [43]. For instance, in drug-based treatments, monitoring ctDNA mutations can give early indications of drug resistance, prompting timely changes in the treatment strategy [44]. This is outweighed by the downsides. One of the most important is the low concentration of biomarkers and need more sensitivity and specificity in the detecting method. This certainly will need future work on the standardization of the methods and optimization of the detection methods. As the technology develops further, liquid biopsy will finally play an important role in the early diagnosis, therapeutic effect monitoring, and prognosis evaluation of NSCLC, which would bring the development of more precise and individualized medicine to the patients [45].

4. Conclusion

Mutation statuses of EGFR, KRAS, and ALK have greatly contributed to the personalization of cancer treatment; however, several problems concerned with acquired resistance, such as new mutation sites, co-mutations, and bypass pathways, continue to emerge.

Clinically, next-generation inhibitors and combination approaches have shown promising effect in outcomes incoming hope for overcoming resistance. Continued research into the molecular mechanisms of these mutations and associated mechanisms of resistance will allow development of more effective, personalized treatments for cancer patients.

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