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EDITORIAL

Recent advances in chemotherapy for advanced gastric cancer

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Abstract

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 choice of optimum standard first-line chemotherapy regimen for AGC remains debatable, and most responses to chemotherapy are partial and of short duration, with a median survival of approximately 7-11 mo and survival at 2 years rarely more than 10%. Recently, remarkable progress in tumor biology has led to the development of new agents that target critical aspects of oncogenic pathways. For AGC, several molecular targeting agents are now under evaluation in international randomized studies, and trastuzumab, an anti-HER2 monoclonal antibody, has shown antitumor activity against HER-2 positive AGC. However, this benefit is limited to only about 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.

Key words: Gastric cancer; Prognosis; Chemotherapy; Cytotoxic agents; Targeted agents

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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, since 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]. The choice of optimum standard first-line chemotherapy regimen for AGC remains debatable, and most responses to chemotherapy are partial and of short duration. As a result, the current median survival is approximately 7-11 mo and survival at 2 years is rarely more than 10%[3].

These facts notwithstanding, an emerging understanding of the molecular pathways that characterize cell growth, cell cycle, apoptosis, angiogenesis, and invasion has provided novel targets in cancer therapy, leading to the development of therapeutic strategies including epidermal growth factor receptor (EGFR) inhibitors, anti-angiogenic agents, cell cycle inhibitors, and apoptosis promoters. For AGC, several molecular targeting agents are now under evaluation in international randomized studies, and trastuzumab, an anti-HER2 monoclonal antibody, has been shown to exhibit antitumor activity against HER-2 positive AGC. Accordingly, this review covers the recent advances, including biologic agents, in the first-line treatment of AGC on the basis of the best available evidence.

OVERVIEW OF "CLASSICAL" CHEMOTHERAPY

At least two phase Ⅲ randomized clinical trials and one meta-analysis have shown that in AGC, systemic chemotherapy leads to improvement in survival and symptoms when compared with best supportive care alone[1-3]. The question of treating AGC with a single agent *vs* combination chemotherapy has been addressed by randomized studies with a total of 1472 patients, pooled in Wagner's meta-analysis[1,4-7]. Most of the studies used 5-fluorouracil (5-FU) in the single-agent arm. The resulting HR of 0.83 (95% CI: 0.74-0.93) for survival in favor of combination chemotherapy provides evidence of a statistically significant survival benefit with combination *vs* single-agent chemotherapy. Although the overall treatment-associated toxicities were higher in the combination chemotherapy arms, this was usually not statistically significant in the individual trials.

Whilst there is no international agreement accepting any particular schedule as the standard of care for AGC, there is a body of evidence coming from randomized trials and one meta-analysis that should be underlined. In several Korean and Japanese randomized trials comparing 5-FU alone with 5-FU based combination regimens, the response rates and progression-free survival in the cisplatin + 5-FU (CF) arm were better than those for the single-agent 5-FU although no combination regimen demonstrated survival prolongation[6, 8-10](Table 1). However, the interpretation of these results, particularly for determining the reference arms of subsequent studies, differed among regions. In most countries other than Europe and Japan, CF was regarded as the reference arm, as the activity of this monotherapy was limited, with a response rate of around 10% and median progression-free survival of around 2 mo. Meanwhile, triplet regimens have been commonly used in Europe. A significant increase in survival (median 6.1 mo *vs* 8.7 mo, $P = 0.0005$) was observed in a trial by Webb *et al*[11] who compared ECF (epirubicin + CF) *vs* FAMTX (5-FU adriamycin + methotrexate). In another phase III trial that compared ECF and Mitomycin-CF, ECF was superior in terms of quality of life and showed similar results to those of Webb's trial for both the overall response rate (42%) and survival (median 9.4 mo)[12]. Thus, given these results, ECF is currently considered by many oncologists in Europe as the standard treatment. Despite a recent meta-analysis with a subanalysis including 501 patients (treated with CF or CF plus an anthracycline) which showed a significant improvement in overall survival when an anthracycline was added to CF (HR: 0.77, 95% CI: 0.62-0.95)[3], both CF and ECF can still only be considered as reference regimens, as there have been no phase Ⅲ studies comparing them directly. Although these regimens have been found to obtain responses in 20%-40% of patients, the response duration is short, with very few complete responses (approximately 5%), the median time to progression (TTP) is about 4-5 mo and the median survival does not exceed 7-10 mo.

Table 1 Treatment results of cisplatin/5-fluorouracil for advanced gastric cancer in randomized trials

	Korea[8]	Japan[6]	EU[9]	US/EU[10]
No. of patients	105	103	134	112
Response rate (%)	34	51	20	23
Median progression-free survival (mo)	3.9	5.0	4.1	3.7
Median overall survival (mo)	7.3	8.5	7.2	8.5

EU: European Union; US: United States.

Prognostic factors

Prognostic factors are important when designing and interpreting therapeutic trials related to human tumors. In general, it is accepted that for advanced gastric or gastroesophageal cancer neither the primary tumor location nor the histological type has any prognostic impact on survival. In a series of 1080 patients with gastric or gastroesophageal cancer treated in three consecutive trials between 1992 and 2001, the probability of responding to chemotherapy was significantly reduced for individuals with a performance status (PS) of 2, liver or peritoneal metastases, and high serum levels of alkaline phosphatase[13]. Meanwhile, in other series of Korean patients with metastatic gastric cancer, the importance of a poor PS and elevated alkaline phosphatase as negative predictors has been confirmed[14,15]. In addition, a multivariate analysis underlined the significance of other negative findings, including the presence of ascites, serum albumin < 3.6 g/dL, bone metastasis, and the absence of primary tumor resection. Thus, the stratification of patients in randomized trials according to well-established prognostic factors can avoid bias and may allow a better balance between different study arms.

CHEMOTHERAPY WITH NEW CYTOTOXIC AGENTS

Given the limitations of classical chemotherapy combinations in this setting, recent studies have focused on examining the role of chemotherapy with new cytotoxic agents, in particular, docetaxel, irinotecan, oxaliplatin, paclitaxel, and oral fluoropyrimidines (capecitabine and S-1) (Table 2).

Table 2 Results of recent randomized trials with new cytotoxic agents

Study	Treatment	*n*	RR (%)	TTP (median, mo)	MST (mo)	*P* value
Van Cutsem *et al* (V325)[10]	CDDP + 5-FU	224	25	3.7	8.6	0.02
	D + CDDP + 5-FU	221	37	5.6	9.2	
Dank *et al* (V306)[16]	CDDP + 5-FU	163	26	4.2	8.7	NS
	I + 5-FU/LV	170	32	5.0	9.0	
Kang *et al* (ML17302)[17]	CDDP + 5-FU	137	29	5.0	9.3	NS
	CDDP + X	139	41	5.6	10.5	
Cunningham *et al* (REAL-2)[18]	ECF	263	41	6.2	9.9	NS
	EOF	245	42	6.5	9.3	
	ECX	250	46	6.7	9.9	
	EOX	244	48	7.0	11.2	
Boku *et al* (JCOG9912)[19]	5-FU	234	9	2.9	10.8	NS
	CDDP + I	236	38	4.8	12.3	
	S-1	234	28	4.2	11.4	
Koizumi *et al* (SPIRITS)[20]	S-1	150	31	4.0	11.0	NS
	CDDP + S-1	148	54	6.0	13.0	

C: Cisplatin; D: Docetaxel; E: Epirubicin; F: 5-fluorouracil; I: Irinotecan; O: Oxaliplatin; X: Capecitabine; MST: Median survival time; TTP: Time to progression.

Docetaxel

Since several phase Ⅱ studies have shown that docetaxel, alone or in combination with cisplatin, is active against AGC, the addition of docetaxel to a doublet including cisplatin and 5-FU (DCF) was studied in a single international randomized trial (V-325).The results of this phase Ⅲ trial indicated a better response rate, longer progression-free survival (median, 5.6 mo *vs* 3.7 mo; $P = 0.0004$), and significantly prolonged overall survival (median, 9.2 mo *vs* 8.6 mo; $P = 0.0201$) for those patients receiving the DCF triplet[10]. DCF caused a higher levels of toxicity symptoms, including neutropenia (grade 3-4, 82% *vs* 57%), febrile neutropenia (29% *vs* 12%), and diarrhea (grade 3-4, 19% *vs* 8%). However, no significant differences were observed in treatment-related death. Although the quantitative benefit for survival was limited, this trial did show for the first time in AGC that DCF can improve the quality of life parameters and induce a more tangible clinical benefit over the control arm[21,22]. In addition, DCF significantly prolonged the time to definitive worsening of Karnofsky PS when compared with CF. Therefore, these findings indicate that DCF can also be considered as a therapeutic option for patients with AGC who have a PS of 0-1 and can tolerate this drug combination. Furthermore, different combinations with capecitabine, S-1, and irinotecan have also been examined in phase Ⅱ studies, with interesting results[23-26].

Irinotecan

The two most tested combinations for AGC have been irinotecan with cisplatin and irinotecan in combination with either leucovorin and 5-FU bolus or as a continuous infusion: ILF/FOLFIRI-either the AIO regimen (ILF) or the DeGramont regimen (FOLFIRI). The most important study is V-306[16], although the results of two randomized phase Ⅱ studies reported by Bouche and Moehler are also interesting[27,28]. Similar to V-325, the V-306 study was designed in two phases, beginning with a randomized phase Ⅱ trial that was then used to select the experimental arm in the subsequent phase Ⅲ trial. The international phase Ⅲ study comparing ILF with CF demonstrated a trend toward a longer TTP and superior overall survival with the ILF regimen, although the differences were not statistically significant (HR, 1.23 and 1.08, respectively). The median TTP for the ILF and CF arm was 5.0 and 4.2 mo, respectively, and the median overall survival was less than 10 mo in both arms. Therefore, the authors concluded that ILF without cisplatin could be considered as a reasonable alternative first-line treatment option, although it provided no definite advantage in efficacy over CF.

Oxaliplatin

A variety of different oxaliplatin combinations have been studied, and all have been associated with response rates in the range of 40%-67%, with median survival durations between 9 and 15 mo[29-31]. At least two trials have directly compared oxaliplatin-based *vs* cisplatin-containing regimens (including ECF), resulting in a comparable efficacy, yet different toxicity profiles.

The substitution of oxaliplatin for cisplatin in combination with epirubicin and a fluoropyrimidine was investigated in the REAL-2 trial, a randomized phase Ⅲ comparison of ECF, ECX, EOF, and EOX[18]. In the final report, the response rates in the two oxaliplatin-containing arms were comparable to those achieved with the two cisplatin-based regimens, and no significant differences were noted in the median survival. However, when the four groups were considered separately, the median survival for the patients treated with EOX was modestly longer than that with ECF (median 11.2 mo *vs* 9.9 mo, HR = 0.80). Furthermore, the patients in both oxaliplatin-containing arms had significantly less grade 3 to 4 neutropenia, alopecia, thrombocytopenia, and renal dysfunction, although they had more peripheral neuropathy and diarrhea.

Similar outcomes were found when substituting oxaliplatin for cisplatin in a randomized phase Ⅲ trial comparing the FLO regimen (infusional 5-FU, leucovorin, and oxaliplatin) and FLP regimen (5-FU, leucovorin, and cisp-

latin)[32]. No statistically significant differences were noted between the two arms in terms of the response rates of 34% and 25%, respectively, or TTP (primary end point) of 5.7 and 3.8 mo, respectively. From a toxicity standpoint, FLO was associated with less nausea and vomiting, fatigue, renal toxicity, and alopecia, yet more grade 3 or 4 sensory neuropathy. Thus, when taken together, these data show that oxaliplatin combinations are at least as effective as cisplatin, and have a more favorable toxicity profile than cisplatin.

Capecitabine

Since both CF and ECF regimens require central venous access and an ambulatory infusion pump, orally active fluoropyrimidines, including capecitabine and S-1, have been actively studied to improve the convenience of combination regimens. A randomized, non-inferiority trial comparing 21 d of capecitabine (1000 mg/m^2 twice daily for 14 d) plus cisplatin (80 mg/m^2 on day 1) with infusional 5-FU (800 mg/m^2 per day, days 1-5) plus the same dose of cisplatin, demonstrated that capecitabine was not inferior to 5-FU: the median TTP and median overall survival were 5.6 and 10.5 mo in the capecitabine/cisplatin arm and 5.0 and 9.3 mo in the CF arm, respectively[17]. Similar results were observed in the REAL-2 trial[18], a randomized phase Ⅲ study comparing capecitabine plus fluorouracil with oxaliplatin plus cisplatin. No significant differences were noted among the groups in terms of the objective response rate, although a statistically non-significant trend towards improved overall survival was found when the outcomes of both capecitabine-containing arms were combined and compared to both 5-FU-containing arms (HR for death 0.86, 95% CI: 0.8-0.99). However, the toxicity profile with capecitabine was different. The patients receiving ECX (epirubicin, cisplatin, and capecitabine) had a higher rate of grade 3 or 4 neutropenia than patients who received ECF (epirubicin, cisplatin, and 5-FU) (51.5% *vs* 41.7%), while the EOX group had a significantly lower rate (27.6%). However, the rates of febrile neutropenia were not significantly different between the arms. The incidence of grade 3 or 4 hand-foot syndrome was higher with ECX than with ECF or EOX (10.3% *vs* 4.3% *vs* 3.1%, respectively).

Thus, based on these results, the substitution of capecitabine for infusional 5-FU in these regimens results in outcomes which are at least equivalent in terms of efficacy. Moreover, the use of capecitabine allows patients to avoid infusion pumps and a central venous catheter, although the cost of capecitabine is significantly higher than that of 5-FU.

S-1

S-1 is a fourth generation fluoropyrimidine and an oral formulation of tegafur, ftorafur: and 4-dihydroxypyridine: potassium oxonate, in a 1:0.4:1 ratio. Extensive phase Ⅱ/Ⅲ trials of S-1 alone or combination with cisplatin have already been conducted in Japan. In the JCOG 9912 (Japan Clinical Oncology Group) trial comparing 5-FU alone, irinotecan/cisplatin, and S-1 alone, both investigational arms (irinotecan/cisplatin and S-1) showed a significantly higher response rate and longer progression-free survival than the control arm of 5-FU alone[19]. In terms of overall survival, this study demonstrated that S-1 was not inferior to 5-FU monotherapy, with a HR of 0.83. However, there was no demonstration of a significant superiority of irinotecan/cisplatin over 5-FU (HR = 0.85). Meanwhile, in the SPIRITS trial, which compared S-1 monotherapy with a combination of S-1 and cisplatin, the combination arm yielded a significantly higher response rate, and longer progression-free survival and overall survival (HR = 0.774) than the control arm[20]. Thus, on the basis of these Japanese results, S-1 plus cisplatin is the most reasonable standard regimen for AGC in Japan. However, in western countries, the FLAGS trial comparing an experimental regimen of S-1 plus cisplatin (CS arm, S-1: 25 mg/m^2 bid for 21 d followed by a 7-d break; cisplatin: 75 mg/m^2 on day 1, every 4 wk) with a reference regimen of 5-FU plus cisplatin (CF arm, 5-FU: 1000 mg/m^2 as a 5-d continuous infusion; cisplatin: 100 mg/m^2 on day 1, every 4 wk) did not demonstrate a superior overall survival (median overall survival, CS: 8.6 *vs* CF: 7.9), although the CS arm did result in a significantly better safety profile when compared to the CF arm[33]. S-1 displays ethnic differences in its effects on metabolism, leading to differential dose tolerance and toxicity. The tolerable S-1 dose is substantially lower in Western patients than in Asian patients, which may explain its poorer acceptance in Western countries.

CHEMOTHERAPY WITH TARGETED AGENTS

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 tumor, many molecular targeting agents have already exhibited significant antitumor activity. Therefore, the incorporation of these biologic agents in therapeutic regimens is also being investigated for gastric cancer patients (Table 3).

Epidermal growth factor receptor inhibitors

EGFR family is composed of four members: HER1 (also known as EGFR1), HER2, HER3, and HER4, amongst which EGFR1 and HER2 represent the targets for drugs currently under development for gastric cancer. EGFR is commonly over-expressed in gastrointestinal malignancies, and its over-expression is associated with a more aggressive phenotype and poorer survival, suggesting that EGFR can be a rational therapeutic target[34]. Following poor reports on the efficacy of the tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib in gastric cancers[35,36], monoclonal antibodies, primarily cetuximab, have been tested in several recently published trials[37,38]. In a phase Ⅱ trial (n = 38) using cetuximab in combination with 5-FU, leucovorin, and irinotecan (FOLFIRI) in chemonaive patients with

Table 3 Ongoing phase Ⅲ clinical studies with monoclonal antibodies for gastric cancer

Study	Drug	Indication
ToGA[a][39]	XP or FP ± trastuzumab	Advanced gastric cancer (HER2-positive)
AVAGAST	XP ± bevacizumab	Advanced gastric cancer
REAL-3	EOX ± panitumumab	Advanced esophagogastric cancer
EXPAND	XP ± cetuximab	Advanced esophagogastric cancer
MAGIC-2	Perioperative ECX ± bevacizumab	Operable gastric cancer

[a]Completed trial.

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 TTP was 8 mo[38]. Similar to the results with colorectal cancer, the EGFR expression levels did not correlate with the treatment efficacy. Meanwhile, in a biomarker analysis included in the trial by Han *et al*[37], 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[18], the median survival is similar to previously published phase Ⅱ clinical trials. Accordingly, an ongoing international phase Ⅲ trial (EXPAND) is expected to define the role of cetuximab in combination with capecitabine and cisplatin in the first-line setting for patients with advanced gastric or GEJ adenocarcinomas.

Trastuzumab is a humanized anti-HER2 monoclonal antibody 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[39]. Among 3807 patients centrally tested for their HER-2 status, 22.1% were HER-2 positive. The median overall survival was significantly improved in the trastuzumab arm when compared to the chemotherapy alone arm (13.5 mo *vs* 11.1 mo, $P = 0.0048$, HR = 0.74, 95% CI: 0.60-0.91). Plus, 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 HER2-positive AGC.

Lapatinib is a dual inhibitor of the tyrosine kinase domains of HER-1 and HER-2, based on its interference with the adenosine triphosphate binding. Lapatinib has also already been shown clinically 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[40]. A randomized trial 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

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), as well as TKIs targeting the VEGFR.

The addition of bevacizumab, a humanized monoclonal antibody against VEGF-A, to chemotherapy has been shown to prolong survival in patients with metastatic colorectal cancer[41]. However, available clinical data on the use of an angiogenesis inhibitor in patients with advanced gastric or GEJ tumors are limited to nonrandomized phase Ⅱ trials using either bevacizumab or sunitinib. Nonetheless, a pivotal phase Ⅱ trial ($n = 47$) using bevacizumab in combination with irinotecan and cisplatin as a first-line therapy in patients with gastric (51%) or GEJ (49%) adenocarcinomas reported a response rate of 65%, median TTP of 8.3 mo, and median survival of 12.3 mo. Although the chemotherapy-related toxicity was 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[42]. In a second, single-arm phase Ⅱ trial ($n = 42$) using a modified docetaxel, cisplatin, and fluorouracil (DCF) regimen in combination with bevacizumab in patients with metastatic gastric or GEJ adenocarcinoma, similar results for efficacy were observed. The incidence of grade Ⅲ/Ⅳ venous thromboembolism was 29%, where 93% of these thromboembolic events were asymptomatic and only identified on protocol-specific scans. One patient developed a gastrointestinal perforation[43]. Accordingly, gastrointestinal perforation and thromboembolic events may present a serious drawback for the use of bevacizumab in gastric cancer, indicating that a careful risk analysis is needed in randomized trials. Thus, based on these efficacy results, a randomized trial (AVAGAST) comparing capecitabine/cisplatin alone with capecitabine/cisplatin plus bevacizumab as a first-line therapy is currently being conducted on 760 patients with AGC. In a perioperative setting, another randomized trial is

also ongoing to compare ECX with ECX plus bevacizumab in the UK.

The multi-TKI, sunitinib, has also exhibited activity against VEGFRs, as well as Raf, platelet-derived growth factor receptor beta, fibroblast growth factor receptors, and c-KIT. At present, suntinib 50 mg/d as a single agent has been studied as a second- or third-line treatment for AGC in two nonrandomized phase Ⅱ studies[44,45]. Preliminary data from an Asian study (n = 42) showed a partial response rate of 5% and stable disease in 36% of the patients, plus sunitinib was well tolerated in these pretreated patients. Thus, a randomized trial of second-line chemotherapy and sunitinib *vs* a placebo is necessary to establish the therapeutic benefit of sunitinib in this pretreated patient population. 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[46]. The median survival in a first phase Ⅱ study (n = 44) in patients with metastatic (80%) or locally advanced (20%) gastric and GEJ cancer using sorafenib (400 mg twice daily orally in combination with docetaxel and cisplatin in a 21 d cycle) was 14.9 mo, with progression-free survival at 5.8 mo and a response rate of 38.6%. Other phase Ⅱ studies using sorafenib combined with capecitabine or S-1 plus cisplatin are also currently being conducted in Korea and Japan.

Other targeting agents

Everolimus (RAD001) is an oral inhibitor of mTOR (mammalian target of rapamycin), which is downstream of the Akt pathway. After obtaining a remarkable response in patients with metastatic gastric cancer in previous phase Ⅰ / Ⅱ studies in Japan, a prospective randomized placebo-controlled study evaluating the efficacy of everolimus as a second- or third-line therapy in patients with AGC is now being conducted. 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 tumor, including gastric cancer[47], suggesting that it may be a suitable therapeutic target for gastric cancer. Therefore, several agents targeting c-Met are now in an early developmental stage, including the evaluation of MK2461, a TKI of activated c-Met, in a joint Korea-Japan study.

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 for the trifunctional bispecific antibody, catumaxomab. The intraperitoneal administration of catumaxomab in patients with malignant ascites due to EeCAM-positive epithelial cancers resulted in a significantly increased puncture-free survival in a randomized study[48]. The side effects were mostly cytokine release-related symptoms (pyrexia, nausea, and vomiting) and abdominal pain, which were generally mild to moderate and fully reversible.

CONCLUSION

Many randomized clinical studies investigating cytotoxic chemotherapeutic agents have been conducted throughout the world, achieving some advances in the treatment of AGC. While no globally accepted standard regimen has yet been established, the combination of 5-FU and a platinum analog is still the most widely accepted reference regimen worldwide, although 5-FU can be replaced by capecitabine or S-1 and cisplatin by oxaliplatin.

Notwithstanding, 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. Recently, the final results of the ToGA study 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 only limited to about 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.

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