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ALK-inhibiting drugs for ALK-positive NSCLC

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Abstract. Lung cancer has already been one of the major reasons of cancer-related deaths, with anaplastic lymphoma kinase (ALK) rearranged non-small cell lung cancer (NSCLC)taking up about 5%. This type of tumor has a high rate of central nervous system metastasis and standard chemotherapy has limited effect to effectively control progression. ALK-targeted inhibitors (ALK-TKIs) have notably extended the lifespan of patients with ALK-positive NSCLC, and third-generation inhibitors, in particular, have made significant progress in overcoming drug resistance and increasing intracranial activity, with particular efficacy in patients with brain metastases. However, these improvements still do not fully meet clinical needs, and drug resistance and adverse effects remain major challenges. This article reviews the molecular mechanisms of ALK rearrangements, the efficacy and resistance mechanisms of various generations of inhibitors, and discusses future therapeutic strategies and challenges.

Keywords: ALK, NSCLC, ALK-TKIs.

1. Introduction

Over the years, the global lung cancer rate has been steadily growing, making it become the most prevalent malignancies with high mortality. Lung cancer primarily consists of non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), occupy roughly 85% and 15% of cases, respectively. Among them, ALK-positive NSCLC constitutes around 5% [1-2], and these patients often show a strong tendency to brain and central nervous system metastasis. ALK is a receptor tyrosine kinase situated on chromosome 2, classified under the insulin receptor superfamily [3]. It is usually voiced only during embryonic development and is inactive in normal adults. However, when the ALK gene fuses with other chromosomes, it activates kinase functions, leading to tumorigenesis through routes such as PI3K-AKTand JAK-STAT. One of the most common fusion chaperone genes is EML4 located on chromosome 2, but other fusion forms such as ALK/NPM1 also exist. Since standard chemotherapy cannot effectively inhibit the progression of ALK-positive NSCLC, ALK-targeted therapy has become a key therapeutic tool. Crizotinib, a first-generation ALK inhibitor, has represented exceptional performance over traditional chemotherapy, though drug resistance appears in most patients within one year. To address this, second-generation inhibitors (e.g., ceritinib, alectinib, brigatinib) have been introduced, which not only work in crizotinib-resistant patients but also effectively target brain and central nervous system metastases. However, these drugs are also more likely to trigger drug-resistant mutations. The third-generation inhibitor, lorlatinib, has shown noteworthy prolongation of progression-free survival (PFS) in clinical trials, with particularly good results against the G1202R mutation, which is difficult to suppress with second-generation drugs. Despite its favourable safety profile, patients may

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still experience mild to moderate adverse reactions such as vomiting, diarrhoea and dehydration. This paper reviews the molecular mechanisms of ALK-positive NSCLC, evaluates current ALK inhibitors, and discusses resistance mechanisms and future treatment directions, offering insights for further research.

2. Fusion mutations in the ALK fusion partner and ALK inhibitor

2.1. ALK gene

The ALK gene has been identified in various tumors and plays a pivotal role in promoting tumorigenesis. ALK cDNA consists of 29 exons, and the full-length ALK protein comprises 1,620 amino acids, with an estimated molecular weight of 177 kilodaltons. Fusion chaperones containing oligomerization domains are often necessary for ALK kinase activation, as they mediate the oligomerization of ALK fusion proteins, giving rise toits continuous activation [4-5]. ALK fusions were initially discovered in anaplastic large cell lymphoma (ALCL), with ALK-NPM becoming the most prevalent fusion variant, found in around 55% of ALCL cases that exhibit ALK gene rearrangements [6].

2.2. ALK fusion partner

In NSCLC, EML4 is the most common fusion partner, responsible for roughly 85% of ALK rearrangements. Both EML4 and ALK are located on chromosome 2, and fusion occurs due to chromosomal inversion. EML4-ALK forms various variants, with variant 1 and variant 3 being the most frequent. Notably, variant 3 is more closely associated with the G1202R mutation, which exhibits strong resistance to second-generation ALK inhibitors [7-8]. Abnormal ALK kinase activation results in unchecked tumor cell growth, making the development of ALK inhibitors a critical therapeutic approach.

2.3. The first-generation ALK inhibitor

Crizotinib, the first-generation ALK inhibitor, is a selective ATP-competitive small molecule initially developed to target ALK and c-MET mutations. Clinical trials have demonstrated that crizotinib significantly surpasses conventional chemotherapy regimens (pemetrexed combined with cisplatin or carboplatin) in terms of PFS and objective response rate (ORR) in NSCLC patients, leading to prolonged overall survival [9-10]. However, most patients develop resistance within approximately 10 months of treatment. Mechanisms of resistance incoporate ALK gene mutations, gene amplification, and metastases to the central nervous system [11-15]. In consequence, second- and third-generation ALK inhibitors have been developed, offering enhanced efficacy against a more extensive spectrum of ALK mutations.

3. Second generation ALK inhibitors

3.1. Ceritinib

Ceritinib is a greatly powerful and selective ATP-competitive oral ALK inhibitor, demonstrating 20 times the potency of crizotinib in inhibiting ALK kinase activity. Clinical studies have confirmed ceritinib's superior effectiveness in treating ALK-rearranged NSCLC, particularly in patients resistant to crizotinib[16]. In one study, the ceritinib group showed a median PFS of 16.6 months, compared to 8.1 months in the chemotherapy group, underscoring its significant benefit in extending PFS [17-18]. Ceritinib is also effective against several ALK resistance mutations (e.g., L1196M, G1269A, S1206Y), though it remains ineffective against G1202R and C1156Y mutations [7, 14, 19]. Safety-wise, higher doses of ceritinib are associated with frequent adverse effects like diarrhea and elevated ALT, but studies suggest reducing the dose can enhance intestinal tolerance [20-21].

3.2. Alectinib

Alectinib is another highly selective ALK inhibitor with proven potency, particularly in patients who have come out resistance to crizotinib. A Phase I trial demonstrated a significantly prolonged median

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PFS in the group of alectinib, reaching 34.8 months, compared to 10.9 months in the crizotinib group [22]. Moreover, it has better central nervous system (CNS) permeability and intracranial activity.Alectinib actually is effective against L1196M and G1269A mutations, but shows reduced efficacy against V1186L and G1202R mutations [7, 23]. In terms of safety, alectinib is associated with relatively few adverse effects, the most common being anemia and elevated blood bilirubin [24].

3.3. Brigatinib

Brigatinib, an oral ALK inhibitor, has demonstrated strong inhibitory effects on multiple ALK resistance mutations. In a study, patients treated with brigatinib had a median PFS of 24.0 months compared to 11.1 months in the crizotinib group, showing brigatinib's superiority in prolonging PFS. Brigatinib is particularly effective against ALK-resistant mutations and excels in controlling intracranial metastases, with a significantly higher intracranial PFS rate compared to crizotinib in patients with baseline brain metastases. Common adverse effects include elevated CPK, AST, and ALT, with elevated CPK being the most habitual grade 3 or higher adverse event [24].

4. Third generation ALK inhibitors

The third-generation ATP-competitive ALK inhibitor,lorlatinib, has shown remarkable efficacy in patients who has been resisting to both crizotinib and second-generation inhibitors. It effectively overcomes several resistance mutations, including G1202R[25-26], and has shown extremely ascendant outcomes compared to crizotinib in first-line therapy. In a research, the 3-year PFS rate was 64% in the lorlatinib group, significantly outperforming the 19% observed in the crizotinib group. Additionally, lorlatinib provides strong control over CNS metastases, with a notably higher PFS rate than crizotinib at the 12-month mark [27]. Common side effects of lorlatinib include hyperlipidemia, cognitive impairments, and mood changes. While these adverse effects can often be mitigated by adjusting the dose, their potential Influence on the quality of life of the patient should not be overlooked [28].

Although second- and third-generation ALK inhibitors have demonstrated significant benefits in prolonging progression-free survival and control of brain metastases, drug resistance remains a major challenge. Common resistance mechanisms include single-site mutations (e.g., L119 6M and G1202R) and off-target mechanisms. In addition, high levels of amplification of the ALK gene can lead to drug resistance [29]. Future therapeutic strategies should focus on combination therapy, precision medicine and the development of novel inhibitors. For example, combining multiple TKIs may be a way to inhibit off-target resistance, and the novel fourth-generation inhibitors NVL-655 and TPX-0131have shown some potential for multi mutagenicity [30]. Next-generation sequencing technology has an important role in the detection of ALK-positive patients and the identification of fusion partners, which can contribute to the development of personalised therapeutic regimens [31]. All in all, the treatment of ALK-positive NSCLC has made significant progress with the help of ALK inhibitors, but sustained efforts are still needed to cope with drug resistance and improve patients' long-term survival and quality of life.

5. Discussion

This article provides a comprehensive look back onthe molecular mechanisms behind ALK-positive NSCLC and the clinical applications of ALK inhibitors, focusing on their efficacy in treating the disease. It discusses the performance of first-, second-, and third-generation ALK inhibitors, highlights resistance mechanisms, and evaluates their outcomes in patients with brain metastases. Crizotinib, the first-generation ALK inhibitor, marked significant advancements in clinical use, enhancing both overall survival and quality of life in ALK-positive patients. However, its therapeutic impact is astricted by the drug resistance occuring and poor CNS penetration. Second-generation inhibitors, like ceritinib, alectinib, and brigatinib, have demonstrated brilliant manifestation in crizotinib-resistant patients and have shown the ability to overcome certain ALK mutations. Alectinib, in particular, stands out for its superior CNS control. Nonetheless, second-generation inhibitors have been unable to fully address the G1202R mutation, and resistance remains an ongoing challenge.

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The third-generation ALK inhibitor, lorlatinib, has shown distinct advantages in prolonging progression-free survival and overcoming resistance, particularly in combating G1202R mutations and controlling brain metastases. However, adverse effects such as hyperlipidemia and CNS-related symptoms require careful management, often through dose adjustments. While the introduction of third-generation inhibitors represents a significant leap forward, resistance and side effects continue to pose major challenges, especially as patients on long-term treatment may develop new resistant mutations. Therefore, further research is crucial for developing novel inhibitors that can more effectively overcome resistance.

Future treatment strategies should prioritize personalized and combination therapies to maximize efficacy and reduce the likelihood of drug resistance. ALK inhibitors could be closely bound up with other targeted agents or immunotherapies, like EGFR or KIT inhibitors, to address potential off-target resistance mechanisms. Additionally, the rise of precision medicine has positioned technologies like next-generation sequencing as essential tools for identifying ALK positivity and fusion partners, which are critical for tailoring individualized treatment plans. Novel ALK inhibitors, such as Iruplinalkib (WX-0593) [32], have shown promising results as first-line treatments with improved CNS penetration and represent a key area of future research. Meanwhile, fourth-generation inhibitors, including TPX-0131 and NVL-655, have demonstrated substantial success in overcoming the G1202R double mutation, offering hope for further improvements in patient outcomes and survival.

6. Conclusion

Fusion mutations in the ALK gene drive NSCLC progression by activating pathways like PI3K, RAS, and JAK. First- to third-generation ALK inhibitors have significantly improved survival, especially in controlling brain metastases. Crizotinib, the first-generation inhibitor, introduced targeted therapy, but resistance and CNS metastasis given rise to the development of newer inhibitors. Second-generation inhibitors, like alectinib and brigatinib, show better CNS control, while lorlatinib excels against the G1202R mutation. However, drug resistance still becomes a major challenge, requiring ongoing development of novel inhibitors and personalized therapies to enhance efficacy and patient outcomes.

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