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MINIREVIEWS

Recent progress of chemotherapy and biomarkers for gastroesophageal cancer

Osamu Maeda, Yuichi Ando

ORCID number: Osamu Maeda (0000-0003-4700-6541); Yuichi Ando (0000-0002-6849-2297).

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Osamu Maeda, Yuichi Ando, Department of Clinical Oncology and Chemotherapy, Nagoya University Hospital, Nagoya 466-8560, Japan

Corresponding author: Osamu Maeda, MD, PhD, Lecturer, Department of Clinical Oncology and Chemotherapy, Nagoya University Hospital, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8560, Japan. maeda-o@med.nagoya-u.ac.jp
Telephone: +81-52-7441903
Fax: +81-52-7441903

Abstract

Key cytotoxic drugs of chemotherapy for gastroesophageal cancer include fluoropyrimidine, platinum, taxanes and irinotecan. Concurrent chemoradiotherapy is one of the main treatment strategies, especially for esophageal cancer. As molecular target agents, the anti-HER2 antibody trastuzumab for HER2-positive gastric cancer and the anti-angiogenesis agent ramucirumab combined with paclitaxel have been proven to improve the survival of gastric cancer patients. Recently, anti-PD-1 antibodies have become available as second- or later-line chemotherapy. Microsatellite instability is also useful as a biomarker to select patients suitable for immunotherapy. Furthermore, genome-wide analysis has improved our understanding of the biological features and molecular mechanisms of gastroesophageal cancer and will provide optimized treatment selection.

Key words: Gastroesophageal cancer; Chemotherapy; Biomarker; HER2

Core tip: This article reviewed the current status and recent developments of gastroesophageal cancer and its related biomarkers for treatment selection. Platinum, fluoropyrimidines, taxanes, irinotecan, trastuzumab and ramucirumab are key drugs. Recently, anti-PD-1 antibodies have become available. PD-L1 expression and microsatellite instability are used to predict the effectiveness of immunotherapy. Genome-wide analysis will provide a better understanding of the biology in gastroesophageal cancer.

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INTRODUCTION

Gastroesophageal cancer is one of the main causes of death worldwide. According to a report by the World Health Organization, gastric cancer and esophageal cancer have the 3rd and 6th highest mortality rates, respectively. The best way to cure gastroesophageal cancer is the complete removal of cancer by surgical resection. Chemotherapy and radiation also contribute to improving the prognosis. Drugs used for systemic chemotherapy include cytotoxic agents and molecular target drugs. Recently, immune checkpoint inhibitors have also become available. Although multiple options can be used as a treatment strategy, the effectiveness and side effects are different depending on individual patients. Therefore, biomarkers to predict the effectiveness for the optimization of treatment selection and individualization are desired. In the present review, current chemotherapy options for gastroesophageal cancer and biomarkers are discussed.

FIRST-LINE CHEMOTHERAPY FOR GASTRIC CANCER

Doublet regimens for gastric cancer

As first-line chemotherapy for gastroesophageal cancer, a combination of platinum and fluoropyrimidine is essential. Doublet or triplet platinum/fluoropyrimidine combinations are recommended for fit patients with advanced gastric cancer[1]. Since oral fluoropyrimidines have the advantage of simplicity, many studies using S-1 or capecitabine have been performed. In the SPIRITS trial, the combination of oral fluoropyrimidine S-1 and cisplatin (SP) improved the survival of advanced gastric cancer patients compared with S-1 alone (median survival time: 13.0 mo *vs* 11.0 mo, $P = 0.04$)[2]. Fluorouracil, leucovorin plus oxaliplatin or cisplatin[3] was also effective. The combination of another oral fluoropyrimidine, capecitabine, with cisplatin showed significant noninferiority for progression-free survival *vs* fluorouracil plus cisplatin (FP)[4]. Cisplatin induces severe nausea and vomiting, *i.e.*, it is highly emetogenic, and it also has strong nephrotoxicity, in which a large amount infusion is necessary to prevent renal impairment. In contrast, oxaliplatin is moderately emetogenic and less nephrotoxic than cisplatin. A study comparing two platinum and two fluoropyrimidine drugs showed that capecitabine and oxaliplatin are as effective as fluorouracil and cisplatin[5]. For oral fluoropyrimidine, the equality of S-1 and capecitabine in effectiveness was evaluated. A comparison between S-1 plus oxaliplatin and capecitabin plus oxaliplatin[6] showed equal efficacy. In a comparison with S-1 plus cisplatin and S-1 plus oxaliplatin (SOX) (G-SOX trial), both showed equivalent efficacy[7]. According to a meta-analysis comparing fluoropyrimidines, toxicity profiles were different, but a lower frequency of relevant adverse events was observed with S-1. This report concluded that choosing fluoropyrimidines should be based on their individual toxicity profiles because their efficacies was similar[8].

Triplet regimens for gastric cancer

To strengthen the efficacy of first-line chemotherapy, triplet regimens including fluorouracil, platinum and taxane have been investigated. In the V325 study, combination with docetaxel, cisplatin and fluorouracil was superior in survival compared with FP[9,10] (median survival time: 9.2 mo *vs* 8.6 mo, $P = 0.02$). However, severe adverse events, including grade 3 or 4 neutropenia and complicated neutropenia, were observed in 82% and 29% of the patients, respectively. In triplet regimens, capecitabine and S-1 were also used as fluoropyrimidines, and oxaliplatin was used as platinum.

The combination of docetaxel, cisplatin and capecitabine (DCX)[11] for advanced cancer achieved a median overall survival of 14.4 mo, but 62.5% of patients experienced grade 3 or 4 neutropenia. DCX was reported to be used as neoadjuvant chemotherapy, which was administered before surgery for resectable diseases[12], and 63% of the patients achieved R0 resection. To maintain effectiveness and avoid severe adverse events, a modified DCX regimen in which docetaxel was reduced was reported[13]. With this regimen, three out of eight patients underwent conversion gastrectomy and achieved long-term survival.

The combination with docetaxel, cisplatin and S-1 for unresectable gastric cancer (KDOG 0601) was also reported[14]. In this study, the objective response rate was 81%, and the median survival time was 18.5 mo. In a study with docetaxel, cisplatin and S-1 (DCS) as neoadjuvant chemotherapy (JCOG1002), the response rate was 57.7%, and R0 resection was achieved in 84.6% of patients[15]. In another study (JCOG1002), neoadjuvant DCS achieved a 90% R0 resection rate[16].

HER2-positive gastric cancer

Approximately 20% of gastric cancer is HER2 positive, and the anti-HER2 antibody trastuzumab is effective. In comparison between combination cisplatin plus capecitabine with or without trastuzumab (ToGA trial), the median overall survival was 13.8 mo with trastuzumab and 11.1 mo without trastuzumab[17]. For HER2-positive breast cancer, lapatinib, trastuzumab emtansine and pertuzumab are available as anti-HER2 agents. However, for HER2-positive gastric cancer, the trials of lapatinib[18,19], trastuzumab emtansine (T-DM1)[20] and pertuzumab[21] did not show a survival benefit and were not used for gastric cancer. Therefore, only trastuzumab as an anti-HER2 agent is available for HER2-positive gastric cancer.

SECOND OR LATER-LINE FOR GASTRIC CANCER

Several phase III trials revealed evidence of a survival benefit in second-line chemotherapy. For example, the COUGAR-02[22] trial showed the benefit of docetaxel, an improvement of survival with irinotecan[23] was proven by Arbeitsgemeinschaft Internistische Onkologie, and a Korean study revealed the effectiveness of docetaxel or irinotecan[24]. The WJOG 4007 study compared paclitaxel and irinotecan and showed an equivalent effectiveness of both agents[25]. Ramucirumab is a molecular target agent that binds to vascular endothelial growth factor receptor-2 (VEGFR2) and inhibits VEGFR-mediated angiogenesis. In the REGARD trial, ramucirumab monotherapy showed a longer survival rate compared with the placebo[26]. The RAINBOW trial revealed the benefit of the addition of ramucirumab to paclitaxel[27]. Apatinib is a tyrosine kinase inhibitor that selectively binds to and strongly inhibits VEGFR-2, with a decrease in VEGF-mediated endothelial cell migration, proliferation, and tumor microvascular density. Apatinib significantly improved the survival of patients for whom two or more prior lines of chemotherapy had failed[28].

Trifluridine/tipiracil (TAS-102) is a cytotoxic chemotherapy consisting of a thymidine-based nucleoside analogue, trifluridine, and a thymidine phosphorylase inhibitor, tipiracil. Trifluridine is incorporated into DNA, resulting in DNA dysfunction, and tipiracil blocks trifluridine degradation by thymidine phosphorylase, increasing trifluridine bioavailability. Trifluridine/tipiracil improved the overall survival compared with the placebo in patients who had previously received two or more regimens[29].

Recently, the effectiveness of immune checkpoint inhibitors has been shown in various cancers. Nivolumab is an anti-PD-1 antibody, and its survival benefit was proven as a third or later-line chemotherapy[30]. Pembrolizumab is also an anti-PD-1 antibody and demonstrated promising activity and manageable safety in patients with advanced gastric or gastroesophageal junction cancer who had previously received at least 2 lines of treatment[31]. In this study, durable responses were observed in patients with PD-L1–positive and PD-L1–negative tumors. In another study, second-line therapy with pembrolizumab and paclitaxel was compared for gastric cancer with a combined positive score (CPS) of 1 or higher of PD-L1. CPS is defined as the number of PD-L1–positive cells (tumor cells, lymphocytes, macrophages) as a proportion of the total number of tumor cells multiplied by 100. Although pembrolizumab did not significantly improve overall survival compared with paclitaxel as a second-line therapy for advanced gastric or gastroesophageal junction cancer, pembrolizumab had a better safety profile than paclitaxel[32].

CHEMOTHERAPY AND CONCURRENT CHEMORADIOTHERAPY FOR ESOPHAGEAL CANCER

Chemotherapy for esophageal cancer

For esophageal cancer, fluoropyrimidines and platinum are essential, and in addition to taxanes, they are also useful in gastric cancer. Perioperative FP was evaluated for gastroesophageal adenocarcinoma, and superiority in overall survival was shown compared with surgery alone[33]. For squamous cell carcinoma, surgery following adjuvant FP was proven to be superior to surgery alone (JCOG9204)[34]. In comparison

between preoperative and postoperative FP for localized advanced squamous cell carcinoma of the esophagus, preoperative FP was superior to postoperative FP (JCOG9907)[35].

Chemoradiotherapy for esophageal cancer

Chemoradiation with FP followed by surgery (CALGB 9781) showed superiority compared with surgery alone[36]. In the FFCD 9102 trial, no benefit was shown for the addition of surgery after chemoradiation with FP compared with the continuation of additional chemoradiation for squamous cell carcinoma in the esophagus[37]. Preoperative chemoradiotherapy with a combination of carboplatin and paclitaxel was superior to surgery alone[38]. For esophageal adenocarcinoma, squamous cell, or adenosquamous carcinoma, a comparison with FP and the combination of oxaliplatin, leucovorin and fluorouracil revealed that both regimens are effective as definitive chemoradiotherapy for patients unsuitable for surgery[39]. For stage II-III esophageal squamous cell carcinoma, definitive chemoradiation with FP was effective. The median survival time was 29 mo, with 3- and 5-year survival rates of 44.7% and 36.8%, respectively, which was comparable to surgery with adjuvant chemotherapy (JOG9906)[40]. For stage I esophageal squamous cell carcinoma, chemoradiation with FP achieved 80.5% of the four-year survival proportion and 68% of the 4-year major relapse-free survival (JCOG9708)[41]. For patients with advanced squamous cell carcinoma of the thoracic esophagus having either T4 tumor or distant lymph node metastasis (M1 Lym), chemoradiation with FP was administered. The response rate was 68.3%, the complete response was 15%, the median survival time was 305.5 days, and the 2-year survival rate was 31.5% (JCOG 9516)[42]. The optimal dose of radiation was also studied. For definitive chemoradiation using FP, the INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial compared 64.8 Gy and 50.4 Gy[43]. The higher radiation dose did not increase survival or local/regional control, and they concluded that the standard radiation dose for patients treated with concurrent 5-FU and cisplatin chemotherapy is 50.4 Gy[43].

Taxanes for esophageal cancer

As for second-line chemotherapy, taxanes are often used. In a phase II trial using docetaxel in which the majority of patients had squamous cell carcinoma, the response rate was 20%, and the median survival time was 8.1 mo[44]. In the COUGAR-02 trial, docetaxel was effective for esophageal adenocarcinoma as well as gastric adenocarcinoma[22]. Paclitaxel was also effective. In a phase II trial for esophageal cancer mainly of squamous cell carcinoma, the response rate was 44.2%, and the median survival time was 10.4 mo[45]. In another trial with the majority of patients in which the histological diagnosis was adenocarcinoma, paclitaxel was also effective[46].

Other molecular targeted agents

As described above, the angiogenesis inhibitor ramucirumab and the anti-HER2 antibody trastuzumab are effective for gastric cancer. Although other molecular targeted agents were investigated in multiple clinical trials, the benefits of most of them have not been proven. Bevacizumab is an angiogenesis inhibitor that is widely used for cancer, including colorectal cancer and lung cancer. For gastric cancer, bevacizumab was examined combined with cytotoxic chemotherapy, and the survival benefit was not proven (AVAGAST trial)[47]. An anti-EGFR antibody, panitumumab, for first-line chemotherapy did not improve survival[48]. The EGFR inhibitor erlotinib is active in patients with gastroesophageal junction adenocarcinomas but appears inactive in gastric cancers (SWOG 0127)[49]. The anti-EGFR antibody cetuximab is useful for head and neck cancers and colorectal cancer with the wild-type RAS gene. A trial of cetuximab for gastric cancer evaluated the effect of the addition to capecitabin and cisplatin (EXPAND). They concluded that the addition of cetuximab to capecitabine-cisplatin provided no additional benefit to chemotherapy alone[50]. In the CALGB 80403 (Alliance)/E1206 trial, cetuximab was applied for esophageal cancer with multiple regimens[51]. However, a trial of chemoradiotherapy with cetuximab in patients with esophageal cancer (SCOPE1) showed a shortened survival time compared with chemoradiotherapy without cetuximab. Therefore, concurrent chemoradiotherapy with cetuximab is not recommended[52]. Another anti-EGFR antibody, panitumumab, was also evaluated for esophagogastric cancer (REAL3)[48]. The addition of panitumumab does not increase overall survival and cannot be recommended.

Microsatellite instability

DNA mismatch repair (MMR) is a mechanism for recognizing and repairing DNA replication errors. Microsatellite instability (MSI) is the condition of having a predisposition to mutations that result from deficient MMR. A potential determinant

of the response to immune checkpoint inhibitors is mutation-associated neoantigens (MANAs) that are encoded by cancers. MMR-deficient cancers are predicted to have many MANAs that might be recognized by the immune system.

The effect of pembrolizumab on patients with advanced MMR–deficient cancers across 12 different tumor types was evaluated[53]. Responses were durable, objective responses were observed in 53% of patients, and complete responses were achieved in 21% of patients. According to another report, the response of pembrolizumab for MMR–deficient colorectal cancers is much better than that for MMR-proficient colorectal cancers. Furthermore, patients with MMR–deficient noncolorectal cancer had responses similar to those of patients with MMR–deficient colorectal cancer[54]. Therefore, MSI/MMR deficiency is useful as a biomarker to predict the effectiveness of immunotherapy for solid tumors, including gastroesophageal cancer.

CURRENT APPLICATION OF BIOMARKERS AND FUTURE PERSPECTIVES

As mentioned above, HER2 overexpression and amplification are applied to define the indication of trastuzumab. The expression of PD-L1 might be useful in predicting the effect of pembrolizumab in some situations. MSI is also useful for selecting patients who are suitable to use pembrolizumab for gastroesophageal cancer as well as other solid tumors.

The Cancer Genome Atlas (TCGA) project proposes a molecular classification dividing gastric cancer into four subtypes[55]: Tumors positive for Epstein–Barr virus, which display PIK3CA mutations, DNA hypermethylation, and an amplification of JAK2, PD-L1 and PD-L2; microsatellite unstable tumors, which show elevated mutation rates; genomically stable tumors, which are enriched for the diffuse histological variant and mutations of RhoA or fusions involving RHO-family GTPase-activating proteins; and tumors with chromosomal instability, which show aneuploidy and the focal amplification of receptor tyrosine kinases. TCGA also showed the biological features of esophageal cancer[56]. According to this information, esophageal squamous cell carcinomas resembled squamous carcinomas of other organs more than they did esophageal adenocarcinomas. In contrast, esophageal adenocarcinomas strongly resembled the chromosomally unstable variant of gastric adenocarcinoma, suggesting that these cancers could be considered a single disease entity.

A study of perioperative chemotherapy for gastric cancer extracted the expression of seven genes (*CDH1, ELOVL5, EGFR, PIP5K1B, FGF1, CD44v8.10* and *TBCE*L) as biomarkers to predict the prognosis of the patient[57]. In another study, the DNA methylation profile was potentially related to a resistance to chemotherapy for gastric cancer[58]. The exploration of new antitumor agents accompanied by the development of a molecular diagnosis with will optimize the selection of therapy for individual patients.

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