REVIEW

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Molecular targeted therapy for advanced gastric cancer

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Although medical treatment has been shown to improve quality of life and prolong survival, no significant progress has been made in the treatment of advanced gastric cancer (AGC) within the last two decades. Thus, the optimum standard first-line chemotherapy regimen for AGC remains debatable, and most responses to chemotherapy are partial and of short duration; the median survival is approximately 7 to 11 months, and survival at 2 years is exceptionally > 10%. Recently, remarkable progress in tumor biology has led to the development of new agents that target critical aspects of oncogenic pathways. For AGC, many molecular targeting agents have been evaluated in international randomized studies, and trastuzumab, an anti-HER-2 monoclonal antibody, has shown antitumor activity against HER-2-positive AGC. However, this benefit is limited to only ~20% of patients with AGC (patients with HER-2-positive AGC). Therefore, there remains a critical need for both the development of more effective agents and the identification of molecular predictive and prognostic markers to select those patients who will benefit most from specific chemotherapeutic regimens and targeted therapies.

Keywords: Stomach neoplasms; Drug therapy; Targeted agents

INTRODUCTION

The survival of patients with gastric cancer is substantially worse than that of patients with most other solid malignancies, and the only treatment that offers a potential cure is complete resection of the tumor. However, because the disease is asymptomatic in its early stages, more than half of gastric carcinomas are diagnosed in the advanced stage, when resection is no longer possible. Thus, although medical treatment has been shown to improve quality of life and prolong survival, there has been no significant progress in the treatment of advanced gastric cancer (AGC) within the last two decades [1,2]. Although the optimum standard first-line chemotherapy regimen for AGC remains debatable, a double regimen comprising fluorouracil (or its oral prodrugs) plus platinum or a triple regimen with the addition of epirubicin or docetaxel is most commonly used [3,4]. However, most responses to chemotherapy are partial and of short duration. As a result, the current median survival is approximately 7 to 11 months, and survival at 2 years is exceptionally > 10% [3-5].

During the past few decades, remarkable progress in tumor biology has led to the development of new agents that target critical aspects of oncogenic pathways. In various tumor types, including hematologic malignancies, colorectal cancer, breast cancer, renal cancer, and gastrointestinal stromal tumors, many molecular targeting agents have already exhibited significant antitumor activity.

An emerging understanding of the molecular pathways that characterize cell growth, the cell cycle, apoptosis, angiogenesis, and invasion has provided novel

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targets in cancer therapy. These therapeutic strategies include epidermal growth factor receptor (EGFR) inhibitors, antiangiogenic agents, cell cycle inhibitors, and apoptosis promoters. In various tumor types, including hematologic malignancies, colorectal cancer, breast cancer, renal cancer, and gastrointestinal stromal tumors, many molecular targeting agents have already exhibited significant antitumor activity. For AGC, many targeted agents have also been evaluated in international randomized studies, and trastuzumab, an anti-HER-2 monoclonal antibody (mAb), has been shown to improve survival in patients with HER-2-positive AGC. Accordingly, this review covers the recent advances in biologic agents for the treatment of AGC on the basis of the best available evidence.

EGFR INHIBITORS

EGFR exists on the cell surface and is activated by the binding of specific ligands, including EGF and transforming growth factor alpha. EGFR possesses an intracellular tyrosine kinase domain that, upon activation, may initiate downstream signaling, ultimately resulting in DNA synthesis and cell proliferation. The EGFR family comprises four members: HER-1 (also known as EGFR-1), HER-2, HER-3, and HER-4. Among these, EGFR-1 and HER-2 represent the targets for drugs currently under development for gastric cancer.

Anti-EGFR mAbs (cetuximab/panitumumab)

EGFR is commonly overexpressed in gastrointestinal malignancies. Its overexpression is associated with a more aggressive phenotype and poorer survival, which suggests that EGFR may be a rational therapeutic target [6]. Following reports of the poor efficacy of the tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib in gastric cancers [7,8], mAbs, primarily cetuximab, have been tested in several published trials [9,10]. In a phase II trial (n = 38) using cetuximab in combination with 5-FU, leucovorin, and irinotecan in chemo-naive patients with advanced gastric or gastroesophageal junction (GEJ) cancers, an objective response rate of 44% was observed in a population of 89% stomach and 11% GEJ cancers, and the median time to tumor progression was 8 months [10]. Similar to the results in patients with colorectal cancer, *EGFR* expression levels did not correlate with treatment efficacy. Meanwhile, in a biomarker analysis included in the trial by Han et al. [9], they confirmed that *K-Ras* mutations or an increased *EGFR* gene copy number are uncommon events in gastric cancer. They also demonstrated that patients with *EGFR* expression and low levels of the major ligands EGF and tumor growth factor-α had a 100% response rate, a finding that deserves urgent confirmation in prospective trials. However, despite a favorable comparison between the reported response rates in these phase II trials for combination chemotherapy with cetuximab and current data for chemotherapy alone [3], the median survival is similar to previously published phase II clinical trials. The results of a randomized phase III trial comparing cetuximab in combination with capecitabine and cisplatin with chemotherapy alone (EXPAND) were reported recently. The median progression-free survival (PFS) and overall survival (OS) were 4.4 and 9.4 months, respectively, in patients assigned to cetuximab plus chemotherapy compared with 5.6 and 10.7 months, respectively, in those assigned to chemotherapy alone (PFS, $p = 0.3158$; OS, $p = 0.9547$) [11]. Panitumumab is a fully humanized IgG2 mAb targeting EGFR. A randomized phase III trial (REAL-3) compared panitumumab plus combination chemotherapy (epirubicin/oxaliplatin/capecitabine, EOX regimen) with combination chemotherapy alone in 553 patients with untreated advanced adenocarcinoma of the esophagus, GEJ, or stomach. However, the survival in the panitumumab arm was inferior to that in the chemotherapy-alone arm (PFS, 6.0 months vs. 7.4 months, $p = 0.068$; OS, 8.8 months vs. 11.3 months, $p = 0.013$) [12]. Accordingly, there is no plan to move forward with anti-EGFR mAbs in further clinical investigation of AGC.

EGFR TKI (erlotinib/gefitinib)

Erlotinib showed no tumor response in patients with gastric cancer, while patients with GEJ cancer had a response rate of 9%. The OS of stomach and GEJ cancer was 3.5 and 6.7 months, and PFS was 1.6 and 3 months, respectively [7]. In a trial involving 70 patients with previously treated AGC, although gefitinib reached tumor concentrations sufficient to inhibit EGFR activation, this did not translate into a clinical benefit [13].

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Moreover, gefitinib combined with 5-FU + cisplatin and radiotherapy as a neoadjuvant treatment did not increase pathologic complete response rates, while the 3-year OS was increased compared with historical controls in patients with locally advanced esophageal and GEJ cancer (42% vs. 28%) [14]. The lack of erlotinib and gefitinib activity in gastric cancer in these trials may be related to the variable etiologies among different tumor locations. For example, GEJ adenocarcinoma is associated with Barrett's esophagus, while gastric cancer is associated with *Helicobacter pylori* infection. The different molecular pathways targeted by EGFR inhibitors could be differentially expressed in proximal versus distal adenocarcinomas.

Anti-HER-2 mAbs (trastuzumab)

Trastuzumab is a humanized anti-HER-2 mAb that is already widely accepted as a standard agent for HER-2-positive breast cancer. In the case of gastric cancer, this agent has also been evaluated in a global randomized trial comparing 5-FU or capecitabine/cisplatin with 5-FU or capecitabine/cisplatin plus trastuzumab based on the examination of HER-2 overexpression in gastric cancer tissues [15]. Among 3,807 patients centrally tested for their HER-2 status, 22.1% were HER-2-positive. Notably, HER-2-positive rates were found to be significantly higher in GEJ cancer than in gastric cancer (33.2% vs. 20.9%, $p < 0.001$) and higher in intestinal than in diffuse/mixed cancer (32.2% vs. 6.1%/20.4%, $p < 0.001$). The median OS was improved significantly in the trastuzumab arm compared with the chemotherapy-alone arm (13.5 months vs. 11.1 months, $p = 0.0048$; hazard ratio [HR], 0.74; 95% confidence interval, 0.60 to 0.91). In subgroup analysis, the patients with HER-2 immunohistochemistry (IHC) 2^+ / fluorescence *in situ* hybridization + or IHC 3^+ had a longer OS compared with the chemotherapy-alone arm (16 months vs. 11.8 months). Moreover, the safety profiles were similar with no unexpected adverse events in the trastuzumab arm. Therefore, it was concluded that trastuzumab is a new, effective, and well-tolerated treatment for HER-2-positive AGC.

HER-2 TKI (lapatinib)

Lapatinib is a dual inhibitor of the tyrosine kinase domains of HER-1 and HER-2 based on its interference with adenosine triphosphate binding. Lapatinib has also been clinically shown to be active against HER-2-positive breast cancer as a monotherapy and in combination with capecitabine. However, a single-agent phase II study demonstrated very modest activity with a response rate of only 5% in unselected patients with metastatic gastric cancer [16]. In a phase II trial of capecitabine and lapatinib combination as first line treatment in patients with gastric (76%) or GEJ cancer (24%), 24% and 36% of patients achieved a partial response and stable disease, respectively [17]. A phase II international study (LOGiG) comparing capecitabine/oxaliplatin with/without lapatinib as first line treatment for AGC has reached its accrual goal and is ongoing for follow-up. In addition, a randomized trial (TYTAN) comparing lapatinib and paclitaxel with paclitaxel alone in patients with HER-2-positive metastatic gastric cancer in a second-line setting is ongoing.

ANGIOGENESIS INHIBITORS

Tumor angiogenesis and metastasis are strongly linked with angiogenesis in most solid tumors. Recognition of the vascular endothelial growth factor (VEGF) pathway as a key regulator of angiogenesis has led to the development of several VEGF-targeting agents, including neutralizing antibodies to VEGF or its receptor (VEGFR) and TKIs targeting the VEGFR.

Anti-VEGF mAbs (bevacizumab)

Bevacizumab is a VEGF-A-blocking mAb currently under investigation for the treatment of gastric cancer. Several phase II trials combining bevacizumab with different chemotherapeutic compounds were conducted on treatment-naïve or pretreated patients with AGC or GEJ cancer, demonstrating results that were initially promising [18-20]. For example, a pivotal phase II trial (n = 47) using bevacizumab in combination with irinotecan and cisplatin as first-line therapy in patients with gastric (51%) or GEJ (49%) adenocarcinomas reported a response rate of 65%, median time to tumor progression of 8.3 months, and median survival of 12.3 months. Although the chemotherapy-related toxicity occurred as expected, the favorable efficacy results

were counterbalanced by the following bevacizumab-related toxicities: two patients with a gastric perforation, one patient with a near-perforation (overall incidence of perforation, 6%), 25% incidence of grade III or IV thromboembolic events, and 4% incidence of grade III hemorrhages [18]. In a second single-arm phase II trial (n = 42) using a modified docetaxel, cisplatin, and fluorouracil regimen in combination with bevacizumab in patients with metastatic gastric or GEJ adenocarcinoma, similar results for efficacy were observed. Moreover, the incidence of grade III/IV venous thromboembolism was 29%, and 93% of these were asymptomatic and identified only on protocol-specific scans. One patient developed a gastrointestinal perforation [19]. Accordingly, gastrointestinal perforation and thromboembolic events may represent a serious drawback in the use of bevacizumab in gastric cancer, meaning that careful risk analysis is needed in randomized trials. Based on these efficacy results, a randomized trial (AVAGAST) comparing capecitabine/cisplatin alone with capecitabine/cisplatin plus bevacizumab as first-line therapy in 774 patients with gastric or GEJ cancer was conducted [21]. Although significant improvement in PFS and overall response rates was noted in the bevacizumab group, the median OS was 12.1 months for the bevacizumab group and 10.1 months for the placebo group (HR, 0.87; $p = 0.1002$), failing to meet the primary end-point. In subgroup analysis, OS for the pan-American subgroup was 6.8 months in the placebo arm versus 11.5 months in the bevacizumab arm (HR, 0.63). For the European and Asian-Pacific subgroups, OS was 8.6 months versus 11.1 months (HR, 0.85) and 12.1 months versus 13.9 months (HR, 0.97), respectively, with all results favoring bevacizumab. The incidence of grades III to V adverse events potentially related to bevacizumab was similar in both arms (20% in the bevacizumab arm vs. 15% in the placebo arm). Another randomized trial to compare epirubicin/cisplatin/capecitabine (ECX) with ECX plus bevacizumab in a perioperative setting in the UK is also ongoing.

Anti-VEGFR mAbs (ramucirumab)

Ramucirumab is a fully humanized mAb targeting VEGFR. Several trials are ongoing, including a randomized phase II clinical trial of mFOLFOX6 (oxaliplatin/5-FU/folic acid) chemotherapy plus ramucirumab versus mFOLFOX6 plus placebo for advanced GEJ cancer and a randomized phase III study of paclitaxel with or without ramucirumab in patients with metastatic gastric cancer after failure of first-line therapy with platinum and fluoropyrimidine.

VEGFR TKI (sunitinib/sorafenib/cediranib/apatinib)

Sunitinib

Multi-TKI sunitinib has exhibited activity against VEGFRs as well as Raf, platelet-derived growth factor receptor beta, fibroblast growth factor receptors, and c-KIT. At present, sunitinib at 50 mg/day as a single agent has been studied as a second- or third-line treatment for AGC in two nonrandomized phase II studies [22,23]. An Asian study (n = 72) showed a partial response rate of 2.6% and a > 6-week stable disease rate of 32.1%, while the median PFS was 2.3 months and median OS was 6.8 months [22]. In another phase II trial, sunitinib monotherapy was conducted on 52 patients with chemorefractory AGC, resulting in a median OS of 5.8 months and displaying less effectiveness than anticipated [23]. Although sunitinib was well tolerated in these pretreated patients, these studies showed little clinical value in a monotherapy setting. Thus, a randomized trial of second-line chemotherapy plus sunitinib versus chemotherapy alone is necessary to establish the therapeutic benefit of sunitinib in this pretreated patient population.

Sorafenib

Sorafenib is a potent inhibitor of the Raf tyrosine kinase as well as several other receptor tyrosine kinases involved in the progression of gastric cancers, such as VEGFR-2 and VEGFR-3 [24]. Based on data derived from hepatocellular carcinoma trials, several studies were designed to investigate the role of sorafenib in AGC. In a first phase II study (n = 44) for patients with metastatic (80%) or locally advanced (20%) gastric and GEJ cancer using oral sorafenib (400 mg twice daily) in combination with docetaxel and cisplatin in a 21-day cycle, the median OS was 13.6 months, with a PFS of 5.8 months and a response rate of 41% [25]. The authors suggested that sorafenib combined with docetaxel and cisplatin was effective and tolerable as a treatment for gastric or GEJ cancer. Other phase II or III studies us-

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ing sorafenib combined with capecitabine or S-1 plus cisplatin are currently being conducted in Korea and Japan.

Cediranib

Cediranib is a highly potent inhibitor of VEGFR-1 and VEGFR-2 that displays activity against c-Kit and platelet-drived growth factor receptor-β [26]. A phase I trial of cediranib with a fluoropyrimidine (S-1 or capecitabine) and cisplatin was conducted as a first-line treatment for 14 Japanese patients with AGC [27]. The most common adverse events were decreased appetite, fatigue, and nausea, and a preliminary efficacy evaluation showed one confirmed and three unconfirmed partial responses. Investigations are expected to continue in the future.

Apatinib

Apatinib (YN968D1) is a small-molecule TKI that inhibits VEGFR-2 (Flk-1/KDR), RET, c-Kit, and c-Src tyrosine kinases [28]. The efficacy of apatinib was evaluated as a third-line treatment for 141 patients with AGC in a three-arm phase II study (placebo vs. apatinib at 850 mg once a day vs. 425 mg twice a day) [29]. The respective survival rates were as follows: (median PFS, 1.4 months vs. 3.4 months vs. 3.4 months; median OS, 2.5 months vs. 4.8 months vs. 4.3 months). Common adverse effects included hypertension and hand-foot syndrome. A phase III trial comparing apatinib to placebo in a third-line setting in AGC is currently being conducted in China.

Other targeted agents

Everolimus

Everolimus (RAD001) is an oral inhibitor of mammalian target of rapamycin, which is downstream of the Akt pathway. The results of a phase II study of everolimus in 53 patients with previously treated AGC showed a disease control rate of 56.0% and median PFS of 2.7 months. At a median follow-up duration of 9.6 months, the median OS was 10.1 months and good tolerability was observed [30]. After obtaining a remarkable response in patients with metastatic gastric cancer in previous phase I/II studies in Japan [30,31], a prospective randomized placebo-controlled study evaluating the efficacy of everolimus as a second- or third-line therapy in 656 patients with AGC was conducted [32]. Although the PFS was significantly improved by everolimus (1.7 months vs. placebo, 1.4 months; $p < 0.0001$), the OS, a primary endpoint of the study, was not significantly different (everolimus, 5.4 months vs. placebo, 4.3 months; $p = 0.1244$).

Onartuzumab

A c-Met is an oncogene encoding a membrane tyrosine kinase receptor; hepatocyte growth factor receptor (HGFR) that plays an important role in tumor development through activation of key oncogenic pathways, angiogenesis, and tumor metastasis. A high level of c-Met expression has been correlated with the metastatic spread of tumors and poor survival in patients with various types of tumors, including gastric cancer [33], suggesting that it may be a suitable therapeutic target for gastric cancer. Therefore, several agents targeting c-Met, including onartuzumab (humanized mAb directed against HGFR) and a TKI of activated c-Met, are now in the developmental stages. A phase II clinical trial of onartuzumab in combination with mFOLFOX6 in patients with metastatic HER-2-negative gastroesophageal cancer is scheduled to begin in the near future.

Vorinostat

Vorinostat, also known as suberoylanilide hydroxamic acid, is an histone deacetylase inhibitor. Preclinical studies have shown that vorinostat has potential anti-gastric cancer activity, with a synergistic effect when combined with taxane [34]. A phase I/II study of vorinostat plus capecitabine and cisplatin as a first-line treatment is being conducted for patients with AGC.

Catumaxomab

The development of ascites is a major clinical problem in patients with AGC, and the epithelial cell adhesion molecule (EpCAM), which has been shown to be highly overexpressed in gastric as well as several other epithelial cancers, is the target of the trifunctional bispecific antibody catumaxomab. The intraperitoneal administration of catumaxomab in patients with malignant ascites due to EpCAM-positive epithelial cancers resulted in a significantly increased puncture-free survival in a randomized study [35], and the side

effects were mostly symptoms related to cytokine release (pyrexia, nausea, and vomiting) and abdominal pain, which were generally mild to moderate and fully reversible.

CONCLUSIONS

Emerging data from the clinical development of molecular-targeted agents have provided novel opportunities that are expected to translate into survival benefits in the treatment of AGC. The final results of the ToGA study recently demonstrated that the addition of trastuzumab to combination chemotherapy can achieve remarkable survival advantages in patients with HER-2-positive AGC. However, this benefit is limited to only ~20% of patients with AGC (patients with HER-2-positive AGC). Therefore, there remains a critical need for both the development of more effective agents and the identification of predictive and prognostic molecular markers to select those patients who will benefit most from specific chemotherapeutic regimens and targeted therapies.

Conflict of interest

No potential conflict of interest relevant to this article is reported.

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