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Third Generation ALK Inhibitors - The Development of Lorlatinib and the Problems that Exist

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Abstract. The malignant tumor with the greatest morbidity and fatality rates in the world today is lung cancer, from which Non-Small Cell Lung Cancer (NSCLC) accounts for 85%. To treat NSCLC, a variety of targeted therapeutics been developed in medicine. ALK inhibitors are one of them, and they're frequently used to treat NSCLC.The 3rd Generation of ALK inhibitors are now in use, starting with the initial 1st generation ALK inhibitors. Because the development of 1st and 2nd generation ALK inhibitors medicines has been motivated by a number of unfavorable factors. These medications include the 3rd generation ALK inhibitor lorlatinib as well as the 2nd and 3rd generation ALK inhibitors ceritinib and alectinib. Current study discusses the clinical features, effectiveness, and side effects of lorlatinib as well as its pharmacological effects.

Keywords: lorlatinib, NSCLC, ALK inhibitor

1. Introduction

Non-small cell lung cancer (NSCLC), which accounts for almost 85% in all lung cancer cases, has outpassed small cell lung cancer as the malignant tumor with the highest rate of morbidity and fatality [1]. NSCLC patients have frequently received ALK targeting, and molecularly targeted therapy based on molecular type has shown excellent effectiveness. The ALK gene is located at the short arm of chromosome 2, which produces the ALK receptor tyrosine kinase. In Japanese lung cancer patients, soda et al discovered the ALK fusion gene for the first time. This gene is produced when the short arm of chromosome 2 is inverted. ALK research exploded once it was discovered that this fusion gene activates a transcriptional activator, raising the production of the fusion protein and encouraging the lung cancer cell growth. The c-ros oncogene 1 receptor tyrosine kinase (ROS1) fusion gene is a relatively rare driver of gene isoforms in NSCLC, and studies have shown that ros1 shares 77% identity with ALK at the ATP binding site in the kinase catalytic domain [2]. As a result, it could be advantageous to utilize ALK inhibitors in the treatment of NSCLC patients who carry the ros1 mutation. The prognosis for those with ALK- and ros1-positive NSCLC has recently improved dramatically as a result of the recent discovery of many ALK therapies [3]. These medications include the 3rd generation ALK inhibitor lorlatinib as well as the 2nd and 3rd generation ALK inhibitors ceritinib and alectinib. The development of ALK inhibitors and the benefits as well as the drawbacks of 3rd generation ALK inhibitors will be covered in this article.

2. Overview of ALK inhibitor research

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A 1st generation ALK inhibitor, crizotinib, is used to treat NSCLC in patients who have tested positive for the ALK gene [4]. Results from the Phase I clinical trail in crizotinib showed an objective response rate (ORR) of 60.8% and a progression-free survival time (PFS) of 9.7 months [5]. Due to mutations in the EML4-ALK gene, which cause recurrence and brain metastases, the majority of patients eventually acquire resistance to crizotinib after the therapy last 1-2 years [6].

Alkaline phosphatase inhibitors of the second generation were created in response to crizotinib resistance. For advanced or metastatic ALK NSCLC patients, who are resistant to crizotinib, their treatment has been given approval [7].

However, it has been demonstrated that 2nd generation ALK inhibitor therapy increases the prevalence of ALK resistance mutations in individuals with ALK positive NSCLC. As a result, lorlatinib have been created because patients urgently require stronger ALK inhibitors to solve the drug resistance issue that has been built up by previous medications [8]. As a result, the innovative 3rd generation alkaline phosphatase inhibitor lorlatinib was created.

Based on the structure and lipophilic potency of crizotinib, Pfizer, USA, developed lorlatinib, a 3rd generation ALK inhibitor, to treat NSCLC that is ALK positive. For patients with ALK positive NSCLC, lorlatinib was authorized by the Japanese FDA in September 2018 and the US FDA in November 2018 [9]. Its macrocyclic structure, which offers superior metabolic stability and blood-brain barrier permeability than crizotinib, is the primary structural difference between the two drugs [10].

3. Mechanism

Lorlatinib possesses remarkable preference for ALK and ROS1. It was shown that lorlatinib inhibits ALK phosphorylation and has inhibitory effects against almost all known ALK resistance mutations [11]. Because of its ability to reduce P-gp-mediated drug efflux, lorlatinib has good brain blood barrier permeability and thus strong activity in patients with ALK gene driven brain metastases [12]. Moreover, lorlatinib potently inhibited ros1 and maintained its inhibitory activity against ROS1 g2032r in vitro and in vivo [13].

Inhibiting the overexpression of ALK in NSCLC cells and interfering with the signaling pathways that ALK mediates can both stop NSCLC cell growth and proliferation. In patients who have relapsed following therapy with several ALK inhibitors, lorlatinib had an excellent PFS and ORR . Lorlatinib also reduces the proliferative effects of ros1 by inhibiting its phosphorylation and disrupting the PI3K-Akt and RAS MEK mitogen activated protein kinase (MAPK) signaling pathways[14].When used in combination, lorlatinib may be a successful therapy for NSCLC that is ALK- and ros1-positive.

4. Pre-clinical studies

Gainor et al [15] treated BA / F3 cells expressing wild-type ALK and multiple ALK resistance mutations with crizotinib, cretinib, and lorlatinib, respectively, and determined the IC50 values (nmol · L-1) of different ALK inhibitors against various resistance mutations and found that lorlatinib displayed more potent inhibitory ability and less toxicity to the parental cells (IC50 values of 763.9, 885.7, and 11293.8 nmol · L-1 against crizotinib, ceritinib, and lorlatinib, respectively), Indicating that lorlatinib has high inhibitory capacity and alk kinase selectivity. The study also found that crizotinib and cretinib were less effective against the ALK double mutations d1203n + e1210k and d1203n + f1174c, whereas the IC50 of lorlatinib was 26.6nmol · L-1 against d1203n + e1210k and 69.8nmol · L-1 against d1203n + f1174c, which were higher than those of crizotinib and cretinib. Lihong Zou et al [16] reported that the inhibitory constant (KI) of lorlatinib against wild-type ALK was less than 0.07 nmol · L-1 (stronger than that of crizotinib and cretinib). Baset et al [17] found that the inhibitory constant (KI) of lorlatinib against wild-type ros1l2026m and mutant ros1g2032r was less than 0.025 and 0.1 nmol · L-1, respectively, compared with first - and second-generation alkaline phosphatase inhibitors. 0.1 and 12.0 nmol · L-1, respectively, indicating that lorlatinib has a stronger inhibitory effect on ros1 than the first - and second-generation ALK inhibitors. This also makes

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comparisons indicating that lorlatinib inhibits wild-type ros1 more significantly than does wild-type ALK. In addition, good anti cranial tumor activity was shown in alkaline phosphatase positive NSCLC patients [18].

In addition, lorlatinib has demonstrated better inhibition to crizotinib in vitro and in vivo studies of resistant alkaline phosphatase-driven neuroblastoma [19,20]. Notably, lorlatinib extended mouse life relative to crizotinib or lorlatinib and caused regression of intracranial EML4-ALK tumors (NSCLC brain metastasis model) in mice [19]. It could also suggest that lorlatinib, in contrast to 1st and 2nd generation ALK inhibitors, increases the blood-brain barrier's permeability.

In vivo, the inhibitory activity of lorlatinib in a murine subcutaneous transplantation model was significantly higher than that of other ALK inhibitors [21].

5. Clinical trials

Lorlatinib had a considerable anticancer impact in patients with advanced NSCLC, according to a review of phase II research results [22]. The New England Journal of Medicine explicitly released the findings of a clinical study with 296 patients to compare lorlatinib with crizotinib as first-line treatment in patients with advanced NSCLC [22]. Crizotinib and lorlatinib groups had objective response rates (ORR) of 76% and 58%, respectively. In comparison to the crizotinib group's (39%), the lorlatinib group's (78%) 12-month progression-free survival rate was significantly greater [22]. Overall, lorlatinib performed better than crizotinib in advanced NSCLC patients who had positive ALK protein testing.

The efficacy of lorlatinib was proven by the global phase II component of a phase I/II study comprising patients with advanced NSCLC who were positive for either ALK or ROS1. Patients were divided into six expansion cohorts (EXP) depending on their ALK and ros1 status as well as any previous therapies in order to provide oral lolatinib 100 mg once daily. Orr and the patient's response to intracranial (IC) metastases were the trial's main objectives. 82% of patients with identifiable brain metastases demonstrated IC responses, 23% of patients demonstrated extracranial (EC) responses, and 71% of patients receiving lorlatinib demonstrated complete IC responses [23].Additionally, models that use data from phase I/II trials to examine reveal that lorlatinib is a very successful option as a 2nd or 3rd line therapy for NSCLC that is ALK positive [24].

In 296 patients with untreated advanced ALK positive NSCLC, the crown study was a randomised phase 3 trial evaluating the effi cacy of lorlatinib and crizotinib as fi rst line therapy. Patients were randomly assigned between the two treatment groups according to stratification characteristics such as ethnicity and the presence of brain metastases. Treatment duration was significantly shorter with lorlatinib[25].

In an interim review of the crown clinical trial, lorlatinib was reported to prolong overall life, boost IC response, and improve cancer management compared to previously untreated patients with advanced ALK positive NSCLC [25].Lorlatinib has been demonstrated to be effective as first-line treatment in conjunction to 2nd generation ALK TKIs. Lorlatinib demonstrated a 61% full response rate in the royal trial, encompassing both detectable and unmeasured brain metastases, among IC complete response rates recorded to date [25]. In patients without baseline brain metastases, lorlatinib achieved a 97% IC control rate at 12 months, which is also higher than previously published data with 2nd generation ALK inhibitors [25]. Thus far, a phase IV clinical trial (nct04362072) has been initiated to evaluate the efficacy of lorlatinib in patients with advanced disease who have deteriorated while receiving ceritinib or alectinib, and preliminary results are expected to be published in 2023 [26].

6. Toxicity

Results from a drug safety evaluation conducted in 54 patients with advanced NSCLC in a phase I clinical trial showed that the most common emergent adverse effects (teaes) of lorlatinib were hypercholesterolemia (72%) [27]. The teaes of grade 3 or higher were mainly hypertriglyceridemia, weight gain, lipase elevation and so on [26]. In the phase II trial, the main teaes of grade 3 to 4 were hypercholesterolemia (81.5%) and hypertriglyceridemia (60.4%) [23]. Seven patients discontinued

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treatment due to teaes, but no treaty related deaths occurred. In 69 ros1 positive patients, the grade 3 to 4 teaes were mainly hypertriglyceridemia (19%) [28]. Serious teaes occurred in 5 patients, with no treatment-related deaths.

In addition, some other reports on the safety of lorlatinib or rare adverse reactions suggest that cytochrome P3a inhibitors such as rifampicin and itraconazole should be avoided in combination with lorlatinib [29]. In addition, some patients experienced rare adverse effects during treatment, such as respiratory distress, bone marrow metastases, and, sarcoidosis, which may be related to the adverse effects of lorlatinib and the underlying diseases of patients [30]. In addition, potential serious adverse effects such as fetal toxicity, and arrhythmias are of concern.

Overall, lorlatinib was well tolerated, with low rates of dose reduction or discontinuation events related to treatment and rates of permanent discontinuation. The dose adjustment can effectively control diarrhea, vomiting, nausea, constipation, rash, slowing of speech, visual impairment, and other grade 1 to 2 adverse reactions. Based on the statistics of major adverse effects in patients with advanced NSCLC treated with 3rd generation ALK inhibitors, the teaes of lorlatinib were mainly hypercholesterolemia and hypertriglyceridemia, while the teaes of other ALK inhibitors were widely distributed [26].

7. Issues

Present developments and problems Treatments for hypercholesterolemia and hypertriglyceridemia are typical of lorlatinib. The side effects reported central nervous system effects on speech (15 / 8%), emotion (19 / 22%), and cognitive function (24 / 23%). Additionally, arthralgia (10 / 10.2%) and diarrhea (10 / 10.5%) were noted. [31]. Lorlatinib is more likely to result in liver failure than Ceritinib, Crisotinib, and Alectinib, per AE reports in the FDA Adverse Event Reporting System database (including liver failure, fulminant hepatitis, and hepatic necrosis). Furthermore, the FDA report claims that lorlatinib causes significant metabolic problems. Lorlatinib has a relatively high frequency of mental side effects (2.8%), making it one of the ALK-TKI medicines FDA authorized for non-small cell lung cancer by 2020. Additionally, a different research found that 1.8% of 170 patients receiving lorlatinib treatment experienced drug-induced lung damage. In conclusion, there are still a lot of issues with lorlatinib, including some serious illnesses.

8. Improvement

How to make improvements A significant advancement in the treatment of non-small cell lung cancer that is ALK positive is the successful development of lorlatinib. However, it is necessary to overcome the acquired resistance to this new drug. At the same time, we should try to reduce the cost of drugs so that more people can use them.

ALK mutations were found in 22 (76%) of the 29 individuals in a study who suffered a lorlatinib recurrence; 14 (48%) of these patients had two or more ALK mutations. Individuals who relapsed with the 2nd generation ALK-TKI were significantly more likely to have two or more ALK mutations (48% vs 23%; P = 0.017) than patients who did not. As a result, the next generation of ALK inhibitors is focused on mutation prevention.

The next significant pharmacological challenge in this area is to create fourth-generation TKIs that are more efficient as well as immuno-oncology treatments that are efficient, like ALK directed cell therapy, which is essential to enhancing patient survival and curative treatment for ALK positive patients.

9. Conclusion

A novel option for ALK inhibitor treatment is lorlatinib. It is anticipated that lung cancer therapy would grow more intricate and precise. Although the effective ALK inhibitor sequences may get more intricate and sophisticated, this is still a constrained approach. More therapy alternatives are anticipated as targeted therapeutics continue to evolve, however this may take years of pharmacological development and clinical confirmation.

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