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Current and New Molecularly Targeted Agents for Metastatic Gastric Cancer

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The discovery of HER2, a biomarker in advanced gastric cancer, and successful clinical trial using trastuzumab that targets this biomarker signaled a revolutionary turning point in treatment of metastatic gastric cancer. Many studies about targeted agents for gastric cancer have been attempted. Among them, ramicirumab, a monoclonal antibody that targets vascular endothelial growth factor receptor-2 (VEGFR-2), and apatinib, a tyrosine kinase inhibitor (TKI) that targets VEGFR2, have shown to improve the survival rates in advanced gastric cancer patients, for whom previous therapies had failed; hence, they are expected to be accepted as one of the standard therapies for advanced gastric cancer.

Key Words: Stomach neoplasms, Trastuzumab, Ramucirumab, Apatinib

INTRODUCTION

Gastric cancer is the fourth most common cancer and is the third and fifth leading cause of cancer-related mortality worldwide in men and women, respectively.[1] In Korea, the frequency of occurrence of gastric cancer is second only to thyroid cancer. It is the third leading cause of cancer-related mortality, after lung cancer and liver cancer, according to the national cancer registry statistics.[2] In Korea, the proportion of patients diagnosed with early-stage gastric cancer has increased thanks to national cancer screenings, but worldwide, many patients with gastric cancer are diagnosed at an advanced stage, and unresectable advanced or metastatic cancer has a poor prognosis. There is no internationally accepted standard palliative chemotherapy regimen for metastatic gastric cancer. The combination therapy of fluoropyrimidine and platinum is usually used as first-line therapy, and easy-to-administer oral fluoropyrimidines such as capecitabine or S-1 are favored over a continuous IV infusion of 5-fluorouracil (5-FU) in Korea.[3,4] With recent advances in molecular oncology, cell signaling pathways and target molecules that are critical for the survival of cancer cells and progression and metastasis of cancer have been discovered, and targeted agents have been developed. In 2010, the addition of trastuzumab, a recombinant monoclonal antibody specifically targeting human epidermal growth factor receptor 2 (HER2), to chemotherapy was reported to be effective in patients with HER2-positive gastric cancer.[5] Fueled by this success, researches have been actively conducted to find new targets in gastric cancer. Studies of various targeted therapies such as epidermal growth factor receptor (EGFR) inhibitors, vascular endothelial growth factor (VEGF) inhibitors, c-mesenchymal-epithelial transition (c-MET) pathway inhibitors, and mammalian target of rapamycin (mTOR) inhibitors have been carried out.[6-13] Positive results from studies using ramucirumab and apatinib were recently reported.[6,11,13] This paper aims to review the applications and latest trends in typical molecularly targeted therapies for gastric cancer.

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1. EGFR and HER2 inhibitors

EGFR is located on the cell surface and is a member of the tyrosine kinase receptor family, which also includes HER2. The binding of ligands such as EGF and transforming growth factor-α to EGFR phosphorylates tyrosine residues in intracellular receptor domains and subsequently activates the signaling pathways of mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K) and serine/threonine kinase, Akt, and signal transduction and transcription (STAT),

thus promoting cell proliferation and inhibiting apoptosis. The incidence of EGFR overexpression has been reported in approximately 30-50% of gastric cancer cases and is associated with a poor prognosis.[14] HER2 forms heterodimers with other HER family receptors such as HER1 (EGFR), HER3, and HER4; the HER2-HER3 heterodimer plays an important role in tumor formation induced by HER2.[15] HER2 gene amplification and overexpression in breast cancer is correlated with a poor prognosis, high mortality, recurrence, and metastasis.[16] However, the correlation between HER2 and gastric cancer still remains controversial; several studies have reported that HER2 amplification or overexpression was correlated with enhanced survival, but a systematic analysis of the literature suggested that HER2 might have a potential role as a negative prognostic factor.[17-19]

1) Trastuzumab

Trastuzumab is a monoclonal antibody targeting the extracellular domain of HER2. The ToGA (Trastuzumab for Gastric Cancer) study demonstrated that trastuzumab in combination with capecitabine/cisplatin (XP) or cisplatin/5-FU (CF) significantly improved overall survival (OS) from 11.1 months to 13.8 months in patients with HER2-positive advanced gastric cancer (hazard ratio [HR], 0.74; 95% confidence interval [CI], 0.60 to 0.91; p=0.0046), compared with XP or CF chemotherapy alone.[5] In subgroup analysis, OS was 16.0 months and 11.8 months for the combination treatment and single treatment, respectively, in the HER2 overexpression group (HER2 immunohistochemistry [IHC] score 2+ and fluorescence in situ hybridization [FISH]+ or IHC score 3+), showing a more distinct difference. There was no difference in grade 3/4 adverse effects between the trastuzumab plus chemotherapy group and the chemotherapy alone group.[5] It has been shown that if the HER2 IHC score is 0, 1+, or 3+ in gastric cancer, the concordance rate with FISH is more than 85%, but if the IHC score is 2+, the concordance rate with FISH is only 50%.[20] Therefore, in cases with a HER2 IHC score of 2+, FISH should be performed in addition to IHC to conclusively determine whether the sample is HER2 positive. Accordingly, it is recommended that a HER2 test be performed in patients with metastatic gastric cancer and that patients with an IHC score of 3+ or an IHC score of 2+ and FISH+ be treated with trastuzumab in combination with fluoropyrimidine plus cisplatin.

Pertuzumab is a monoclonal antibody, which acts on an antigen in HER2 different from that acted upon by trastuzumab, thereby inhibiting dimerization of HER2 with other HER family receptors. A phase III trial demonstrated that pertuzumab in combination with trastuzumab was effective in improving OS in patients with HER2-positive metastatic breast cancer.[21] A phase III trial (NCT01774786) investigating the efficacy and safety of the combination therapy of pertuzumab, trastuzumab, and chemotherapy in HER2-positive metastatic gastric cancer or gastroesophageal (GE) junction cancer is ongoing.

T-DM1 (trastuzumab DM1) is an antibody-drug conjugate (ADC) comprised of trastuzumab bound to emtansine (DM1), a cytotoxic drug.[22] The trastuzumab part of T-DM1 binds to HER2 and enters the tumor cells where the DM1 part then exerts its microtubule-inhibiting activity. A clinical trial (NCT-01641939) comparing the efficacy of T-DM1 versus taxane as a second-line anti-cancer agent in patients with HER2-positive gastric cancer is ongoing.

2) Lapatinib

Lapatinib is an oral tyrosine kinase inhibitor (TKI) that simultaneously inhibits EGFR and HER2. It is known that lapatinib alone or in combination with capecitabine is clinically effective in HER2-positive breast cancer.[23] The results of the LOGiC (Lapatinib Optimization Study in HER2 Positive Gastric Cancer) trial, which evaluated the efficacy of lapatinib in combination with capecitabine/oxaliplatin (XELOX) in HER2-positive advanced or metastatic gastric, esophageal, and GE junction adenocarcinoma, were recently reported. These results showed that there was no significant difference in OS, the primary endpoint, between the XELOX plus lapatinib group and the XELOX group (12.2 months vs. 10.5 months, respectively); however, there were improvements in OS in Asian patients and those under 60 years of age.[7] Progression-free survival (PFS) and overall response rate (ORR) showed improvement in the lapatinib group. There were increased rates of diarrhea and skin toxicity in the group receiving XELOX plus lapatinib.

The TyTAN (lapatinib [Tykerb] with paclitaxel [Taxol] in Asian ErbB2+[HER2+] Gastric Cancer Study) compared the combination of lapatinib plus paclitaxel with paclitaxel alone as second-line therapy in HER2-positive metastatic gastric cancer.[24] OS was 11.0 months in the lapatinib plus paclitaxel group and 8.9 months in the paclitaxel alone group (p=0.20), showing no significant improvement. However, subgroup analysis showed that, for patients with a HER2 IHC score of 3+, OS was 14.0 months and 7.6 months in the lapatinib plus paclitaxel and paclitaxel alone groups, respectively, demonstrating a significant improvement in the lapatinib group (p =0.017). These results revealed that the characterization of HER-2 positive advanced cancer is critical for the development of anti-HER2 agents.

3) EGFR inhibitors

Recently, the EXPAND (Erbitux in Combination with Xeloda and Cisplatin in Advanced Esophagogastric Cancer) study, a phase III study evaluating the addition of cetuximab, an IgG1 monoclonal antibody inhibiting EGFR to cytotoxic chemotherapy in patients with advanced gastric cancer, was conducted. In the study, 904 patients were randomly assigned to the XP-alone group or the XP plus cetuximab group at a 1:1 ratio; the primary endpoint was PFS. Median progress-free survival for the XP plus cetuximab group and the XP-alone group was 5.6 months and 4.4 months (p=0.32), respectively, and OS was 9.4 months and 10.7 months, respectively (p=0.95), showing no significant difference.[8] The addition of cetuximab was found to provide no additional benefit in the first-line treatment of advanced gastric cancer.

Panitumumab is a humanized IgG2 monoclonal antibody targeting EGFR. The REAL-3 (Randomized Trial of EOC plus Panitumumab for Advanced and Locally Advanced Esophagogastric Cancer) study compared epirubicin/oxaliplatin/capecitabine (EOC) alone with panitumumab plus EOC in a reduced dose, which was based on the results of a previous study in 553 patients with metastatic gastric, GE junction, or esophageal cancer.[10] The median OS for 275 patients assigned to the EOC-alone group and 278 patients assigned to the EOC plus panitumumab group was 11.3 months and 8.8 months (HR, 1.37; 95% CI, 1.07 to 1.76; p=0.013), respectively, showing a poorer OS in the EOC plus panitumumab group. The EOC plus panitumumab group had a higher incidence of grade 3/4 diarrhea, rash, mucositis, and hypomagnesaemia, but a lower incidence of hematological toxicity.

2. Angiogenesis inhibitors

Tumor growth and metastasis are very strongly associated with angiogenesis in most solid tumors. Particular attention has been paid to VEGF as a therapeutic target since it is a key regulator of physiological and pathological angiogenesis. VEGF binds to VEGFR (VEGF receptor)-1 and -2 and is involved in the survival and proliferation of endothelial cells.

1) Bevacizumab

Bevacizumab is an IgG1 monoclonal antibody targeting VEGF-A. AVAGAST (Avastin in Gastric Cancer), a randomized phase III trial, compared bevacizumab plus XP therapy with placebo (PBO) plus XP therapy as first-line treatments for 774 patients with advanced gastric and GE junction cancer.[9] OS, the primary endpoint, was 12.1 months in the bevacizumab group and 10.1 months in the PBO group, with no significant difference, although there was an improved OS (of 2 months) in the bevacizumab group. However, PFS was 6.7 months and 5.3 months, respectively, showing a significant improvement, and the ORR (46% vs. 37%) was improved by 9% with bevacizumab. Subgroup analysis found that OS was likely to improve in particular patient groups: patients enrolled in Europe or pan-America appeared to show significant improvements in survival, whereas patients enrolled in Asia appeared to show no difference in OS. Patients in Asia receive second-line anti-cancer therapy (salvage therapy) more often than patients in Europe or pan-America, possibly causing a dilution effect in the difference in OS, which is thought to be one of reasons for the lack of improvement in OS. As high plasma VEGF-A levels and low neuropilin-1 in tumors tend to indicate improvement in survival, their potential as biomarkers has been proposed. The incidence of adverse events was mostly similar in both groups and the incidence of hypertension was higher: 6% in the bevacizumab group and 1% in the PBO group.

2) Ramucirumab

Ramucirumab is a humanized IgG1 monoclonal antibody that targets VEGFR-2. REGARD (Ramucirumab Monotherapy for Previously Treated Advanced Gastric or Gastroesophageal Junction Adenocarcinoma), a phase III trial, compared ramucirumab (8 mg/kg, once every 2 weeks) with the best supportive care (BSC) as second-line therapy for metastatic gastric and GE junction cancer.[6] OS, the primary endpoint, was 5.2 months in the ramucirumab group and 3.8 months in the PBO group, showing a significant difference (HR, 0.776; 95% CI, 0.603 to 0.998; p=0.0473); PFS was 2.1 months in the ramucirumab group and 1.3 months in the PBO group (HR, 0.483; 95% CI, 0.376 to 0.620; p< 0.0001); disease control rate was 49% in the ramucirumab group and 23% in the PBO group, also showing a significant difference. The most common grade 3 or higher adverse event was hypertension. Thus, ramucirumab was found to have statistically significant benefits in OS and PFS as second-line treatment in advanced gastric cancer and to have a favorable safety profile. However, in view of the fact that studies using docetaxel or irinotecan as second-line therapies also showed an increased OS of about 1.5 months, it is not yet clear whether ramucirumab may replace the existing chemotherapy.

RAINBOW, a phase III trial, evaluated the efficacy and safety of paclitaxel plus ramucirumab versus paclitaxel alone in 655 patients with metastatic gastric and GE junction cancer who did not respond to first-line therapy.[25] Median OS was 9.6 months in the paclitaxel plus ramucirumab group and 7.4 months in the paclitaxel group, with an increased OS of more

than 2 months (HR, 0.807; 95% CI, 0.678 to 0.962; p= 0.0169). PFS was 4.4 months in the ramucirumab group and 2.9 months in the paclitaxel group (HR, 0.635, 95% CI, 0.536 to 0.752; p<0.0001) and the ORRs were 28% and 16%, respectively, showing a clinically significant improvement (p=0.0001). Neutropenia occurred more frequently in the paclitaxel plus ramucirumab group, but the incidence of febrile neutropenia was comparable between the groups. These findings suggested that the addition of ramucirumab to the existing paclitaxel treatment could become a standard regimen for the second-line treatment of metastatic gastric cancer.

The results of a multi-center phase II trial evaluating the efficacy of ramucirumab in combination with cytotoxic chemotherapy as first-line therapy were released in 2014.[26] One hundred and sixty-eight patients with previously untreated esophageal, GE junction, and gastric adenocarcinoma were randomized to ramucirumab plus 5-FU/leucovorin/oxaliplatin (mFOLFOX6) or mFOLFOX6. PFS, the primary endpoint, was 6.4 months in the ramucirumab plus mFOLFOX6 group and 6.7 months in the mFOLFOX6 group, showing no difference between the two groups. The ORRs were 45% and 46%, respectively, with no difference observed. Accordingly, the efficacy of ramucirumab as first-line therapy has not yet been proven.

3) Apatinib

Apatinib is a small-molecule TKI that targets VEGFR-2. A phase III trial evaluating the efficacy of apatinib as third-line treatment in 273 patients with metastatic gastric cancer who were randomized to the apatinib group (850 mg, once daily) or the PBO group in a 2:1 ratio was conducted in China and its results were recently released.[13] The primary endpoint was median OS. Median OS was 6.5 months in the apatinib group and 4.7 months in the PBO group showing a significant improvement with apatinib (HR, 0.71; 95% CI, 0.53 to 0.96; p=0.0149); PFS was 2.6 months and 1.8 months, respectively, also showing improvement with apatinib. Overall, adverse events were more commonly reported in the apatinib group, but there was no difference in serious adverse events between the two groups.

3. Other targeted therapies

1) c-MET pathway inhibitors

c-MET is a tyrosine kinase receptor for hepatocyte growth factor (HGF) that is expressed in epithelial and endothelial cells. c-MET is expressed in 26-74% of gastric cancers, and is involved in the invasion and metastasis of tumor cells, which is correlated with poorer outcomes.[27]

Rilotumumab is a monoclonal antibody that binds to HGF, a ligand of the c-MET receptor, and onartuzumab is a monoclonal antibody that binds to c-MET to inhibit cell signaling. A phase III trial (NCT01697072) evaluating the combination of ECX plus rilotumumab as first-line therapy in patients with MET-positive advanced gastric cancer and a phase III trial (NCT01611857) evaluating onartuzumab in combination with mFOLFOX6 have been conducted. However, both trials were terminated due to unfavorable interim results. In contrast, a recently released study using AMG 337, a MET TKI in gastric, esophageal, and GE junction cancers with MET amplification showed that the ORR was 62% (8/13), which is expected to be effective in some patients.[28]

2) mTOR pathway inhibitors

Mammalian target of rapamycin (mTOR) is a core protein kinase which acts as a regulator of cell growth and division, cell metabolism, and blood vessel growth. Mutations in the mTOR gene may lead to an inappropriate activation of mTOR. Dysregulation of the mTOR pathway appears in many types of cancer including gastric cancer.[29] GRANITE-1 (Gastric Anti-Tumor Trial with Everolimus-1), a phase III trial, compared everolimus, an oral mTOR inhibitor, with BSC in patients with advanced gastric cancer who had been previously treated with first-line or second-line treatment. The PFS was 1.7 months in the everolimus group and 1.4 months in the BSC group, showing an improvement (HR, 0.66; 95% CI, 0.56 to 0.78; p<0.001), but OS, the primary endpoint, was 5.4 months and 4.3 months, respectively, showing no significant difference (HR, 0.90; 95% CI, 0.75 to 1.08; p=0.124).[12]

3) Immuno-oncology

The area of immuno-oncology targeting programmed death 1 (PD-1)/programmed death-ligand 1 (PD-L1) has recently come into the spotlight. When PD-1 in T-cells and PD-L1 of tumor cells interact, tumor cells could escape the immune response. In other words, they could avoid attack from tumor-specific T-lymphocytes by activating immune checkpoints in tumor cells. Pembrolizumab is a humanized IgG4 monoclonal antibody that binds to the PD-1 receptor and blocks its interactions with the ligand; in this way, it blocks the PD-1 pathway-mediated inhibition and once again activates the host immune response to tumors. When pembrolizumab was used in gastric and GE junction cancer with PD-L1 expression, the ORR was 33% according to an investigative review and 22% according to a central review. The development of new drugs in this area is expected in the near future.[30]

CONCLUSION

Recently, studies of targeted agents for gastric cancer have been actively conducted. Based on the researches on the molecular biological characteristics of gastric cancer, it is thought that gastric cancer is a heterogeneous disease with several subtypes, rather than a single disease; it is believed that there are driving genetic changes in some cases of gastric cancer.[31,32] A commonality among studies which failed to prove enhanced efficacy of targeted therapies in gastric cancer appears to be that patient selection by using specific biomarkers was not made. Therefore, if targeted therapies that affect the driving genetic changes are used after the appropriate selection of patients, improved outcome could be expected. We expect that the researches on the pathogenic mechanisms of gastric cancer may lead to the identification of biomarkers that can predict molecular targets and the treatment outcome for individual patients with gastric cancer. Therefore, individualized therapy tailored for each patient may be possible in the future.

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