

Research progress of VEGFR/c-Met dual inhibitors as potent anticancer agents

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Abstract: Vascular endothelial growth factor receptor (VEGFR) is a vital anticancer target that shows closely correlated with angiogenesis, cell growth, metastasis, and apoptosis of cancer cells. Recently, VEGFR inhibitors have become outstanding therapeutic agents for the treatment of various solid tumors such as hepatocellular carcinoma, renal cell carcinoma, medullary thyroid carcinoma, ovarian cancer, etc. However, it is drug resistance that restricts the long-term benefits of patients who have received the treatment of VEGFR inhibitors. Mechanism research revealed that c-Met overexpression is one of the important factors for the resistance of VEGFR inhibitors, which is manifested by the combination therapy of VEGFR and c-Met inhibition. Moreover, c-Met, the receptor of hepatocyte growth factor (HGF), elicits many different signaling pathways involved in cell proliferation, migration, differentiation, and survival, showing correlation with aggressive tumor growth, poor prognosis in cancer patients. Thus, small molecules targeting both VEGFR/c-Met kinases are identified as effective approaches to treat solid tumors and overcome the drug resistance of VEGFR inhibitors. Herein, VEGFR/c-Met inhibitors under clinical evaluation were described for reviewing the research progress of this area.

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1. Introduction

Tumor growth and metastasis are intimately linked with angiogenesis which is regulated by various growth factors. Vascular endothelial growth factor (VEGF) is the most prominent one which strongly stimulates the proliferation of endothelial cells and promotes the formation of tumor blood vessels [1-3]. Therefore, anti-angiogenesis by blocking the VEGF-related signaling system is a remarkable approach to treat cancer, which has been corroborated by the clinical results. Recently, numerous VEGFR inhibitors were developed and applied to treat various solid tumors, such as Dovitinib, Sunitinib, Brivanib, Pazopanib, Axitinib, etc[2, 4]. Though VEGFR inhibitors bring significant advances in the treatment of cancers, the high incidence of drug resistance became another challenge [5, 6]. Some mechanistic investigations and clinical evidence have stated that strongly VEGFR inhibition causes the induction of hypoxia and aberrant upregulation of hypoxia-inducible factor-1 α (HIF-1 α) and c-Met expression, and the upregulation of c-Met promoted the resistance of tumor cells to VEGFR inhibitors [7]. c-Met, the receptor of hepatocyte growth factor (HGF), is also a promising target for the treatment of cancer [8-10]. HGF/ c-Met pathway plays a critical role in the regulation of tumor invasion, metastasis, and angiogenesis by activation of downstream pathways

such as PI3K/AKT and Ras/ERK [11]. Therefore, VEGFR/c-Met dual inhibition is a theoretically attractive method for cancer treatment and overcoming drug resistance of VEGFR inhibitors. Several kinds of research have demonstrated that simultaneously inhibiting VEGFR/c-Met by a combination of diverse inhibitors or dual-targeted macromolecules had synergistic antitumor effects in different tumor models [12, 13]. Herein, we presented several potential VEGFR/c-Met inhibitors to review the research progress and discuss the further development of this area (Figure 1).

2. Approved VEGFR/c-Met dual inhibitors

Cabozantinib is the only approved oral potent VEGFR/c-Met inhibitor with several indications such as medullary thyroid cancer (MTC), advanced renal cell cancer (RCC) and hepatocellular carcinoma (HCC, second-line therapy). Except for VEGFR and c-Met, Cabozantinib exhibits inhibitory activity against a panel of kinases implicated in tumor pathogenesis, including RET, c-Kit, FLT1, FLT3, FLT4, Tie2, AXL, etc. Preclinically, Cabozantinib could reduce phosphorylation of VEGFR/c-Met at low concentrations in cellular assays, and disrupt tumor vasculature and proliferation in a dose-dependent manner in vivo[14].

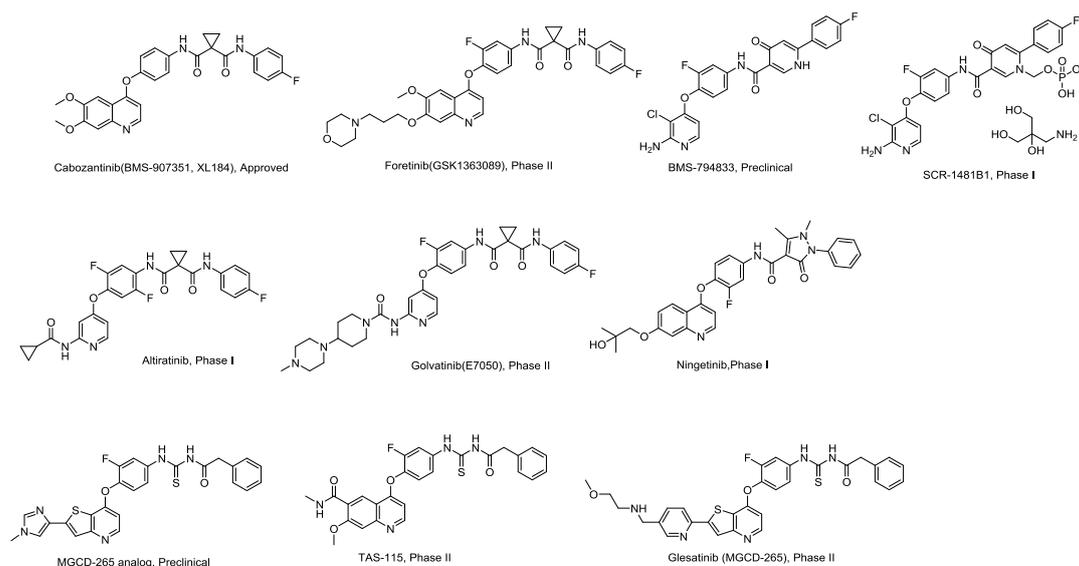


Figure 1. The potential VEGFR/c-Met inhibitors in clinic.

The safety profile and pharmacokinetics of Cabozantinib have been evaluated by a phase I dose-escalation study (NCT00215605). Eighty-five patients with advanced solid tumors or lymphomas were enrolled, including 37 with MTC (35 MTC patients with measurable disease). Overall, 41% of MTC patients (15/37) had stable disease last for more than 6 months. As for 35 MTC patients with measurable disease, ten of them (29%) had a partial response and 17 of them experienced tumor shrinkage of 30% or more. Treatment-related adverse events (AE) were reported by 77 of 85 patients (90%). Dose-limiting toxicities were palmar-plantar erythrodysesthesia (PPE, Grade 3), mucositis, and AST, ALT, and lipase elevations and mucositis (Grade 2) that resulted in dose interruption and reduction.

The EXAM (NCT00704730) trial, a large phase III trial in medullary thyroid cancer, was directly initiated following the positive responses in MTC patients from the above phase I study. 330 MTC patients were enrolled and randomized in a 2:1 ratio to Cabozantinib versus placebo. Prolonged PFS (estimated median PFS 11.2 vs. 4.0 months) and increased response rate (28% vs. 0%) with cabozantinib were observed across all subgroups compared to the placebo group, including those patients who have prior treatment with TKIs. Common Cabozantinib-associated adverse events included diarrhea, palmar-plantar erythrodysesthesia, decreased weight and appetite, nausea, and fatigue and resulted in dose reductions in 79% and holds in 65% of patients, leading to treatment discontinuation in 16% of Cabozantinib-treated patients [15, 16].

Another randomized, open-label, phase 3 trial (METEOR) evaluated the efficacy of Cabozantinib in RCC (renal cell carcinoma) patients that had progressed after VEGFR-targeted therapy, setting

progression-free survival (PFS) as the primary endpoint, and overall survival (OS)/response rate (RR) as secondary endpoints. This study demonstrated that treatment with Cabozantinib achieved longer progression-free survival (7.4 months vs. 3.8 months), higher objective response rates (21% vs. 5%), and improved overall survival (21.4 months for vs. 16.5 months) than everolimus[17]. The most common Grade 3 or 4 adverse events in the Cabozantinib group were hypertension (15%), diarrhea (13%), fatigue (11%), palmar-plantar erythrodysesthesia syndrome (8%), anemia (6%), hyperglycemia (1%), and hypomagnesemia (5%)[18]. Adverse events were managed with dose modifications and supportive care in both treatment groups. The results of the Quality of Life Outcomes questionnaire indicated that Cabozantinib extended time to deterioration (TTD) overall compared with everolimus and patients with bone metastases gain remarkably longer TDD[19].

CELESTIAL (NCT01908426) is a randomized, double-blind, phase 3 trial to evaluate the efficacy of Cabozantinib in previously treated patients with advanced hepatocellular carcinoma. Treatment with Cabozantinib led to longer overall survival (10.2 months vs. 8 months) and progression-free survival than placebo (5.2 months vs. 1.9 months). However, the rate of high-grade adverse events in the Cabozantinib group was higher, and the most common serious events were palmar-plantar erythrodysesthesia (17%), hypertension (16%), increased aspartate aminotransferase level (12%), fatigue (10%), and diarrhea (10%)[20].

Cabozantinib treatment substantially could improve clinical benefits for different cancer patients with a manageable AE profile. Among these cases, patients who were previously treated by VEGFR inhibitors

(Vandetanib, Sorafenib) still had responses to Cabozantinib, supporting that drug resistance of VEGFR inhibitors may be overcome by c-Met inhibition. Although Cabozantinib is the only approved VEGFR/c-Met inhibitor up till now, the outstanding clinical benefits of these kinds of agents have been verified. Recent clinical trials of Cabozantinib focused on the combination therapy with PD-1/PD-L1, which showed strong synergistic activity.

3. VEGFR/c-Met inhibitors in different clinical phases

3.1. Foretinib

Foretinib (XL880, GSK1363089), an oral multi-kinase inhibitor that targets c-Met, RON, Axl, Tie-2, VEGFR, has a similar structure and biological activity with Cabozantinib. Preclinically, Foretinib significantly inhibited tumor cell proliferation, invasion, and tumor angiogenesis [20,21]. The safety profile of Foretinib was supported by several phase I clinical trials. Dose-limiting toxicities included grade 3 elevations in aspartate aminotransferase and lipase. Additional adverse events included hypertension, fatigue, diarrhea, vomiting, proteinuria, and hematuria. Responses were observed in two patients with papillary renal cell cancer and one patient with medullary thyroid cancer. Stable disease was identified in 22 patients[21, 22].

Further exploration of Foretinib in phase II studies were conducted to assess the efficacy in advanced solid tumors including recurrent/metastatic breast cancer[23], squamous cell cancer of the head and neck[24], papillary renal-cell carcinoma (PRC)[25], metastatic gastric cancer[26]. Overall, moderate anticancer activity and tolerated adverse events were shown in these clinical trials, even though some primary endpoints were not achieved. Some combination therapies were developed such as Erlotinib and Lapatinib for higher response and more indications, but the incremental toxicity should be considered[22, 27]. The development of Foretinib may have been halted in consideration of the fact that no more clinical trials conducted for quite a while.

3.2. Golvatinib

Golvatinib (E7050), a highly potent c-Met and VEGFR-2 dual inhibitor, significantly inhibited the growth of the tumor and endothelial cells in vitro and showed antitumor activity with tumor regression against various tumors in vivo. Eight phase I/II clinical trials have been completed to estimate the antitumor activity against various solid tumors[28]. Even though Golvatinib exhibited excellent activity in preclinical research, most results of clinical trials were not revealed and no more ongoing trials were shown on

the website of clinicaltrials.gov.cn. Moreover, a clinical trial referred to combination therapy of Golvatinib (with cisplatin and capecitabine) was terminated probably considering the high rate of serious adverse events (71.4%)[29]. The development prospect of Golvatinib was fairly uncertain, given the disclosed efficacy and safety profile.

3.3. Glesatinib

Glesatinib (MGCD-265) is a highly potent, orally-available small molecule designed to inhibit c-Met, VEGFR, Tie-2, and Ron kinases which are potentially relevant for the initiation, progression, metastasis of a variety of human cancers. Glesatinib inhibited HGF/c-Met signaling pathway, demonstrating remarkable regression of METex14 del-driven patient-derived xenografts. A durable RECIST partial response occurred in a METex14 del mutation-positive patient who was enrolled in phase I clinical trial[30]. Prolonged treatment of nonclinical models with selected c-Met inhibitors resulted in differences in resistance kinetics and mutations within the c-Met activation loop (i.e., D1228N, Y1230C/H) that conferred resistance to type I MET inhibitors but remained sensitive to Glesatinib. Besides, the reversal effects of Glesatinib to P-glycoprotein (P-gp) mediated MDR have been reported recently. Glesatinib can sensitize paclitaxel, doxorubicin, colchicine resistance to P-gp overexpressing KB-C2, SW620/Ad300, and P-gp transfected Hek293/ABCB1 cells, suggesting new applications in the clinic[31]. A phase II clinical trial of Glesatinib in combination with Nivolumab for the treatment of non-small cell lung cancer (NSCLC) is in progress.

3.4. Nintetininib

Nintetininib (CT053PTSA) is a potent, orally bioavailable small molecule tyrosine kinase inhibitor (TKI) against c-Met, VEGFR as well as Axl, Mer, and FLT3. In cell-based assays, it could inhibit HGF and VEGF-stimulated HUVEC proliferation and microvascular angiogenesis in rat aortic rings. In vivo, Nintetininib disrupted the phosphorylation of c-Met and its downstream signaling kinases AKT and ERK1/2 in U87MG tumor-bearing nude mice, and exhibited significant antitumor efficacy against various solid cancer xenograft models, including Caki-1 (kidney carcinoma), U-87MG (glioblastoma), NCI-H441 (lung adenocarcinoma), MDA-MB-231 (breast adenocarcinoma), SMMC-7721 (hepatoma), 5637 (bladder carcinoma) and SK-OV-3 (ovarian carcinoma). Besides, prolonged the median survival time (MST) and the significant increase in life-span value (ILS = 32%) were obtained in orthotopic U87MG human glioblastoma xenograft model by comparing the antitumor efficacy between Nintetininib and vehicle

treatment. Given the excellent biological activity as well as favorable PK profile, Nintedanib is currently under phase I evaluation against non-small cell lung cancer, acute myeloid leukemia, and metastatic renal cell carcinoma[32].

3.5. TAS-115

TAS-115 is a VEGFR/c-MET inhibitor bearing distinct skeleton as Cabozantinib, Foretinib, with approximately equal VEGFR/c-Met inhibitory activity to that of the other reported VEGFR or c-Met-targeted kinase inhibitors such as Sunitinib, Sorafenib, and Crizotinib. Kinase selectivity assay of TAS-115 revealed PDGFR, Axl, c-Kit Src, FLT1 were also involved, which play vital roles in several tumorigenic signal pathways. TAS-115 markedly inhibited the phosphorylation of c-Met in cmet-amplified MKN45 cells as well as that of signal transduction factors located downstream from c-Met, including ERK 1/2, AKT, FAK, S6, and STAT3. In cellular assays, VEGFR or c-Met dependent cell growth was suppressed in a highly selective manner, causing minimal damage to normal cells. In cmet-amplified human cancer transplanted models, TAS-115 markedly induced tumor regression and prolonged survival by consecutive inhibition of angiogenesis. An open-label, dose-escalation phase I study of TAS-115 was conducted to assess the safety profile [33, 34]. Commonly treatment-related adverse events were neutropenia (24.6%), hypophosphatemia (21.3%), anemia, and thrombocytopenia (14.8%), and leukocytopenia (11.5%), occurring in $\geq 10\%$ of patients. Despite the stable disease was achieved in 37.8% of patients (31/82), no patients showed a complete or partial response by RECIST evaluation[33]. The phase II clinical trial of TAS-115 is ongoing.

3.6. Altiratinib

Altiratinib (DCC-2701) inhibited a panel of kinases including VEGFR/c-Met, Tie2, TRK, FLT3, c-Kit, etc. Distinctively, it could potentially bind with mutated c-Met kinases like D1228H, D1228N, Y1230C, Y1230D, Y1230H, M1250T, which Cabozantinib and Crizotinib hardly target. Altiratinib exhibited a balanced potency for inhibiting these multiple angiogenic signaling pathways, suppressing proliferation of met-amplified cancer cells, disturbing capillary tube formation and tumor growth in several xenograft models. Besides, Altiratinib could penetrate the murine blood-brain barrier, which might have benefits for brain cancers and brain metastases[34]. However, the only phase I study has been terminated for some unrevealed reasons.

3.7. BMS-817378 (a prodrug of BMS-777607)

BMS-777607, a multitarget kinase inhibitor,

potentially binds with c-Met, VEGFR, RON, Axl, Mer, FLT3, Aurora B, and blocks constitutively phosphorylation of c-Met and related downstream cascade in cancer cells, showing significant inhibition of the proliferation and migration of the cancer cells. This molecule also inhibited tumor growth in the xenograft models of SKOV3 (ovarian cancer)[35], U118MG (glioblastoma)[36], KHT (lung tumor)[37], GTL-16 (gastric carcinoma)[38]. Generally, multitarget kinase inhibitors have more potent anticancer activity than that targeting specific kinases. However, the complex mechanism resulted from multiple kinase inhibition of BMS-777607 induce polyploidy and senescence of breast cancer cell which increased resistance to cytotoxic chemotherapeutics[39, 40]. BMS-777607 in combination with mTOR inhibitor AZD8055 could overcome that negative resistance and sensitizes breast cancer cells to cytotoxic chemotherapeutics, providing a potential application for clinical use[41]. BMS-817378, a clinical candidate in phase I evaluation, is a phosphate prodrug of BMS-777607, which probably is designed for higher solubility and bioavailability. However, the clinical trial has been withdrawn and the further development of BMS-817378 has been bogged down.

4. Conclusion and Prospect

Recently, many VEGFR inhibitors such as Sorafenib, Lenvatinib, Sunitinib, Cabozantinib are developed and widely used in solid tumor therapeutics, significantly improving the survival and quality of life of cancer patients, although the drug resistance phenomena are common in clinic. The VEGFR/c-Met dual inhibitors have remarkable antitumor efficacy even though for patients who have prior treatment with VEGFR inhibitors, and the promising clinical benefits have been manifested by Cabozantinib. Several VEGFR/c-Met inhibitors were presented here for a discussion of the research progress of this area. Though some of them showed exciting results in vitro and in vivo, there are no outstanding agents in clinical trials comparing to Cabozantinib. The development of VEGFR/c-Met inhibitors is confronted with the following challenges:

(1) Structural similarity

As shown in Figure 1, the structures of Foretinib, Golvatinib, Altiratinib have high similarity with Cabozantinib, resulting in similar efficacy, targets, adverse events, etc. The research on Cabozantinib analogs restricts the breakthrough of VEGFR/c-Met inhibitors, and novel skeletons are urgently demanded to break the existing shackles of Cabozantinib.

(2) Complex mechanism derived from multiple targets inhibition

Nearly all of the reported VEGFR/c-Met inhibitors target a panel of kinases, resulting from distinctive,

complex, ambiguous anticancer mechanisms that might induce the opposite effects and reduce the antitumor efficacy.

(3) The safety concerns

Based on the failure clinical results of candidate agents, it principally was the narrow therapeutic window that hampered the further evaluation. The high adverse events rates lead to makeshift dose reduction or discontinued treatment, even for the approved drug Cabozantinib.

In conclusion, VEGFR/c-Met inhibitors have potential efficacy for the treatment of solid tumors, especially for those showing resistance to VEGFR inhibitors. There is still unmet clinical need for the VEGFR/c-Met inhibitors, considering Cabozantinib is the only approved drug in this area. The development of novel agents should focus on innovative structures, definite targets and mechanisms, wider therapeutic window.

Declaration of competing interest

The authors declared that they had no known competing for financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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