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
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].