Application of C-MET Inhibitors in the Treatment of Non-small Cell Lung Cancer

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Abstract. Non-small cell lung cancer (NSCLC) is a kind of refractory lung cancer. Under traditional cisplatin treatment, it is difficult for patients, especially the advanced cancer patients, to have a high cure rate and survival rate. Abnormal histological variants may lead to NSCLC. Mutations in C-MET may lead to abnormal downstream metabolism, which in turn triggers unrestricted cell growth and metastasis. Therefore, C-MET inhibitors can inhibitive the overexpression and activation of C-MET by blocking the gene pathway, in result in that the growth and the spread of cancer cell can be inhibited. A variety of C-MET inhibitors such as crizotinib, cabonitinib, capmatinib, etc., have been found to have good therapeutic activity and considerable clinical data. This paper discussed the C-MET as a therapeutic target in NSCLC, and outline the applications in clinical and therapeutic effects of various C-MET inhibitors.

Keywords: Non-small cell lung cancer (NSCLC), C-MET, Inhibitor.

1. Introduction

The patient with Lung cancer patients have high morbidity and mortality, ranking first in the world, of which NSCLC accounts for the most of lung cancer patients (75% ~80%). More than half of patients dying within one year of diagnosis and less than 18% surviving five years after the disease, which seriously endangers human life and health. Meanwhile, research shows that the prognosis of patients with advanced NSCLC is poor [1].

There are many factors in the occurrence of NSCLC, the greatest risk factor for development of lung cancer is tobacco use and cancer-driven mutations are also considered to be one of the risk factors. The most prominent representatives of current molecular drivers of cancer causing NSCLC are epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) or c-Ros oncogene 1(ROS1) rearrangements, and v-Raf mouse Sarcoma virus oncogene homolog B (BRAF), the identification of these genetic alterations and the inhibition of associated targets are considered key to current global clinical practice [2]. MET is expressed to a certain extent in various human cells, and the highest expression level is found in placental cells and epithelial cells. MET is overexpressed in tumor tissues such as NSCLC, more than in normal tissues cells [3].

Since C-MET has an important effect on the growth and spread of cancer cells, it is very feasible to design drugs with C-MET as a target. At present, C-MET inhibitors have entered clinical application and have shown good therapeutic effects in NSCLC. This paper aims to summarize the characteristics of MET gene abnormalities, mechanism of MET inhibitors, analyze the efficacy, advantages and disadvantages of marketed drugs, and describe the future development direction and challenges of MET inhibitors.

2. Mechanism of NSCLC with C-MET mutation

2.1. Protein conformation of C-MET

C-MET is a receptor for hepatocyte growth factor (HGF), which is processed to transmit information and regulate cell growth and metabolism. Mature C-MET is chimeric on the cell membrane and is divided into two parts, the extracellular and intracellular. The extracellular part includes the Sema domain, the sequence domain related with MET, the immunoglobulin (Ig) structure that can bind to HGF. Binding of HGF molecules to specific structure outside the cell of C-MET
results in the catalytic domain of tyrosine kinase transphosphorylation, which in turn leads to autophosphorylation, providing conditions for adaptor protein binding. When HGF binds to C-MET, downstream proteins such as GAB1 will increase the sites for signaling molecules, leading to activation of downstream pathways associated with cell proliferation. If C-MET is overexpressed or abnormally activated, the cell proliferation pathway will continue to be stimulated, resulting in abnormal histological changes and the formation of cancer [4].

2.2. Mutations in C-MET cause cells to become cancerous

Aberrant activation and overexpression of C-MET often occur in NSCLC patients and become an important cause of carcinogenesis, which in turn triggers phosphorylation and the opening of downstream pathways. It has also been found that the overexpression of C-MET (25-27%) will not only cause abnormal tissue proliferation (cancer), but also promote tumor cell METastasis and invasion, which causes the spread of cancer, reducing the survival rate and cure rate of patients. MET gene also suggested that the resistance of EGFR-TKL regimens to NSCLC (5-10%) [5]. Structural mutations in the C-MET protein are also one of the predisposing factors for cancer formation. There are multiple abnormal structural mutations in the Sema/juxtamembrane domain of the C-MET protein in NSCLC patients caused by the heterozygous MET gene sequence mutations, which causes the downstream pathway to be continuously activated.

Most striking of the C-MET mutations are splicing mutants of MET that lead to exon 14 (METex14) skipping which can prolong signaling and may contribute to cancer. METex14 skipping (approximately 2%-4%) causes the truncation of MET receptor lacking a ubiquitin ligase binding site, reducing ubiquitination and the MET protein degradation, the persistent of MET activation, the tumorigenesis, have poorer outcomes [6]. In fact, METex14 mutations in female patients, ex-smokers, and occurred in older patients (median age 74 years) were more prevalent [7]. Since C-MET plays a prominent role in the formation and maintenance of cancer cells, it is very important to use C-MET as a drug target for the treatment of NSCLC.

3. Application of C-MET inhibitors in NSCLC treatment

C-MET inhibitors, with good drug activity, can effectively induce apoptosis of cancer cells, inhibit the invasion and metastasis of cancer cells. C-MET inhibitors were divided into three broad categories: multi-kinase inhibitors, single-enzyme inhibitors, and monoclonal inhibitors of c-antibodies against MET and HGF ligands [5]. Both multi-kinase inhibitors and single-enzyme inhibitors are small-molecule tyrosine kinase inhibitors, competing with ATP for target binding to block intracellular signaling pathways in tumor cells. Among them, non-selective inhibitors (multi-kinase inhibitors) can simultaneously target multiple tyrosine kinases, which means that the inhibitors can be used as broad-spectrum drugs to have therapeutic activity against a variety of cancers. Selective C-MET inhibitors (single enzyme inhibitors) can specifically inhibit specific targets, have higher drug activity, and have the advantage of no off-target effects [8]. Monoclonal antibodies blocking-up the HGF to C-MET and target C-MET, thus inhibitive the HGF-C-MET axis and the C-MET activity.

3.1. Multi-kinase MET Inhibitors

Multi-enzyme inhibitors have more gene targets than selective inhibitors and act on multiple proteins at the same time, so they play a role in broad-spectrum cancer therapy. At the same time, the drug is more susceptible to changes in the body's environment and is prone to a wider range of side effects.

3.1.1. Crizotinib (PF-02341066)

Crizotinib was approved initially by the FDA in 2011, and is the first MET inhibitor for the advanced. As a multi-target inhibitor, it also has ALK and ROS inhibitory activities. In a 2012 report on ROS therapy, Bergethon, K. el at. found that a young man who had never smoked was found to have ALK-negative and EGFR-negative NSCLC. Then he showed disease exacerbation and ROS
genomic alterations after first-line erlotinib therapy [9]. The patient subsequently received two doses of 250 mg crizotinib and significantly improved associated pathological symptoms within 7 days and reduced radiation malignancy within 8 weeks. Although crizotinib was effective against multiple genes, docking with C-MET showed the strongest interaction compared to other targets.

Patients receiving crizotinib may experience adverse reactions such as diarrhea, nausea, or visual impairment, and in severe cases, even severe adverse events such as dyspnea and pulmonary embolism. According to statistics, 2.3% of patients will develop symptoms such as acute re-breathing failure, septic shock, and diabetic ketoacidosis, leading to fatal AEs. Most ARs in the crizotinib group were grades 1 and 2.

Apart from the possible side effects and adverse reactions, the most difficult problem to solve in the course of crizotinib is its drug resistance, which leads to ineffectiveness of subsequent treatment. Cancer cells are resistant to crizotinib for two reasons: first, the drug targets are mutated, and then other signaling pathways are activated. According to studies, ROS1 mutations, ALK mutations (30%) and MET mutations (44%) have been found in patients treated with Crizotinib, which significantly reduced the cure rate. Crizotinib can be used in combination with other inhibitors such as ponatinib to prevent the activation of other pathways to solve this problem [10].

3.1.2. Cabozantinib (XL184)

As a quinoline derivative, Cabozantinib, is a tyrosine kinase inhibitor (TKI) that inhibits the expression and enzymatic activation of various genes such as VEGFR, MET, KIT, and AXL. The drug was approved by the FDA in November 2012 and subsequently put into the clinical application of NSCLC. In a phase 2 trial in 2010, 10% of the NSCLC patients with cabozantinib achieved PR and 40% achieved SD. At the end of 12 weeks, NSCLC was effectively controlled in 50% of patients [11].

Cabozantinib blocks MET phosphorylation in vivo and can significantly inhibit MET activation without affecting total MET expression levels. In addition, Cabozantinib inhibits wild-type MET and KIT through activating mutations, which have been shown to play relevant roles in other solid tumors [12]. Cabozantinib also has inhibitory activity against VEGF and is a potent vascular endothelial growth factor receptor 2 (VEGFR2) inhibitor. Since VEGFR2 can induce parietal cell migration, resist apoptosis, lead to pericyte coverage of new blood vessels, and promote vascular maturation, Cabozantinib's inhibitory effect on VEGFR2 can effectively reduce cell proliferation and prevent the formation of vascular networks around cancer cells, to prevent cancer cell metastasis and obtain nutrients and oxygen [13].

Cabozantinib is extensively metabolized in the body, producing more than 17 metabolites. Four metabolites were present if the exposure of the plasma drug concentration area (AUC) is greater than 10%. The metabolites as inhibitory molecules in vitro inhibited MET, RET and VEGFR2 in only 10% of the parental molecules. Metabolism occurs essentially in the liver, with insufficient evidence in vitro. In addition to this, both in vivo and in vitro, cabozantinib exhibits high binding to plasma proteins mainly albumin (about 99.7%). The half-life of cabozantinib is 80-172h in humans, about 13h in rats, and about 3.5h in mice, and the binding force and binding time are sufficient to satisfy most of the inhibitory activities of cabozantinib [14].

The clinical use of cabozantinib was found to have a series of adverse reactions. Cabozantinib has had a BBW for perforated tubes, perforated fistulas, and bleeding since its first approval. During clinical use of cabozantinib, the most common event was increased blood pressure/hypertension, accounting for approximately 96%/61% of adverse reactions. In a 2017 study by Giuseppe Tridente et al, the incidence of hypertension was approximately doubled in patients using cabozantinib compared with the control group in particular 6% of cabozantinib-treated patients died from respiratory failure, bleeding, sepsis, pneumonia, cardiac arrest, fistulas, and other unknown causes. Some common adverse reactions, such as diarrhea, HFSR, weight loss, decreased appetite, nausea and fatigue, also tend to occur after medication [15].
3.2. Anti-MET and Anti-HGF Antibodies

3.2.1. Onartuzumab (METMab)

Onartuzumab binds to the C-MET extracellular part, the sema domain, and is able to block up attachment of HGF’s alpha chain, but does not exert agonistic activity or induce C-MET dimerization and block up the signaling mediated by HGF. In patients with C-MET-positive NSCLC, the combined use of onartuzumab and erlotinib not only did not improve the clinical outcomes, but the combined use of the experimental group had a shorter OS than erlotinib alone. Onartuzumab cannot bring any clinical benefit in the combination with chemotherapy regimens during squamous NSCLC [16].

3.2.2. Ficlatuzumab (AV-299)

Ficlatuzumab can specifically act on HGF and neutralize the bind-up the HGF/C-MET, the activation of the C-MET receptor, and then inhibitive the signaling pathway, and has antitumor activity. Preclinical studies in NSCLC xenograft models have shown that the combination of filazumab and an inhibitor of EGFR (erlotinib or cetuximab) shows better anticancer activity than single agents. Patients, who express low C-MET, demonstrated better ORR (41%) (22% ORR in the monotherapy arm) and longer median PFS (extend from 5.5 months to 11 months). To date, ficlatuzumab has been well tolerated in this population [17].

Phase 2 trial in Asian patients with NSCLC showed severe refractory cicatricial alopecia in NSCLC patients receiving ficlatuzumab (AV-299) and gefitinib. Single-dose gefitinib or erlotinib use may result in severe scalp inflammation and alopecia, but these cases represent the most severe forms of scarring, including cases of alopecia and folliculitis, and the fastest onset of this scalp side effect, which was not present in previous reports. Therefore, it is speculated that the combination of fetuzumab and gefitinib may lead to the simultaneous inhibition of HGF and EGF to produce synergistic toxicity, resulting in severe scarring alopecia [18].

3.3. Selective MET Inhibitors

Selective inhibitors are specific enzyme inhibitors that inhibit the activation and overexpression of C-MET without affecting other enzymes, and can treat C-MET-dependent cancers and inhibit the spread and metastasis of cancer cells.

Capmatinib (INC280) is the first targeted drug in NSCLC approved by the FDA in 2020 for patients with locally advanced or MET 14 skipping mutations (NSCLC). Capmatinib restrains the proliferation and the survival of MET-dependent cancer cells by restraining METex14 cancer cell growth, HGF-binding-induced MET phosphorylation, MET amplification, and MET-mediated downstream signaling protein phosphorylation and other types of abnormal MET gene expression [19].

As an ATP-competitive and reversible inhibitor, Capmatinib has a strong inhibitory effect on C-MET phosphorylation, the half-inhibitory concentration value IC₅₀ is about 0.6 nmol/L, and the inhibitory effect on C-MET at a concentration of about 4 nmol/L exceeds 90%. In vitro, Capmatinib proved more effective than other MET inhibitors: approximately 30-fold stronger than crizotinib (IC₅₀ 22 nmol/L) and 1-fold stronger than tepotinib (IC₅₀ 3.0 nmol/L) [20].

Capmatinib potently inhibits aberrant activation of C-MET because of exon 14 deletions and protein structural mutations, such as tyrosine residue 1003 mutation. The inhibition in C-MET phosphorylation by capmatinib treatment was reversible, with a marked decrease in inhibition within hours of compound removal and complete disappearance within 48 hours. Capmatinib effectively inhibits more than 90% of all detected signaling proteins at about 4 nmol/L. Capmatinib also potently induces DNA fragmentation and PARP cleavage, which in turn triggers tumor cell death. Based on experimental data, capmatinib decreased hepatocyte growth factor-stimulated cell migration in a concentration-dependent manner, and tumor growth inhibition increased with increasing compound exposure. Tumor regression was achieved when compound exposure sustained greater than 90% inhibition of C-MET.
Capamatinib only has an abnormally strong inhibitory effect on cancer cells related to MET gene mutation, and does not affect the growth and proliferation of other cancer cells that do not express C-MET. At a concentration of 2 mmol/L Capamatinib, all kinases were inhibited by no more than 30% except C-MET, which was completely inhibited [21]. The high selectivity of Capamatinib for C-MET may be due to the unique way it binds to C-MET. Structural modeling revealed that the phenolic part of C-MET directly interacts with capmatinib bound to the central aromatic ring, and the other parts are interconnected to form salt bridges to stabilize the activation cycle. conformation to support the interaction of the phenolic site with capmatinib. When cells were mutated in the C-MET kinase domain and then treated with capmatinib, significant drug resistance was observed with a significant reduction in the half-inhibitory concentration. This proves that Capamatinib and C-MET have a very suitable action conformation and a closely related action mode.

Capamatinib has good safety after clinical trials and can significantly prolong patients survival caused by MET gene mutations (especially MET ex14 skipping mutations) and alleviate pathological symptoms. In a clinical trial completed in February 2016, the overall response rate (ORR) of capmatinib treatment was 22% with the overall disease control rate was 51% [22].

Capamatinib has good cure rates for MET ex14 mutations. MET exon 14 skipping decreased internalization and the MET receptor degradation, thereby increasing MET signaling. Capmatinib MET-specific therapy significantly prolongs advanced MET ex14 NSCLC patients survival, better than patients treated with other therapies. BIRC-assessed overall sustained-release ORR of capmatinib was 72.0%, confirming that Capmatinib is effective in MET ex14-mutated advanced NSCLC patients. Clinically meaningful response rates have been shown in NSCLC patients [23].

It has been found that the combination of Capamatinib with other drugs can overcome the resistance of other drugs and obtain better therapeutic effects. Preclinical data show that combination therapy with capmatinib is more effective than EGFR-targeting agents alone. For example, in some patients C-MET dysregulation is found in 5-22% of resistant patients. However, after co-administration with Capamatinib, EGF816 exposure (AUC) increased by approximately 35% at steady state [24]. As an oral drug, capmatinib has good distribution properties, can be absorbed by cells throughout the body, and has good food tolerance, and the pharmacokinetics of before and after meals do not change significantly. According to a report by Giorgio V. Scagliotti in 2013, during capmatinib administration, patients were prone to adverse events such as nausea (47%), vomiting (37%), etc., as well as grade 3/4 AEs such as anemia (7%), pneumonia (7%).

4. Conclusion

NSCLC is difficult to obtain a relatively considerable survival rate and cure rate under conventional treatment. In the research process of various related enzyme inhibitors, it is found that C-MET has become a target for consideration due to its own characteristics. The C-MET pathway is indispensable in tumor growth, reproduction, and migration, leading to drug resistance, resulting in low cure and survival rates. The abnormal activity of C-MET often occurs in other metabolic pathways such as ALK and ROS gene-dependent cancers, causing drug resistance, resulting in low cure rates and survival rates.

Multi-enzyme MET inhibitors have played a good therapeutic effect, such as crizotinib, cabozantinib, etc., but because multi-enzyme inhibition easily leads to off-target effects, drug resistance appears more or less in clinical trials and may cause Other metabolic disorders. As a specific enzyme inhibitor, capmatinib well fills the shortage of multi-enzyme inhibitors, not only does not affect other metabolic pathways, but also greatly improves the sensitivity to MET, with obvious therapeutic effects. Experimental progress has also been made with monoclonal antibodies such as ficlatuzumab, showing clear reactivity and survival benefits in phase II trials. Compared with chemotherapy alone, monoclonal antibody combined with other drugs can prolong progression-free survival and produce better treatment effect.
Identifying biomarkers associated with the biological activity of MET inhibitors will provide a basis for comprehensive optimization of personalized treatment regimens for more effective treatment of NSCLC.

References


