cMET as a potential therapeutic target in gastric cancer (Review)

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Abstract. Gastric cancer is one of the most common malignancies worldwide. Despite improvements in surgery and chemotherapy, the outcomes in patients with advanced gastric cancer remain poor. cMET is a member of the receptor tyrosine kinase family, and plays a key role in tumor survival, growth, angiogenesis and metastasis. cMET overexpression and/or gene amplification occurs in a significant proportion of gastric cancers. cMET is associated with a high tumor stage and poor prognosis. Several cMET inhibitors have been investigated in clinical trials, and the initial results are encouraging. It has become increasingly apparent that cMET is a promising therapeutic target in gastric cancer. In this review, we summarize the development of cMET inhibitors in the preclinical and clinical environment. In addition, we discuss the challenges of cMET-targeted therapy in gastric cancer and explore possible solutions.

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1. Introduction

Gastric cancer (GC) is the fourth most commonly diagnosed cancer and the second major cause of cancer-related mortality worldwide (1,2). Despite improvements in surgery and chemotherapy, the outcomes in patients with advanced gastric cancer remain poor, with a five-year survival rate of <20% (3).

Over the past decade, targeted therapies have greatly improved the outcome of a number of malignancies, including breast, colorectal and lung cancer. However, less progress has been made with regard to gastric cancer. The Trastuzumab for Gastric Cancer (ToGA) study, investigating the effectiveness of trastuzumab in human epidermal growth factor receptor 2 (HER2; ERBB2)-positive advanced gastric or gastrooesophageal junction (GEJ) cancer (4), represents a milestone in the targeted therapy of gastric cancer. Moreover, a recent study developed a genomic molecular map of gastric cancer and suggested that collectively 37% of cases may be potentially treatable by receptor tyrosine kinase (RTK)/RAS directed therapies (5).

Similar to HER2, cMET is another member of the RTK family, and plays a key role in tumor survival, growth, angiogenesis and metastasis (6-10). A significant proportion of gastric cancers harbor cMET overexpression and/or gene amplification (11,12), and the aberrant signaling of cMET pathways in gastric cancer has been shown to correlate with a high tumor stage and poor prognosis (11,13). The alternative activation of the cMET pathway is considered to be an important mechanism responsible for resistance therapeutics targeting HER family members, such as HER2 and epidermal growth factor receptor (EGFR) (14,15). Recently, several cMET inhibitors have been investigated in clinical trials, and the initial results are encouraging (16,17). cMET is emerging as a promising therapeutic target in gastric cancer, and may provide a potential approach to overcoming resistance to other agents in targeted therapy.

Although a number of review articles have focused on the role of cMET in various malignancies, there is a lack of data on its role in gastric cancer. Therefore, a greater understanding of the role of cMET in gastric cancer is required.

In this review, we assess the role of cMET in gastric cancer, summarize the preclinical and clinical trials of cMET inhibitors, and discuss the challenges of cMET targeted therapy. Finally, we present possible solutions, including the exploration of biomarkers for population selection and drug response assessment, and the establishment of patient-derived human tumor tissue (PDHT) xenograft models for drug sensitivity screening.

2. The cMET pathway

cMET was first identified in 1984 in a human osteogenic sarcoma cell line treated with the carcinogen, N-methyl-
N’-nitrotrinitrosoguanidine (18), by a genomic rearrangement that fused the sequence from the translocated promoter region (TRP) locus on chromosome 1 to a sequence from MET on chromosome 7 (19). A subsequent study revealed that the encoded protein was an RTK (20).

Both hepatocyte growth factor (HGF) and scatter factor (SF), are the ligands of cMET (21). HGF was originally identified as a liver mitogen, while SF was recognized as a fibroblast-derived modulator of epithelial cell mobility, then they were found to be identical (22,23). Binding of HGF/SF to cMET leads to receptor homodimerization and tyrosine residue phosphorylation, recruitment of adaptor and effector proteins, which ultimately triggers downstream activation of the RAS/mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)/AKT, signal transducer and activator of transcription (STAT), Ras-related C3 botulinum toxin substrate 1 (RAC1)-cell division cycle 42 (CDC42) and p21 activated protein kinase (PAK) pathways (Fig. 1) (24-29).

The cMET signaling pathway can be disrupted at different levels, from the cMET receptor to the downstream pathway. CDC42, RACI-cell division control protein 42; GRB2, growth factor receptor-bound protein 2; GAB1, GRB2-associated protein 1; PAK, p21-activated kinase; STAT3, signal transducer and activator of transcription 3.

3. The role of cMET in gastric cancer

The cMET pathway can be oncogenic and is activated by multiple mechanisms including, gene amplification, gene mutation, protein overexpression and ligand-dependent autocrine and paracrine, receptor crosstalk (10,28). The role of cMET in gastric tumorigenesis was first identified in the human gastric tumor cell line, GTL-16 (37). The overexpression of TPR-MET RNA was detected in superficial gastritis lesions with hyperplasia of glandular neck cells, suggesting the possible involvement of this oncogene at an early stage of gastric tumorigenesis (38). Similar results were reported in another study (39).

cMET protein overexpression, as well as gene amplification and mutation have been detected in gastric cancer tissues and cell lines. Protein overexpression and gene amplification can be determined by immunohistochemistry (ICH) and RT-PCR/fluorescence in situ hybridization (FISH), respectively. Among the retrospective studies (5,11-13,40-46) (Table I), the increased expression of cMET was detected in approximately 43% of patients with gastric cancer, while gene amplification was detected in almost 12% of patients. Protein overexpression and/or gene amplification significantly correlated with the depth of tumor invasion and metastasis (11,13,45) and poor prognosis (5,11-13,40,43-46). Based on available evidence, it can be inferred that gene amplification is likely to be more
study testing the safety and pharmacokinetics of rilotumumab in gastric cancer and a rationale for the development of cMET inhibitors.

4. The development of cMET inhibitors in gastric cancer

The increased understanding of the cMET pathway has led to the development of cMET inhibitors, which focus on one of the steps in the cMET pathway. Clinical trials investigating monoclonal antibodies and small-molecule inhibitors directed at the cMET axis are currently underway. The initial results of these clinical trials are optimistic; thus, targeting the cMET pathway is becoming a promising therapeutic strategy for gastric cancer. The main strategies include, monoclonal antibodies or antagonists against HGF or cMET, cMET selective or unselective tyrosine kinase inhibitors (TKIs) and downstream pathway inhibitors (Fig. 1 and Table II).

5. Monoclonal antibodies to HGF

Rilotumumab (AMG 102) is a fully human monoclonal antibody to HGF/SF. In vitro and in vivo studies have confirmed the antitumor activity of rilotumumab (51,52). A phase 1 clinical study testing the safety and pharmacokinetics of rilotumumab in 40 patients with refractory advanced solid tumors, demonstrated that rilotumumab was safe and well tolerated, and had a favorable pharmacokinetic profile. A total of 16 of 23 (70%) evaluated patients had a best response of stable disease (SD) with progression-free survival (PFS) ranging from 7.9 to 40 weeks (53).

A multicenter, double-blind phase 1b/2 study, assessed rilotumumab in combination with epirubicin, cisplatin and capecitabine (ECX) in 121 advanced or metastatic gastric or esophagogastric junction (EGJ) cancer patients (54). This study reported that the addition of rilotumumab to the chemotherapeutic regimen improved the median PFS from 4.2 to 5.6 months [hazard ratio (HR), 0.64; 80% confidence interval (CI), 0.48-0.85], and the median and overall survival (OS) from 8.9 to 11.1 months (HR, 0.73; 80% CI, 0.53-1.01). Further analysis of this study (54), revealed that the addition of rilotumumab to the chemotherapeutic regimen in patients with gastric tumors with high cMET expression improved median OS from 5.7 to 11.1 months (HR, 0.29; 95% CI, 0.11-0.76). Conversely, in patients with low cMET expression, the addition of rilotumumab to chemotherapy was associated with a trend towards an unfavorable OS (HR, 1.84; 95% CI, 0.78-4.34). In the chemotherapy-only arm, patients with a high cMET expression had a worse OS (HR, 3.22; 95% CI, 1.08-9.63) than those with a low cMET expression; similar trends were observed with PFS (16).

A phase III study to confirm the efficacy of rilotumumab in advanced gastric and gastroesophageal cancer in patients with high cMET expression is currently ongoing (55). Another phase II trial, assessing [folinic acid (FOL, fluorouracil (F) and oxaliplatin (OX); FOLFOX] alone or in combination with AMG 102 or panitumumab as first-line therapy in patients with advanced gastroesophageal adenocarcinoma, is also currently ongoing (56). In addition to the typical outcome measures, such as PFS, OS, objective response rate and safety, the study has been designed to identify candidate predictive and prognostic biomarkers among functional molecular alterations of the EGFR/RAS/RAF and HGF/cMET pathways.

Table I. Overexpression and amplification status of cMET in gastric cancer.

<table>
<thead>
<tr>
<th>Authors/(Refs.)</th>
<th>Year</th>
<th>Patients</th>
<th>OP (%)</th>
<th>Method</th>
<th>AP (%)</th>
<th>Method</th>
<th>Poor prognostic marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsugawa et al (44)</td>
<td>1998</td>
<td>70</td>
<td>10</td>
<td>Slot blot hybridization</td>
<td>AP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nakajima et al (11)</td>
<td>2000</td>
<td>128</td>
<td>41.6</td>
<td>ICH</td>
<td>10.2</td>
<td>Southern blot hybridization</td>
<td>OP/AP</td>
</tr>
<tr>
<td>Park et al (43)</td>
<td>2000</td>
<td>43</td>
<td>67</td>
<td>ICH</td>
<td></td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>Tang et al (13)</td>
<td>2004</td>
<td>232</td>
<td>68.8</td>
<td>ICH</td>
<td></td>
<td></td>
<td>OP/AP</td>
</tr>
<tr>
<td>Retterspitz et al (42)</td>
<td>2010</td>
<td>94</td>
<td>50</td>
<td>ICH</td>
<td></td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>Janjigian et al (41)</td>
<td>2011</td>
<td>38</td>
<td>63</td>
<td>ICH</td>
<td>0</td>
<td>FISH</td>
<td>NR</td>
</tr>
<tr>
<td>Lee et al (12)</td>
<td>2011</td>
<td>482</td>
<td>21.2</td>
<td>RT-PCR/FISH</td>
<td></td>
<td></td>
<td>AP</td>
</tr>
<tr>
<td>Graziano et al (45)</td>
<td>2011</td>
<td>230</td>
<td>10</td>
<td>RT-PCR/FISH</td>
<td></td>
<td></td>
<td>AP</td>
</tr>
<tr>
<td>Lee et al (40)</td>
<td>2012</td>
<td>438</td>
<td>23.7</td>
<td>ICH</td>
<td>3.4</td>
<td>SISH</td>
<td>AP</td>
</tr>
<tr>
<td>Deng et al (5)</td>
<td>2012</td>
<td>193</td>
<td>4</td>
<td>SNP arrays</td>
<td></td>
<td></td>
<td>AP</td>
</tr>
<tr>
<td>Shi et al (46)</td>
<td>2012</td>
<td>128</td>
<td>30</td>
<td>RT-PCR</td>
<td></td>
<td></td>
<td>AP</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>42.8</td>
<td>12.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OP, cMET protein overexpression; AP, gene amplification; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; SISH, silver in situ hybridization; NR, not reported.
Table II. Development of cMET inhibitors in gastric cancer.

<table>
<thead>
<tr>
<th>Company</th>
<th>Compound</th>
<th>Type of agent</th>
<th>Development phase</th>
<th>Initial results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amgen</td>
<td>Rilotumab</td>
<td>HGF mAb</td>
<td>II and III</td>
<td>Rilotumab + CT vs. CT: median PFS 4.2 months vs. 5.6 months; OS 5.7 months vs. 11.1 months; suggest MET expression as predictive biomarker (54).</td>
</tr>
<tr>
<td>Roche</td>
<td>MetMab</td>
<td>cMET mAb</td>
<td>III</td>
<td>MetMab: a patient with chemo-refractory metastatic gastric cancer of the liver achieved complete response lasting for 2 years by MetMab monotherapy (17). Suggesting circulating HGF is a therapeutic response biomarker.</td>
</tr>
<tr>
<td>Daiichi Sankyo</td>
<td>Tivantinib</td>
<td>cMET selective TKI</td>
<td>II</td>
<td>Tivantinib: Median PFS 43 days, disease control rate 36.7%. No objective response (64).</td>
</tr>
<tr>
<td>Exelixis</td>
<td>Cabozantinib</td>
<td>CMET unselective TIK</td>
<td>II</td>
<td>Cabozantinib: 8/19 patients SD observed at 12 weeks, overall disease control rate 32% at 12 weeks. No objective response was observed (73).</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Crizotinib</td>
<td>CMET unselective TIK</td>
<td>I</td>
<td>Crizotinib: 2/4 patients with MET-amplified gastroesophageal cancer, tumor shrinkage, (-30 and -16%) progression after 3.7 and 3.5 months; MET, EGFR and HER2 amplification status may be evaluable (67).</td>
</tr>
<tr>
<td>Exelixis</td>
<td>Foretinib</td>
<td>CMET unselective TIK</td>
<td>II</td>
<td>Foretinib: 15/73 patients SD (median 3.2 months); no response observed (70).</td>
</tr>
<tr>
<td>Otsuka</td>
<td>OPB-31121</td>
<td>STAT3 inhibitor</td>
<td>I</td>
<td>OPB-31121: 1/5 SD patients (&gt;12 months) (75).</td>
</tr>
<tr>
<td>EMD Serono</td>
<td>EMD 1214063</td>
<td>CMET unselective TIK</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>Merck</td>
<td>MK-2461</td>
<td>CMET unselective TIK</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>Goetsch et al</td>
<td>h224G11</td>
<td>cMET mAb</td>
<td>Preclinical</td>
<td></td>
</tr>
<tr>
<td>SGX</td>
<td>SGX523</td>
<td>cMET selective TKI</td>
<td>Preclinical</td>
<td></td>
</tr>
<tr>
<td>Eliai</td>
<td>E-7050</td>
<td>CMET unselective TIK</td>
<td>Preclinical</td>
<td></td>
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<tr>
<td>Takeda</td>
<td>T-1840383</td>
<td>CMET unselective TIK</td>
<td>Preclinical</td>
<td></td>
</tr>
<tr>
<td>Samsung</td>
<td>F46</td>
<td>HGF antagonist</td>
<td>Preclinical</td>
<td></td>
</tr>
</tbody>
</table>

HGF, hepatocyte growth factor; TKI, tyrosine kinase inhibitor; mAb, monoclonal antibody; Samsung, Samsung Advanced Institute of Technology; SGX, SGX Pharmaceuticals; SD, stable disease; PFS, progression-free survival; OS, overall survival; CT, chemotherapy.

6. Monoclonal antibodies to cMET

MetMab (onartuzumab) is a monoclonal single-arm humanized immunoglobulin (Ig) G1 antibody directed against cMET. In an in vitro study, onartuzumab was first investigated in the human glioblastoma cell line, U87, suggesting that the antibody may exert tumor inhibitory effects, such as anti-proliferative, anti-angiogenic and pro-apoptotic effects (57). MetMab has also been shown to be effective against tumor xenografts (57).

In a phase I clinical trial, a patient with chemo-refractory metastatic gastric cancer achieved a complete response with MetMab monotherapy that lasted for two years. The primary tumor had high cMET gene polysomy, as shown by FISH, and a high cMET expression (2+), as observed by IHC. Intriguingly, HGF serum levels were extremely high prior to treatment and declined precipitously immediately after drug exposure, and remained low, even at the time of widespread recurrence of the disease. This observation suggests that circulating HGF is a biomarker for therapeutic response (17). Similar results have been reported in non-small cell lung cancer (NSCLC); circulating HGF levels were measured as a pharmacodynamic biomarker of onartuzumab activity (58). Other studies using PET with (89)Zr-df-onartuzumab and (76)Br-onartuzumab in gastric carcinoma xenografts showed that the uptake of both tracers significantly correlated with tumor mass and cMET expression and was not affected by the presence of plasma shed cMET (59).
Currently, a randomized, double-blind, phase II study evaluating the efficacy and safety of onartuzumab in combination with mFOLFOX6 in patients with metastatic HER2-negative gastroesophageal cancer is ongoing (60).

Another currently ongoing phase III study introduced an enrichment biomarker, enrolling patients with metastatic HER2-negative, cMET-positive gastroesophageal cancer (61). The results of clinical trials on potential biomarkers may provide recommendations on patient selection and drug response assessment.

7. Tyrosine kinase inhibitors of cMET

Tivantinib is a selective, non-ATP competitive, small-molecule inhibitor of cMET. In vitro and in vivo studies have demonstrated that ARQ-197 inhibits cMET activation in numerous human gastric cancer cell lines and xenografts (62). Recent evidence suggests that tivantinib inhibits microtubule polymerization, in addition to inhibiting cMET; thus, tivantinib exerts its antitumor activity in a manner independent of the cMET status (63). In a single-arm phase II study on Asian patients with previously treated metastatic gastric cancer, 30 patients received tivantinib; cMET gene amplification (5 copies/cell) was observed in four patients (13.3%), and the disease control rate was 36.7% (11/30). The median PFS was 43 days (95% CI, 29.0-92.0). No objective response was observed. Grade 3 or 4 adverse events (AEs) occurred in 13 patients (43.3%), in whom neutropenia (n=4) and anemia (n=4) were recognized to be drug-related. Only two patients discontinued treatment due to AEs. There were no treatment-related deaths and no new reported AEs. No obvious correlation was identified between treatment outcome and specific biomarkers, including cMET gene amplification, cMET, p-cMET and HGF expression in tumor and serum (64). Currently, a phase I/II trial is recruiting patients to evaluate the response rate of the combination of tivantinib plus FOLFOX as first-line therapy for metastatic gastroesophageal cancer (65).

Crizotinib is an ATP competitive small-molecule inhibitor for cMET and anaplastic lymphoma kinase (ALK), which has shown marked antitumor activity in vitro and in vivo, specifically in gastric cancer cell lines, positive for MET amplification (66). A recent study followed up four patients as part of an expanded phase I cohort study; two of four patients with MET-amplified gastroesophageal cancer treated with crizotinib experienced tumor shrinkage (-30 and -16%) and experienced progression after 3.7 and 3.5 months. The research group also assessed MET, EGFR and HER2 amplification status using FISH in 489 patients with gastroesophageal cancer. The gene amplification rate of MET, EGFR and HER2 was 2, 4.7 and 8.9%, respectively. The majority (84%) of the samples were amplification in 489 patients with gastroesophageal cancer. The gene amplification rate of MET, EGFR and HER2 was 2, 4.7 and 8.9%, respectively. The majority (84%) of the samples were

8. Resistance to cMET inhibitors

The clinical efficacy of targeted therapy is hindered by the emergence of primary and acquired resistance. In the ToGA trial, the addition of trastuzumab to the chemotherapeutic regimen only led to an absolute increase in response rate of 12% (4), indicating the existence of de novo resistance. Moreover, a large proportion of those patients initially responding to trastuzumab developed acquired resistance. With the introduction of cMET inhibitors into the clinical setting, the same question cannot be avoided. To date, little is known about the mechanisms responsible for resistance to cMET inhibitors.

An in vitro and in vivo study indicated that gastric cancer tumors bearing constitutive activation of HER family members responded poorly to MET inhibition (83). cMET activation may mediate resistance to EGFR and HER2 in gastric cancer (14,15). Another study observed that the acquisition of a mutation in the MET activation loop (Y1230), destabilized the
autoinhibitory conformation of MET and abrogated an important aromatic stacking interaction with the inhibitor (84). In a recent study, a cMET-sensitive gastric cancer cell line was chronically exposed to the cMET inhibitor, PF-04217903. As a result, a novel SNAIL/BRAF fusion was observed and proven to be responsible for the resistance (85).

The RTK family accounts for a high percentage of the potential treatable genomic-targeted map of gastric cancer (5); the crosstalk between RTKs may also play an important role in drug resistance. Moreover, the prolonged exposure of a gastric cancer cell line to TKIs has been shown to lead to amplification and overexpression of wild-type Kras and to overcome the inhibitory effects of cMET TKIs (86). These data suggest that targeting cMET may be crucial to overcoming potential resistance to other agents in targeted therapy. Thus, close attention should be paid to this issue during the development of cMET inhibitors.

9. Conclusion

Increasing evidence suggests that cMET plays a key role in the development of gastric cancer. A total of 12.1% of gastric cancer patients harbor gene amplification and 42.8% have protein overexpression (Table I). cMET protein overexpression and/or gene amplification have been shown to significantly correlate with the depth of tumor invasion and metastasis and poor prognosis (11,13). cMET inhibitors have been investigated in clinical trials, with encouraging initial results (16,17). On the basis of these findings, cMET is considered to be a promising therapeutic target in gastric cancer.

However, with the rapid development of cMET inhibitors, a number of trials have been published which show less than favorable outcomes (70,73). These results can largely be attributed to a lack of appropriate biomarkers for patient selection and drug response assessment. Moreover, while a proportion of gastric cancers harbor cMET overexpression and/or amplification, it is unclear whether the cMET alteration is acting as an oncogenic driver or a passenger. Recent clinical trials have been designed with molecular alterations of cMET, EGFR/RAS/RAF as biomarkers (56,61,84). Future clinical trials may also assess molecular derangements such as cMET mutation, K-ras amplification, EGFR and HER2 status as predictive markers (14,15,83,84,86).

Drug resistance is another critical issue in the development of cMET inhibitors that needs to be addressed. Combined therapies against different pathways and at different levels may be a feasible approach to settle this issue. PDTT xenograft models, which can reliably mimic disease response in humans, is an ideal platform to study biomarker selection and drug resistance (87). PDTT can be used as a drug sensitivity model to investigate whether AFPGC is a special subgroup for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 376: 687-697, 2010.

References


