

Research and Treatment Progress of Capmatinib in Hepatocellular Carcinoma

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Abstract. Hepatocellular carcinoma (HCC) cases account for the vast majority of liver cancer with high mortality. There is no particular therapy for HCC, and it has been claimed that only around 25% of individuals with HCC are candidates for curative surgery. The only drug approved FDA for HCC is Sorafenib, however it is prone to drug resistance. Abnormal c-met activity is linked to Tumorigenesis and tumor metastasis, implying that inhibiting relevant pathway might be therapeutic. HGF/c-Met pathway is related HCC exacerbation and metastasis, abnormal met signaling leads to activated downstream pathways and causes tumorigenesis. also, the HGF/c-Met induces the VEGF pathway to enhance tumor angiogenesis. Met is becoming a key target in HCC treatment, especially in advanced patients. As a small molecule met inhibitor, Capmatinib has high sensitivity of Met receptor, it can be absorbed rapidly, with good pharmacokinetic characteristics. It has good antitumor activity in clinical efficacy, well tolerated and with slight side effects. In addition, it is irrelevant to food which means patients have the same concentration of capmatinib in plasma regardless of their eating habits, which will be an effective and safe treatment strategy for HCC. Application of Capmatinib as HCC target treatment remains popular in HCC research, and clinical trials designed in diverse dimensions are ongoing to study the benefits of capmatinib.

Keywords: Hepatocellular carcinoma, c-Met pathway, capmatinib.

1. Introduction

Hepatocellular carcinoma (HCC) takes up for 75-85% of primary liver cancer. In the statistics of cancer-related mortality, primary liver cancer ranks third in 2020[1, 2]. For patients in early stage of HCC, surgical resection can effectively treat diseases [3]. Unfortunately, it is reported that only less than 25% of patients with HCC are suitable can be treated by curative surgery [4]. Early detection and treatment are difficult for most HCC patients because HCC is asymptomatic. When symptoms of HCC occur, they are usually similar to those of chronic disease. That is the reason why HCC is always found at an advanced stage [2, 3]. Other therapeutic options are limited. The only FDA-approved drug for HCC is Sorafenib, a small molecular multi-targeted receptor TKI capable of blocking tumor angiogenesis and cell proliferation. Sadly, sorafenib does not have a satisfactory efficiency and might lead to drug resistance after one year treatment [4, 5]. The c-Met pathway is an initial pathway in liver and draws people's attention as a therapeutical target. Capmatinib (INC280) is an oral met inhibitor with high efficiency and selectivity. This paper aims to conduct the MET/HGF pathway in HCC, capmatinib, and the development of combination therapy in clinical application to prove the potential therapeutic effect of capmatinib in HCC.

2. Met, a promising target in HCC treatment

2.1. The HGF/c-MET Axis

The Met gene which was found in chemically induced human osteosarcoma cell lines for the first time encodes disulfide-linked heterodimeric receptor tyrosine kinase (RTK). Met receptor contains α and β subunit which contains 5 catalytic tyrosines in a cytoplasmic. By disulfide. Y1003 regulates c-Met negatively and the function of the other four hotspots is to regulate c-Met in positive mediation. Cbl-mediated Met lysosomal degradation is conciliated by Y1003[31]. HGF, the ligand of MET works as a hepatocyte mitogen for primary hepatocytes which can promote the cell motility of

epithelial [7]. Met can be activated either in canonical or non-canonical patterns. Met RTK binds to ligand HGF activates a series of downstream pathways and then plays an important role in tissue pattern formation, wound recovery and organ regeneration in early embryogenesis [8]. In absence of HGF, c-Met phosphorylation can occur through interacting with EGR receptors or other membrane receptors, for example CD44, the FAS cell surface death receptor and Plexin B. These relevant cell signal network are thought to be associated with malignant transformation and targeted therapies resistance [9, 10].

2.2. The HGF/c-Met pathway in HCC

More than three fourth of all cases of HCC are associated with liver disease. HBV (Hepatitis B virus) infection takes nearly 50%, HCV (Hepatitis C virus) is the other precipitating factor for 25% cases [11]. Met overexpression and met mutation can be observed in over half the number of hepatocellular carcinomas. And also, it relates to poor prognosis and limited survival time [12]. Chronic liver diseases may lead to homodimerization and autophosphorylation of Met receptor. Activated c-Met then activates kinase signaling pathways associated with gene expression regulation and cytoplasmic function activity for example the MAPK/ERK, PI3K, and PKB pathways. Furthermore, the HGF/c-Me pathway promotes tumor angiogenesis by activating the VEGF pathway. Although some studies showed that the upregulating of MET has the possibility of promoting liver tissue recovery from chronic liver disease. However, the activation of Met may promote HCC development. Abnormal met signaling leads to activated downstream pathways and causes tumorigenesis. HGF/c-Met are proposed as promising therapeutic targets owing to their initial role in HCC.

3. MET tyrosine kinase inhibitor capmatinib(INC 280)

3.1. Introduction of capmatinib

Met inhibitors belong to tyrosine kinase inhibitors. After TKIs (tyrosine kinase inhibitors) are absorbed and enter cells, inhibitors interact with a group of receptors and signaling molecules inside cells and block a series of downstream pathways like the RasRaf/MEK/MAPK pathway and PI3K/AKT/mTOR pathway [14]. Met inhibitors are divided into non-selective inhibitors and selective inhibitors. Nonselective Met kinase inhibitors failed to demonstrate significant efficacy in clinical trials. In the contract, c-Met activity in tumor can be inhibit if patients take a determinged dose selective met inhibitors [16].

Capmatinib(INC280) is an ATP-competitive MET TKI. In November 2009, Novartis made a worldwide exclusive agreement with Inctye Corporation about developing an oral target therapy for some kinds of cancer. They conducted the development of INC280(also known as capmatinib) worldwide. Capmatinib is highly sensitive to MET. In biochemical and bonding assays, capmatinib revealed 1000-fold selectivity to Met versus other 57 human kinase [15]. In order to further study the affinity of capmatinib, a binding test with a set of 442 kinase was conducted at the KINOMEScan selectivity screening platform. According to the outcomes, Met and two mutant types had the top three binding constants which is approximately 1000 fold compared with all other hits [7]. The imidazotriazine core of capmatinib binds MET residue Y1230 through aromatic stacking interaction, while the quinoline part binds with the kinase's hinge region. MET residues D1228 and K1110 form a salt bridge between each other which ensures the stability of the particular structure of the kinase activation loop [6]. An experiment used a group of MET kinase domain mutant BaF3 cells. After that, the results show that BaF3 cells with Met D1228 and K1110 mutants reveal strong resistance to capmatinib [16]. Capmatinib can be absorbed rapidly. After giving an absolute 400mg dose of capmatinib, the peak plasma concentration (C_{max}) reached in 1-2 hours. Oral absorption of capmatinib is 70% and manifested as linear pharmacokinetics [17]. Meanwhile, another advantage of capmatinib is that the exposure to capmatinib is irrelevant to food which means patients have the

same concentration of capmatinib in plasma regardless of their eating habits. Also, it shows the convenient medication of capmatinib [18].

3.2. Advances of capmatinib in clinical research

3.2.1. Capmatinib as a single drug treatment in HCC

phase I

NCT01324479, a phase I, open label, multicenter, non-randomized, two-part trial, containing dosage escalation and expansion, included 38 patients. This research intends to evaluate the safety and tolerability of capmatinib and all participants had advanced MET-positive solid tumors (including HCC). 600mg bid capsule and 400mg bid tablet of capmatinib are the RP2D investigated in this phase I trial. Capmatinib was well tolerated and its safety is controllable (only 3 dose-limiting toxicities reported) across all explored doses and showed antitumor activity (46% of patients in the HCC achieved tumor reduction) [19].

NCT01546428 was conducted from 10 February 2012 to 22 January 2016 with the aim to investigate MTD and to find out how about the capmatinib exerts preliminary antitumor activity with solid tumors in Japanese patients. In general, 65.9% participants received eight dose levels of capsule capmatinib separately and 34.1% took two dose levels of capmatinib, totally 44 adults were enrolled in the experiment. The endpoint is 38 patients (86.4%) occurred disease progression. As for Japanese patients, capmatinib is well tolerated which is similar in non-Japanese patients. During the median duration of treatment exposure, only 2 DLT was observed. 95.5% of patients appeared at least one or AE during the clinical period which is similar to the safety profile in non-Japanese patients [20].

In addition, a study mainly about 2 drug cock-tail therapy of digoxin and rosuvastatin and capmatinib was investigated to figure out the influence of capmatinib on the pharmacokinetics in patients. Both P-gp and BCRP are kinds of drug transporters and their probe drugs are digoxin and rosuvastatin. In vivo trials, capmatinib inhibits the drug transporters at therapeutic dosage. Data from this study will provide safety guidance for the combined use of capmatinib and P-gp and BCRP substrates. In addition, it also found that capmatinib had good clinical safety and was easy for patients to accept [21].

phase II

NCT01737827 was conducted from 25 March 2013 to 28 February 2017 with the purpose of evaluate the safety of the drug and its pharmacokinetics. All patients in this phase II had advanced HCC. At the signal-seeking efficacy endpoint, a total of 38 patients were taken capmatinib. According to the pharmacokinetic analysis, capmatinib 300 mg BID capsules can be absorbed rapidly ($T_{max}=2.0$ h). Nausea was present in 42% of patients, vomiting was present in 37% of patients, and diarrhea was present in 34% of patients, which were common Adverse Event (AEs >30%). Besides, both aspartate transaminase (AST) (34%) increased and appetite decreased (34%) were include in common AEs. Capmatinib showed its considerable anti-tumor capacity. The ORR is 10% and the disease control rate is 33% in expansion cohort (totally n=30) [22]. Thus, for HCC patients capmatinib proves its prospect as a small molecule inhibitor in target treatment.

3.2.2. Capmatinib in combination therapy in HCC

Combination therapy has always been the main treatment method, especially tumor diseases, with improving the efficacy of therapeutic regimens overcoming primary or acquired resistance.

Combinate YAP1 inhibitor with capmatinib suppresses SIX4-mediated HCC

SIX homeobox 4 (SIX4) has a close relationship to tumor metastasis, development, deterioration, and poor prognosis in human HCC. Experimental study analyzed mRNA level in SIX4 from 3 aspects. The first group is HCC tissue (n=50) and healthy tissue (n=10). Next study is about comparing patients with or without recurrence or metastasis. The subsequent research is comparing 30 pairs HCC specimens of primary and metastatic HCCs. In general, the amount of SIX4 expression is higher in metastatic HCC samples, which proved SIX4 has a close relationship with HCC metastasis. Data indicated that both c-Met and YAP1 are the direct transcriptional targets of SIX4 [23]. In this

combination drug experiment, PLC/PRF/5SIX4 cells were treated with capmatinib, Verteporfin (A kind of YAP1 inhibitor), and the combination of them. And the outcomes revealed that the trails rugs lowered the transfer rate of cells (number of invasion and migration cells was less than 100 compared with other groups of approximately 200-400). In vivo trials with nude mice, the combination therapy prolonged survival time (survival rate remained 1. 0 for 60 days before it had a slight drop) [24].

Improving antitumor activity using PD-L1 antibody and met inhibitor

Programmed cell death ligand-1(PD-L1) can be easily observed in tumor. In many scenarios, PD-L1 expression enables tumor cells to evade detection immune system [25]. Not only do tumor cells express PD-L1, but so do immunological cells. For example, PD-L1 assist HCC hide and escape from T cells, allowing them to transfer to other parts in body. T cells can solve the problem and better identify and kill tumor cells with the help of tumor cells [26, 27]. This trial revealed that a complete immune system affects MET inhibitors' efficacy. In comparing experiment constructed in HCA-1 liver model, combination treatment of capmatinib and PD-L1 antibody is better than one drug treatment. The combination group results in smaller tumor size and had a longer survival time than single-agent therapy ($P < 0. 1$)[28].

Other trials shows capmatinib promising treatment for HCC

At present, some clinical research concentrating on the combination therapy between EGFR-TKIs and MET inhibitors are ongoing, such as the combination of newly improved EGFR-TKIs and capmatinib (NCT02335944) [30]. EGFR has always been a hot target for drug development. Overexpression of EGFR has been shown to be a potential determinant of initial resistance to sorafenib and erlotinib in HCC cells, while EGFR activation has been shown to be a potential determinant of sorafenib and erlotinib resistance in HCC cells [29]. However, there is not much clinical evidence in this regard, it needs further exploration and confirmation in the future.

4. Conclusion

HCC still has a high mortality and less optional therapies, which needs to bring to attention. The Met receptor has gained more and more attention for its important role in liver. Capmatinib was proved its antitumor ability in advanced solid tumor with Met maladjustment. and suppressd MET overexpression. Meanwhile, capmatinib has some advantages such as rapid absorption, reaching effective dose below the toxicity concentration. With the development of clinical researches, mechanism of durg-resistance in HCC are discovered and relevant receptors and ligands are found. Capmatinib as MET inhibitor combining with drugs in different mechanism are demonstrated that their efficiency, thus it can be used as a promising treatment strategy for hepatocellular carcinoma.

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