Role of Tepotinib, Capmatinib and Crizotinib in non-small cell lung cancer

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Abstract. c-MET is a receptor tyrosine kinase involved in cell proliferation. However, when c-MET is abnormally activated, it becomes a carcinogen through some genetic mechanism. Mutation of METex14 is one of the reasons of abnormal activation of MET, which has been found in non-small cell lung cancer (NSCLC) patients. NSCLC is unresectable, prone to recurrence, and threatens the life of patients. Currently, only a few multi-targeted drugs are available to treat the disease. This review summarizes the effect of three targeted drugs on NSCLC. The drug tepotinib has shown promising clinical effects in the treatment of NSCLC by inhibiting MET mutations. Crizotinib is a drug widely used to treat NSCLC, but it needs to be determined whether crizotinib is effective in other cancers. Capmatinib is also a MET inhibitor, which has high selectivity and powerful curative effect, as well as safety in clinical trials. Further studies are needed to explore the clinical application of tepotinib, capmatinib, and crizotinib.

Keywords: NSCLC, MET, Tepotinib, Capmatinib, Crizotinib

1. Introduction

Lung cancer poses a serious threat to people's lives, and it is the second leading cause of death in European and American countries. NSCLC is a disease caused by mutation of amino acid kinase receptors in lung cells, which is unresectable, prone to recurrence, and threatens the life of patients. However, the incidence and mortality rates of NSCLC had raised respectively a 3.3% and 1.0% percentage per year during 2000 to 2015, and were estimated to increase another 11% till 2030 [1].

MET is the gene encoding the receptor for tyrosine kinase (c-MET), a protein necessary for the regulation of various physiological activities, such as the receptor for hepatocyte growth factor (HGF). Common c-MET gene mutations include MET exon 14 skipping mutations, MET amplification, and MET protein overexpression, which may lead to cancer, and the use of existing drugs makes mutated MET resistant to drugs [2,3]. MET exon 14 skipping mutations occur in 3-4% of patients with advanced or metastatic NSCLC that cannot be surgically removed, and the MET inhibitor tepotinib has been shown to be effective in patients with exon 14 skipping mutations. Additional MET clinical efficacy in NSCLC patients [4].

However, few drugs are effective in treating NSCLC. In addition, chemotherapy can harm a patient's health. The identification of METex14 has greatly contributed to the development of targeted drugs. Many advanced drugs have been discovered recently, and Capmatinib is one of them [5].

To eliminate the side effects of chemotherapy, the identification of METex14 has been studied to develop advanced drugs, and Capmatinib is one of them [4]. Capmatinib is an inhibitor that can prevent mutation of METex14, which shows protective effects on treating NSCLC caused by METex14 skipping, especially in the later period of cancer. Moreover, it is the first drug that was approved to treat this disease, which can control MET expression and signals that may turn normal cells into cancer cells [5]. Capmatinib showed some side effects in the treatment process, therefore, many medical research institutions curried out safety tests by using it in clinical treatment and watching the symptoms of patients. The researchers finally confirmed that capmatinib is safe [6].

During the investigation, our team found that capmatinib is not only active in treating NSCLC, but also plays a role in treating brain metastases when it was combined with other kind of drugs.

Another possible pathway that leads to NSCLC is anaplastic lymphoma kinase (ALK) rearrangements. ALK gene locates at the short arm of the 2nd human chromosome and encodes ALK. It is one of the members of the insulin receptor family. Mutant ALK may abnormally activate the downstream signal pathway and finally lead to cancer. ALK mutations, especially fusion mutations, occur in many cancer patients. In NSCLC patients, about 3% to 5% are found the existence of rearrangement of ALK. Crizotinib has been proved to have strong efficacy on mutation of ALK and MET tumor, and is approved for patients with metastatic NSCLC which is caused by ALK [7].

This review summarizes the MET pathway leading to NSCLC and the basic efficacy of three targeted agents and their use in clinical trials.

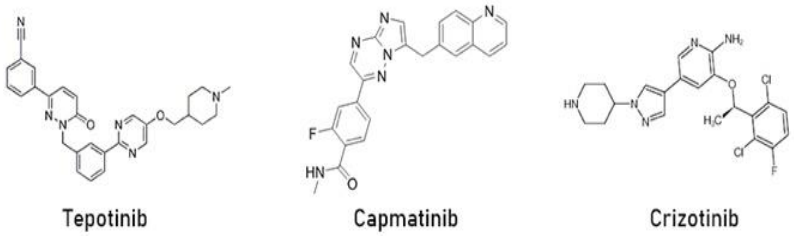

Figure 1 Structure of Tepotinib, Capmatinib and Crizotinib

2. Role of Met Pathway

Studies have shown that MET amplification is one of the most important resistance mechanisms of EGFR-TKIs [8]. The MET gene is located on the long arm of human chromosome 7 (7q21-31), about 125 kb in length, and contains 21 exons [9]. Cellular-mesenchymal epithelial transition factor (c-MET) is a trans-membrane receptor with auto phosphorylation activity encoded by the MET gene, belonging to tyrosine kinase receptors (RTKs), mainly expressed in epithelial cells, and a protein necessary for regulating human physiological activities [9]. c-MET is a proto-oncogene that plays an important role in embryonic development and postnatal recovery. In adults, c-MET typically plays a role in wound healing and tissue regeneration [9]. However, overactivated c-MET is harmful. There are four types of c-MET activation: point mutation, amplification, protein overexpression and rearrangement, among which rearrangement is considered to be a new oncogenic method.

ALK rearrangements and its fusion with EML4 have been proved to exist in various NSCLC models and become an oncogenic driver of tumors. In the clinical trials, the EML4-ALK fusion have shown its activity in tumors, highlighting the significant role ALK plays in oncogenesis [10]. EML4-ALK can be divided into various types, among which V1 and V3 are the most occurring types. As protein in V1 fusion contains tandem atypicalβ-propeller (TA, PE) structure which does not exist in V3 fusion, V1 fusion protein is less stable than V3 and thus more sensitive to drugs [11].

3. Met Inhibitors

3.1. Tepotinib

3.1.1. Tepotinib inhibits oncogenic MET receptor signaling

The incidence of c-MET gene mutation in lung cancer is 3%, and the most common type of mutation is exon 14 skipping mutation [4]. Current studies on clinicopathological characteristics have shown that MET exon 14 skipping mutations are most common in NSCLC, with lung sarcoid-like carcinoma and adenocarcinoma [4]. Existing drugs are not effective at inhibiting this mutation, and drugs like tivantinib cause MET amplification that confer resistance [11]. Tepotinib is an oral inhibitor targeting MET mutations with high selectivity, which can overcome MET resistance and achieve better therapeutic effects [12].

Tepotinib is designed to inhibit oncogenic MET receptor signaling caused by MET alterations, including MET exon 14 skipping alterations, MET amplification, and MET protein overexpression [13]. It is highly selective and has the potential to improve outcomes in aggressive tumors with poor prognosis and these specific alterations.

In the flash plate assay, tepotinib interacts with c-Met kinase, and the 50% inhibitory concentration (IC_{50}) of tepotinib is 3nmol/L, demonstrating its potent inhibitory activity. Second, tepotinib is highly selective for the c-Met kinase, and of the 242 human kinomes analyzed with tepotinib, only 5 were inhibited by more than 50% [4]. In addition, the researchers demonstrated low cytotoxicity and cell persistence, with no severe weight loss or mouse death under all tepotinib treatments. In treatment of cells incubated with tepotinib for 30 to 45 minutes, washed, and read with the original ligand hepatocyte growth factor (HGF), tepotinib persisted for more than 14 hours with a mean IC_{50} of 5 nmol/L. In contrast to monoclonal antibodies, tepotinib remains active on ligand-independent cancers [14]. Hence, tepotinib may be an inhibitor of MET receptor signaling.

3.1.2. Safety and efficacy of tepotinib

In NSCLC patients, approximately 3-4% of splice site mutations result in loss of transcription of the oncogenic driver gene MET exon 14. The phase II study assessed the efficacy and safety of tepotinib in this patient population. In the study, patients with advanced or metastatic NSCLC confirmed to harbor METex14 skipping alterations received tepotinib monotherapy (500 mg per day). The primary adjudicative endpoint is objective response rate (ORR) in patients with at least 9 months of follow-up after independent review. Response rates are judged based on whether METex14 hopping changes were detected on liquid biopsy (LBx) or tissue biopsy (TBx)[4].

Of 152 NCSCLC patients with MET exon 14 skipping mutations who received tepotinib, 99 completed at least nine months of follow-up. In the combined biopsy group (LBx or TBx), the ORR as judged by independent review was 46% (95%CI: 36-57) and the mean duration (DOR) of response was 11.1 months (95%CI: 7.2-NE). The ORR was 48% (95% CI: 36-61) in 66 patients in the LBx biopsy group and 50% (95% CI: 37-63) in 60 patients in the TBx biopsy group. Twenty-seven patients had positive results in both biopsy modalities [4].

The investigators assessed an established ORR of 56% (95% CI: 45-66) regardless of prior treatment regimen, with similar response rates to tepotinib in patients with advanced or metastatic lung cancer. In this study, the researchers considered the incidence of grade 3 or higher adverse events related to tepotinib treatment in 28%, including peripheral edema (7%). Of these, 11% of patients permanently discontinued tepotinib due to adverse events.

About 3% of NSCLC patients carry mutations in the MET proto-oncogene, resulting in loss of MET exon 14 transcription. The METexon14 skipping mutation-positive receptor has kinase activity and accumulates to high levels on the cell surface. The VISION study evaluated the efficacy and safety of tepotinib in this patient population. 152 patients with advanced or metastatic NSCLC with METex14 skipping alterations received tepotinib monotherapy (500 mg once daily) [4,13]. The primary endpoint for determining whether the drug was effective was ORR in patients who had been independently reviewed and had at least 9 months of follow-up. The magnitude of the response rate was judged according to whether METex14 hopping changes were found in liquid biopsy (LBx) or tissue biopsy (TBx) [4].

3.1.3. Tepotinib has therapeutic potential for NSCLC

Investigator-assessed ORR of 56% (95% CI: 45-66) based on tepotinib treatment in 152 patients with manageable side effects, with 28% of patients reporting grade 3 treatment-related adverse events event. The most common side effect was peripheral edema, with 11 percent of patients discontinuing treatment due to adverse events [4]. These suggest that METex14 is an active target in NSCLC and that tepotinib has the potential to improve treatment outcomes in patients with aggressive tumors harboring specific MET alterations.

3.2. Capmatinib

3.2.1. Capmatinib treats NSCLC

Capmatinib can selectively bind with c-MET, to cut the signal pathway of c-MET and thus cause the death of cancer cell, which has been proposed as the mechanism of capmatinib treatment effects on NSCLC [5].

A clinical trial of capmatinib studied patients with radiation therapy. Under the condition of fasting for 21 days, patients took 400mg camatinib tablets twice a day and observed their condition. As a result, about 69% of the patients are in stable condition [15]. Another research showed that patients had never received any medical treatment before had better results. In *vitro* studies by using NSCLC cells which was proliferated artificially, it turned out that when the concentration of capmatinib reached 16nM, the cancer cells were almost not able to complete any migration. It shows a high degree of sensitivity and selectivity [16]. They concluded that capmatinib is effective in treating, especially in patients that are never being treated by target drugs. Meanwhile, its high selectivity can make it precisely induce apoptosis of cancer cells without affecting other cells.

Except for the in *vitro* and in *vivo* studies, clinical trials have been conducted. In a trial capmatinib has shown good activity against colon cancer, and it did not need to be a particularly large dose, another *in vivo* study gave 10 tumors-only mice 10mg of capmatinib once a day. After a period, they found a partial recovery in six of the mice, and it was also well tolerated by patients [16]. Another clinical trial showed that patients with advanced NSCLC can live longer after being treated by target drugs including capmatinib [6].

3.2.2. Safety and tolerance of capmatinib

The safety of drugs is the topic of most public concern. In materials our group member found from the Internet, many researchers conducted trials to test the safety of capmatinib. In the first phase of clinical trials,20% of the patients showed symptoms such as vomiting and 10% of the patients suffered from edema because of the side effect, and most of the adverse reactions occurs in patients that never accepted target treatment. The researchers wondered wether eating can reduce the side effect of capmatinib, they devided patients into two groups and one of them was told to eat before taking the drug. The team found that both two groups have about 30% of patients suffered from side effects, they drew the conclusion that whether capmatinib has side effects is not affected by whether or not the patients eating [17].

3.3. Crizotinib

3.3.1. Crizotinib in clinical trials

Since the release in 2011 in the U.S., crizotinib has been used as an effective treatment against NSCLC harboring ALK gene arrangements. Crizotinib itself, however, may be settled to more kinds of targets. A study proves that crizotinib is also a selective and effective protein receptor tyrosine kinase (RTK) dual inhibitor with targets on MET and ROS1 through molecule docking. Furthermore, crizotinib does good effects on targets that are widely acknowledged (such as c-Met and ALK) in the treatment of NSCLC. Besides, crizotinib targets on NTRK1 in adjuvant therapy, as well as BRAF and well with PD-1 and POM121 in treating breast and prostatic cancer [7].

For NSCLC, crizotinib has been used for treating metastatic NSCLC with either ALK or ROS1 positive on adult patients. The recommended dose for crizotinib is 250mg twice orally per day. Its common function is through competitively inhibiting adenosine triphosphate from interacting with ALK receptor, thereby cutting down downstream events including inhibiting the growth of cells that are dependent on ALK and their surviving rates [19]. In a study concerning patients with ALK-positive advanced non-squamous NSCLC, crizotinib has shown a superior performance compared with the chemotherapy, including a better progression-free survival (PFS, 11.1 months versus 6.8 months), objective response rate (ORR, 87.5% versus 45.6%), and patient-reported outcomes (PROs) in the quality of life [20].

3.3.2. Drug resistance of crizotinib

Since the release of crizotinib, the most severe consequence using crizotinib has been its drug resistance. A study reports that YES1 and MYC amplifications show an effective potential to judge whether there exists a quick resistance to crizotinib. Such amplifications are found in both pericardial effusion and the pleural effusion from patients. Furthermore, an increasing chromosomal instability from diagnostic biopsy to pleural effusion is also observed. A combination strategy of crizotinib with dasatinib could be effective to overcome such drug resistance [21].

Another possible reason that leads to crizotinib resistance is MET exon 14 skipping mutation, which has been reported by several clinical cases [22]. Patients firstly received chemotherapy, followed by crizotinib treatment until they reached the statement of partial response (PR). At last, a gene detection is supplied. New mutations on MET D1228N and D1010H were found on a patient, with the latter being the pre-existing Met exon 14 skipping mutation [23]. On the other hand, several changes of several mutations occurred on the second patient. For example, the level of MET Y1230C mutation increased to 3.5% while that of D1010H decreased to 10.9% [23]. Both cases indicated that MET exon 14 skipping mutations might become a reason why patients resist crizotinib.

Table 1. Functions and clinical applications of tepotinib, capmatinib and crizotinib

Compound	Function	Clinical Application	References
Tepotinib	Inhibition of MET receptor signaling caused by MET gene mutations.	Tepotinib was well tolerated and efficacious, and the most common treatment-related adverse event (TRAE) was peripheral edema, a promising clinical therapeutic target.	[4]
Capmatinib	Inhibitor that can prevent mutation of METex14	Capmatinib shows protective effects on treating NSCLC caused by METex14 skipping, especially in the later period of cancer.	[6]
Crizotinib	Inhibition of ALK receptor leading to ALK rearrangements and fusion, as well as MET and ROS1 receptor.	Crizotinib has long been a treatment against NSCLC with either ALK- or ROS1- positive.	[7]

4. Conclusion

The protein encoded by the MET gene has tyrosine kinase activity and is related to a variety of oncogene products and regulatory proteins. Studies have shown that many tumor patients have c-met overexpression and gene amplification in the process of tumorigenesis and metastasis. This review summarizes multitargeted drugs that can be used to treat the disease. Tepotinib has the potential to improve outcomes in patients with aggressive tumors harboring specific MET alterations. Capmatinib can cut the signal pathway of carcinogenic signals and inhibit abnormal activities of METex14, its high selectivity makes it able to bind with METex14 accurately without a big dose, and its sensitivity makes it treat NSCLC effectively. Capmatinib has fewer side effects and is safe. Crizotinib plays a significant role as a first-line treatment against NSCLC and has a potential to fight more kinds of cancer. Future research should be conducted on the problem of drug resistance to get better efficiency, as well as clinical trials to explore broader clinical applications.

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