REVIEW

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Chemotherapy for Advanced Gastric Cancer: Review and Update of Current Practices

Sung Chul Park* and Hoon Jai Chun†

Division of Gastroenterology and Hepatology, Department of Internal Medicine, Kangwon National University School of Medicine, Chuncheon, and †Division of Gastroenterology and Hepatology, Department of Internal Medicine, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Korea

No standard adjuvant or palliative chemotherapy regimen has been internationally approved for patients with advanced gastric cancer. Adjuvant chemoradiotherapy is administered prior to surgery and is used in the Unitied States, and intensified chemotherapy is administered prior to and after surgery and is used in Europe. Limited D1 dissections are also frequently performed in the United States and Europe. In Korea, patients undergoing D2 resection appear to benefit from postoperative adjuvant chemotherapy using S-1 or capecitabine plus oxaliplatin. Fluoropyrimidine, platinum, taxane, epirubicin, and irinotecan may be employed alone or in combination as a first-line therapy in a palliative chemotherapy regimen. In Asia, an orally administered fluoropyrimidine, such as capecitabine or S-1, is favored over the continuous infusion of 5-fluorouracil because of its convenience. Trastuzumab has been integrated into the current standard chemotherapy for human epidermal growth factor receptor 2-overexpressing gastric cancers. There is currently no standard regimen for secondary palliative chemotherapy. Clinical studies of several targeted therapies are ongoing. **(Gut Liver 2013;7:385-393)**

Key Words: Stomach neoplasms; Drug therapy

INTRODUCTION

Gastric cancer is the fourth most common cancer worldwide and the second leading cause of cancer death.[1] In Korea, gastric cancer is the second most common cancer after thyroid cancer and the third most common cause of cancer death after lung cancer and liver cancer in Korea.[2] The 5-year survival rate for gastric cancer in Korea is 65.3%, which is substantially higher than what has been reported in North America and Europe.[2,3] The early detection of gastric cancer has increased in Korea due to national cancer screenings. Moreover, the natural course of the disease and the treatments used are different from those in Western countries.[4]

The purpose of this paper is to review current methods for advanced gastric cancer in Korea, to compare these methods with the National Comprehensive Cancer Network (NCCN) guidelines, and to evaluate the most recent studies.

PERIOPERATIVE ADJUVANT CHEMOTHERAPY

Recurrence of gastric cancer after undergoing surgical treatment has been reported in approximately 45% of cases in Western countries and about 22% of cases in Korea and Japan.[5] Several studies have suggested that adjuvant chemotherapy improves overall survival (OS) for gastric cancer when it is administered prior to and after surgery. A meta-analysis by the global advanced/adjuvant stomach tumor research international collaboration group in 2010 demonstrated that adjuvant chemotherapy leads to a 6% increase in the 5-year OS rate compared with surgical treatment alone.[6-8]

The British medical research council adjuvant gastric cancer infusional chemotherapy (MAGIC) prospective and randomized phase III trial reported on the improved OS and disease-free survival (DFS) in patients with stage II or greater gastric, esophagogastric (EG) junctional, and low esophageal adenocarcinoma that received preoperative and postoperative chemotherapy using epirubicin/cisplatin/5-fluorouracil (5-FU) (ECF). The 5-year survival rate was 23% in the control group and 36% in patients who had received chemotherapy (hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.60 to 0.93; p=0.009) (Table 1).[9-13]

Correspondence to: Hoon Jai Chun
Division of Gastroenterology and Hepatology, Department of Internal Medicine, Korea University Anam Hospital, Korea University College of Medicine, 73 Inchon-ro, Seongbuk-gu, Seoul 136-705, Korea
Tel: +82-2-920-6555, Fax: +82-2-953-1943, E-mail: drchunhj@chol.com
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Table 1. Perioperative Adjuvant Chemotherapy in Gastric Cancer

Study	Treatment	No. of patients	Median survival, mo	Survival rate, %
MAGIC[9]	Pre/Postoperative ECF	250	24	5-yr SR, 36.3
	Surgery-only	253	20	23.0
SWOG 9009/INT 0116[10]	5-FU/LV+RT	281	36	3-yr SR, 50
	Surgery-only	275	27	41
ACTS-GC[11]	S-1	529	-	5-yr SR, 71.7
	Surgery-only	530	-	61.6
CLASSIC[12]	XELOX	520	46	3-yr SR, 83
	Surgery-only	515	25	58
CALGB 80101[13]	5-FU/LV	280	37	3-yr SR, 50
	ECF	266	38	52

MAGIC, medical research council adjuvant gastric cancer infusional chemotherapy; ECF, epirubicin, cisplatin, 5-fluorouracil; SR, survival rate; 5-FU, 5-fluorouracil; LV, leukovorin; RT, radiotherapy; ACTS-GC, adjuvant chemotherapy trial of TS-1 for gastric cancer; CLASSIC, capecitabine and oxaliplatin adjuvant study in stomach cancer; XELOX, capecitabine and oxaliplatin; CALGB, Cancer and Leukemia Group B.

However, there are two important limitations to the MAGIC trial. First, esophageal and EG junctional cancer accounted for 25% of all of the data collected. Second, the surgical procedure that was used may not have been standardized. Similar to MAGIC, the evidence of survival benefit for postoperative adjuvant chemoradiotherapy was also observed in the Southwest Cancer Oncology Group trial (SWOG) 9009/INT 0116 study, which took place in patients with resected stage IB-IV(M0) gastric adenocarcinoma in the United States.[10] This trial provided convincing data, including a 36-month median OS for adjuvant chemoradiotherapy and a 27-month median OS outcome for surgery alone, to support the use of postoperative adjuvant chemotherapy in the management of stomach cancer. The adjuvant chemotherapy trial of TS-1 for gastric cancer (ACTS-GC) study in Japan, which collected data on patients with stage II and III gastric cancer that had received extended lymph node dissections (D2), showed that postoperative S-1 chemotherapy improves the 5-year OS rate to 72% from 61% when compared with patients that had received surgery only (HR, 0.67; 95% CI, 0.540 to 0.828).[11] The capecitabine and oxaliplatin adjuvant study in stomach cancer (CLASSIC) study in Korea, which collected data on patients with stage II, IIIA, and IIIB gastric cancer that had also received extended D2 lymph node dissections, showed an improvement in 3-year DFS after postoperative adjuvant chemotherapy using capecitabine plus oxaliplatin (XELOX) to 74%, compared to 60% for those who had received surgery alone (HR, 0.56; 95% CI, 0.44 to 0.72; $p<0.001$).[12] These studies verified that postoperative adjuvant chemotherapy enhances survival outcomes. Surgery-only treatment is no longer advocated as the optimal method of treatment.

There is no standard regimen for adjuvant chemotherapy. The evidence of survival benefits for adjuvant chemoradiation and perioperative chemotherapy after suboptimal surgical operation have been reported by American and European trials, respectively. Studies in Asia, including Korea and Japan, have confirmed the survival benefit of adjuvant chemotherapy following optimal surgical procedures. Western surgeons perform limited D1 dissections more frequently. Extended D2 lymph node dissections were performed in as few as 10% of the cases in the INT 0116 study in the United States in 2001 and 41% according to the MAGIC study in England in 2006. On the other hand, extended D2 lymph node dissections have been routinely performed in Korea and Japan. However, extended D2 lymph node dissection is currently recommended worldwide. A recent Dutch trial reported an improved 15-year survival rate after the D2 procedure compared with the D1 dissection (48% for D2 and 37% for D1).[14] The survival benefit that is associated with extended D2 lymph node dissection has been accepted in the United States and in Europe, and the standard of treatment has changed on this basis. The difference in surgical practice is also reflected in the adjuvant chemotherapy itself. In the United States and Europe, limited D1 dissection is more frequently performed. Adjuvant chemoradiotherapy is administered prior to surgery and is used in the Unitied States, and intensified chemotherapy is administered prior to and after surgery and is used in Europe.

An appropriate adjuvant chemotherapy regimen is highly controversial. Many studies have been performed to determine the optimal postoperative chemotherapy regimen for certain subgroups of patients. In the ACTS-GC study, adjuvant chemotherapy with S-1, which is a 5-FU-based regimen following complete surgical resection, was administrated. In the intergroup Cancer and Leukemia Group B (CALGB) 80101 study, the ECF regimen was not more efficient than the 5-FU/leukovorin (LV) regimen.[13] The intergroup trial of adjuvant chemotherapy in adenocarcinoma of the stomach (ITACA-S) trial showed that a sequential treatment with irinotecan (CPT-11) plus 5-FU/LV followed by docetaxel and cisplatin did not have better clini-

cal outcomes in regard to associated tolerability and feasibility than a 5-FU/LV regimen as a postoperative method of treatment for radically resected gastric cancer.[15] Furthermore, the CLASSIC trial evaluated the use of XELOX, which is the combination of 5-FU and platinum. XELOX showed the same effectiveness in patients with stage II, IIIA, and IIIB cancer according to subgroup analysis. XELOX was found to show more favorable benefit in patients with N1 or N2 nodal status than patients whose disease was limited to N0. Therefore, XELOX is likely to be more effective than S-1 in patients with an aggressive status. In a French FNCLCC-FFCD trial and the English MAGIC trial, cisplatin/5-FU (CF), and ECF-based perioperative chemotherapy were applied, respectively.[9,16]

The adjuvant chemoradiation therapy in stomach cancer (ARTIST) trial investigated the role of postoperative chemoradiotherapy in patients with extended D2 lymph node dissection in Korea. This trial evaluated the efficacy of capecitabine plus cisplatin (XP) with radiotherapy versus XP alone.[17] The results of this study did not support the benefit of additional postoperative radiation to the treatment of patients with extended D2 lymph node dissection. However, in the subgroup analysis, additional radiotherapy to XP significantly increased the DFS in stomach cancer patients with lymph node metastasis. A subsequent trial, ARTIST II, is currently planned to study patients with lymph node-positive gastric cancer.

Recurrence rates of peritoneal dissemination after gastrectomy remain high and range from 40% to 50% according to reports.[18] A meta-analysis of ten studies (1,475 stomach cancer patients) on adjuvant intraperitoneal chemotherapy did not show a prolongation of the survival rate; however, the subgroup analysis suggested the efficacy of hyperthermic intraoperative intraperitoneal chemotherapy.[18] The Korean AMC 0101 phase III randomized trial evaluated intraperitoneal chemotherapy to determine an appropriate adjuvant chemotherapy treatment in nonmetastatic gastric cancer with grossly serosal invasion. The intraperitoneal cisplatin/mitomycin C/doxifluridine/cisplatin (iceMFP) treatment begins with cisplatin (P) administered intraperitoneally during surgery, and 1 day afterward, mitomycin-C (M) is injected. Doxifluridine (F) was administered orally for 4 weeks after surgery, and cisplatin (P) was administered parenterally a total of six times every month. They compared the iceMFP along with mitomycin-C/doxifluridine (Mf) treatment, which consists of an injection of mitomycin-C (M) 3 to 6 weeks after surgery, followed by oral administration of doxifluridine (f) for 3 months.[19] The iceMFP group had a significantly longer recurrence free survival (7% higher) as well as a higher OS (9% higher) compared to the Mf group. That is, intraperitoneal administration of cisplastin and early mitomycin-C reduces the recurrence rate of peritoneal dissemination. The Korean AMC 0201 Phase III randomized trial compared the Mf with the MFP (mitomycin-C, fluoropyrimidine, cisplatin) regimen.[20] For MFP, mitomycin-C (M) was injected 3 to 6 weeks after surgery, and doxifluridine (F) was administered orally for 12 months along with cisplatin (P). The MFP group, which had prolonged administration of doxifluridine (f) with the addition of cisplastin (P), did not have improved treatment outcomes for advanced gastric cancer patients during long term follow-up. Overall, these trials have demonstrated a reduced recurrence rate in patients treated with adjuvant chemotherapy administered intraperitoneally.

Currently, the NCCN guidelines recommend adjuvant chemoradiation for selected patients with T2, patients that have a poorly differentiated or high grade cancer, lymphovascular invasion, neuronal invasion, or are younger than 50 years of age, and all patients with T3, T4, or lymph node metastasis. The NCCN guidelines also recommend adjuvant chemotherapy with the XELOX regimen following extended D2 lymph node dissection.[21] In Europe, the administration of ECF as a perioperative chemotherapy regimen in patients with stage II and III disease has been recommended according to the MAGIC study. In Korea, patients undergoing definite tumor resection do appear to benefit from postoperative adjuvant chemotherapy using either S-1 or XELOX. In Korea, when treated with adjuvant chemotherapy with S-1, 3-year survival rate was 91.6%.[22] S-1 chemotherapy showed a high compliance and its toxicity was tolerable. Korean insurance committee approved S-1 in the adjuvant setting in January 2013. Postoperative chemoradiation may also be recommended in these situations. However, the impact of preoperative chemotherapy in the patients who received D2 dissection is quantitatively less clear-cut. A large clinical PRODIGY trial that evaluate the docetaxel/oxaliplatin/S-1 regimen as neoadjuvant chemotherapy in advanced gastric cancer in addition to postoperative S-1 is currently ongoing and it will help address these questions.[23]

PALLIATIVE CHEMOTHERAPY FOR PATIENTS WITH ADVANCED OR RECURRENT GASTRIC CANCER

1. First-line chemotherapy

Palliative chemotherapy in patients with advanced gastric cancer yields better results regarding the improvement of OS and the relief of symptoms with minimal mortality and morbidity compared to patients treated with the best supportive care (BSC).[24] Fluoropyrimidine (5-FU, S-1, or capecitabine), platinum (cisplatin or oxalipatin), taxane (docetaxel or paclitaxel), epirubicin, and irinotecan may be employed alone or in combination for the first line of therapy of advanced gastric cancer. A meta-analysis showed a trend toward improved survival with combination therapy.[25]

There is no standard international regimen that has been approved for palliative chemotherapy in patients with advanced gastric cancer. NCCN guidelines have recommended docetaxel/cisplatin/5-FU (DCF), ECF, and fluoropyrimidine (5-FU or capecitabine) plus cisplatin as category 1 treatments. The V325 trial has suggested that DCF may be more capable of improving

OS and response rate (RR) than CF; however, DCF produced severe myelosuppression.[26] Therefore, the underlying performance status of patients should be carefully verified in order to avoid or anticipate the toxicity of the DCF regimen. Since cisplatin is intensely emetogenic and nephrotoxic, oxaliplatin, which has similar efficacy as cisplatin but is also less toxic, appears more prominently. European patients with advanced gastric cancer often receive ECF or its modification, epirubicin/oxaliplatin/capecitabine (EOC) as a standard regimen of chemotherapy.[27] In Asian countries such as Korea and Japan, two-drug combination therapy with fluoropyrimidine and cisplatin has been used, and oral fluoropyrimidine, such as capecitabine or S-1, is favored instead of continuous infusion of 5-FU due to its convenience.[28,29] A meta-analysis explored the efficacy of combination therapy with capecitabine and cisplatin compared with CF.[30] No relevant phase III studies have cited the ability to detect differences between S-1 and capecitabine. The S-1 plus cisplatin versus S-1 in RCT in the treatment for stomach cancer (SPRITS) trial in Japan documented RR of 54% with the S-1/cisplatin (SP) regimen (Table 2).[26-29,31-33] This result seems to favor DCF (37%) and ECF (45%). Time to progression (TTP) was similar to other regimens; it was 6 months with SP, 5.6 months with DCF, and 7.4 months with ECF.[26,29,31] However, the SP regimen significantly improved OS by 13 months, compared with DCF and ECF, which had an OS of less than 10 months.[26,29,31] It is thought to be one of the reasons for the increased survival that more patients have been treated with second-line chemotherapies in Japan than in Western countries. The S-1 and taxotere (docetaxel) therapy for advanced gastric cancer randomized phase III trial (phase III START) study, which compared S-1 plus docetaxel with S-1 alone in patients with advanced gastric cancer, indicated no improvement in OS.[34] However, this regimen can be provided on an outpatient basis, when compared with S-1 plus cisplatin, which requires hospitalization.

In the GATE phase II trial, the docetaxel/oxaliplatin/5-FU (DOF) regimen was compared to docetaxel plus oxaliplatin and docetaxel/oxaliplatin/capecitabine. The DOF regimen showed an improvement in the median TTP and OS compared to other regimens.[35] The neutropenia occurred less frequently in the DOF regimen (6%) when compared with DCF (82%) and modified DCF (54%), in which the doses of the regimen were reduced.[36] There was also low frequency (5%) of thromboembolism in the DOF regimen. Docetaxel 75 mg/m^2 was administered every 3 weeks in the DCF regimen and the dose of docetaxel was reduced to 50 mg/m^2 at a 2-week interval in the GATE study. Therefore, the regimen of DOF was well tolerated among taxane-platinum triplet type regimens.

In a randomized phase II study conducted in Korea, a continuous S1/oxaliplatin (SOX) regimen was compared to intermittent treatment until the advanced gastric cancer progressed in patients that showed partial or complete remission after six cycles of SOX regimen every 3 weeks.[37] A total of 250 patients participated in this study, but 126 of these patients were excluded due to disease progression or refusal to participate before they completed all six cycles of the treatment. A subset of 59 and 62 patients were randomized into continuous and intermittent treatment groups, respectively. As expected, the continuous and the intermittent group had progression-free survival (PFS) of 10.5 months and 7.2 months, respectively, but there were no differences between the two groups with regard to OS at 22.6 months and 22.7 months, respectively. There were more reports of fatigue and neuropathy higher than a grade 3 in the continuous group, and there were no differences in other toxicities between the two groups. Therefore, a large randomized phase III study about intermittent therapy is necessary.

A greater incidence of treatment-related toxicity for bolus

Table 2. First-Line Chemotherapy in Advanced Gastric Cancer

Study	Treatment	No. of patients	Response rate, %	Median TTP, mo	Median OS, mo
SPRITS[29]	SP	305	54	6.0	13.0
Kang *et al*.[28]	XP	160	41	5.6	10.5
V325[26]	DCF	221	37	5.6	9.2
Webb *et al*.[31]	ECF	126	45	7.4	8.9
Cunningham *et al*.[27]	EOF	213	42	6.5	9.3
Cunningham *et al*.[27]	EOX	199	48	7.0	11.2
Cunningham *et al*.[27]	ECX	213	46	6.7	9.9
V325[26]	CF	224	25	3.7	8.6
Al-Batran *et al*.[32]	FLO	102	35	5.8	10.7
Dank *et al*.[33]	ILF	170	32	5.0	9.0

TTP, time to progression; OS, overall survival; SPRITS, S-1 plus cisplatin versus S-1 in RCT in the treatment for stomach cancer; SP, S-1, cisplatin; XP, capecitabine, cisplatin; DCF, docetaxel, cisplatin, 5-fluorouracil; ECF, epirubicin, cisplatin, 5-fluorouracil; EOF, epirubicin, oxaliplatin, 5-fluorouracil; EOX, epirubicin, oxaliplatin, capecitabine; ECX, epirubicin, cisplatin, capecitabine; CF, cisplatin, 5-fluorouracil; FLO, 5-fluorouracil, leukovorin, oxaliplatin; ILF, irinotecan, leukovorin, 5-FU.

5-FU and capecitabine in colon cancer cases has been reported in the United States compared to other countries.[38] Moreover, there has been higher toxicity of the S-1 regimen in the West compared to Asia. Regional differences for the toxicity of S-1 seem to be due to the drug metabolizing enzyme gene polymorphism.[39] In the United States, the use of capecitabine and 5-FU continuous infusion is regarded as the backbone of fluoropyrimidine therapy, and there is a similar trend in Europe, although to a lesser extent.

Fluoropyrimidine, taxane, and irinotecan may be used as palliative monotherapy in patients with advanced or recurrent gastric cancer according to performance status and age.

2. Targeted therapy

As trastuzumab was integrated as a current standard of chemotherapy, the advent of the era of targeted therapy in gastric cancer began. Many clinical trials have evaluated the antitumor efficacy of using targeted agents against the epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), vascular endothelial growth factor (VEGF), and the mammalian target of rapamycin (mTOR).

The incidence of HER2 overexpression in gastric cancer is approaching 15% to 25% and there are differences according to tumor location and histologic type.[40,41] EG junction adenocarcinoma and intestinal type have higher positive rates of HER2. In the trastuzumab for gastric cancer (ToGA) study, which is a study of patients that are positive for HER2, anti-HER2 trastuzumab was found to improve the median OS when combined with XP or CF (13.5 months) when compared with XP or CF alone (11.1 months) by 2.4 months (HR, 0.74; 95% CI, 0.60 to 0.91; p=0.0046) (Table 3).[41-44] NCCN guidelines recommend a combination therapy of trastuzumab with the fluoropyrimidine plus cisplatin regimen in patients that show HER2-neu overexpression (category 1). In Korea, a combination therapy of trastuzumab and CF is recommended in patients with HER2 overexpressing adenocarcinoma.

HER2 in gastric cancer may be correlated with poor prognosis, similar to patients with breast cancer. However, a randomized controlled ToGA trial demonstrated a similar median OS (11.1 months) in patients who had received the XP regimen. Additionally, in a recent report, HER2 was not a significant prognostic factor in patients with advanced gastric cancer that had been treated with chemotherapy.[45] Therefore, being positive for HER2 is no longer considered a poor prognostic factor. However, in a retrospective evaluation of the HER2 gene amplification as a prognostic marker in patients that had participated in the INT 0116 study, there was a significant treatment response in patients that had no HER2 gene amplification.[46]

In the avastin in gastric cancer (AVAGAST) trial, bevacizumab, the VEGF monoclonal antibody, showed little statistical difference in OS, although its combination with the XP regimen improved the median OS (12.1 months) by 2 months when compared with its use alone (10.1 months).[42] However, this study found a significant difference in regard to the PFS, which was 6.7 months for bevacizumab combination therapy and 5.3 months for the XP regimen alone. Interestingly, the integration of bevacizumab in chemotherapy has produced markedly improved OS over chemotherapy alone for patients from Europe and the United States with diffuse and distal gastric cancer in comparison with a proximal type of cancer, which is associated with EG junction or cardia invasion.[47] A recent study, which examined the plasma and tumor specimens of patients in the AVAGAST study, showed promising results in the pattern of biomarker expression among gastric cancer subgroups. High plasma VEGF-1 level and low tumor neuropilin-1 expression were associated with bevacizumab efficacy in the AVAGAST study, although these improved outcomes only appeared in non-Asian patients.[48] A recent report investigated whether there are differences in the genetic profiles that are involved in angiogenesis and that may also predict the effect of bevacizumab among Japanese, Hispanics, and Caucasians.[49] Seven genetic polymorphisms were evaluated, and five of the polymorphic variants were expressed

Table 3. Targeted Therapy in Advanced Gastric Cancer

Study	Treatment	No. of patients	Response rate, %	Median TTP, mo	Median OS, mo
ToGA[41]	Trastuzumab+XP/FP	294	47	6.7	13.8
	XP/FP	290	35	5.5	11.1
AVAGAST[42]	Bevacizumab+XP	387	46	6.7	12.1
	Placebo+XP	387	37.4	5.3	10.1
GRANITE-1[43]	Everolimus+BSC	439	4.5	1.7	5.4
	Placebo+BSC	217	2.1	1.4	4.3
REAL3[44]	Panitumumab+mEOC	278	46	6.0	8.8
	EOC	275	42	7.4	11.3

TTP, time to progression; OS, overall survival; ToGA, trastuzumab for gastric cancer; XP, capecitabine, cisplatin; FP, 5-fluorouracil, cisplatin; AVAGAST, avastin in gastric cancer; GRANITE-1, gastric antitumor trial with everolimus-1; BSC, best supportive care; mEOC, modified EOC; EOC, epirubicin, oxaliplatin, capecitabine.

differently between the Asian and Western patients. Caucasians have more polymorphisms that predict a favorable clinical outcome of bevacizumab.

The gastric antitumor trial with everolimus-1 (GRANITE-1) study of patients with previously treated advanced gastric cancer showed that oral everolimus, an mTOR inhibitor plus BSC, had little effect on the median OS (5.39 months) when compared to the placebo (PBO) plus BSC (4.34 months) (HR, 0.90; 95% CI, 0.75 to 1.08; p=0.1244).[43] However, this study also showed encouraging results regarding improved PFS for everolimus therapy (1.68 months), when compared with PBO (1.41 months) (HR, 0.68; 95% CI, 0.56 to 0.78; p<0.0001).

The results of the randomized ECF for advanced and locally advanced esophagogastric cancer 3 (REAL3) study were recently released, and this study compared the EOC regimen with modified EOC in combination with panitumumab, which is the anti-EGFR monoclonal antibody, in metastatic or inoperable gastric cancer patients.[44] The interim analysis of the REAL3 trial shows that the addition of panitumumab was associated with significantly worse median OS (8.8 months vs 11.3 months). The study was terminated early, and the modified EOC plus panitumumab group was switched to the EOC regimen.

Both the mesenchymal-epithelial transition factor (MET) receptor and its ligand, hepatocyte growth factor (HGF), play an important role in the growth and activity of several cancers. MET expression ranges from 26% to 74% in gastric cancer and has been reported to be associated with invasion, metastasis, stage of cancer, and a poor prognosis. Rilotumumab is a HGF monoclonal antibody. In a recent double-blind, randomized phase II study, patients that had untreated metastatic gastric cancer were randomly assigned to a epirubicin/cisplatin/capecitabine (ECX) regimen with either 15 mg/kg, 7.5 mg/kg of rilotumumab or a PBO. OS in the ECX plus rilotumumab group and the ECX group was 11.1 and 8.9 months, respectively, which showed a nonsignificant tendency to slightly improved survival. When set apart from a group showing the MET protein expression of more than 50% in gastric cancer tissues, the OS of the ECX plus rilotumumab group and the ECX group was 11.1 and 5.7 months, respectively, which showed a significant increase in survival.

According to a recent report, fibroblast growth factor receptor 2 (FGFR2) gene application showed a prevalence of 4% and 7% in Korea and Caucasian cohort, respectively.[50] It was associated with lymph node metastasis and poor OS. The SHINE study on the efficacy and safety of FGFR2 inhibitor (AZD4547) is underway.

Phase III trials that use combination chemotherapy with lapatinib and cetuximab for the management of advanced gastric cancer are currently ongoing.

Targeted agents that act on multiple and different pathways need to be developed and a combination of targeted agents that can act on the same pathway or downstream of an identified pathway is necessary. Further investigation is also needed to identify biomarkers that are able to predict the patients in which the targeted agents will optimally work.

3. Second-line chemotherapy

Chemotherapy improves survival and relieves the associated symptoms with minimal morbidity in patients with advanced gastric cancer. However, there have been only a few large clinical trials that have investigated the role of second-line chemotherapy in patients with gastric cancer which has progressed after first-line chemotherapy.

Recently, an AIO study evaluating 40 patients demonstrated a significant difference with regard to RRs in patients that were treated with second-line chemotherapy with irinotecan alone versus the BSC (44% vs 5%) (Table 4).[51-53] There was improved OS in the irinotecan chemotherapy (4.0 months) compared to BSC (2.4 months) (HR, 0.48; 95% CI, 0.25 to 0.92; p=0.012).

A Korean study evaluated 202 patients with previously treated advanced gastric cancer by chemotherapy containing 5-FU and cisplatin. It demonstrated a significant improvement in OS when treated with second-line chemotherapy with docetaxel or irinotecan (5.3 months) versus BSC (3.8 months) (HR, 0.66; 95% CI, 0.49 to 0.89; p=0.007).[52] Some factors such as the number of prior chemotherapy treatments, patients' performance status, and the interval between chemotherapy treatments were influential in univariate and multivariate analysis. Second-

Table 4. Second-Line Chemotherapy in Advanced Gastric Cancer

Study	Treatment	No. of patients	Response rate, %	Median TTP, mo	Median OS, mo
AIO[51]	Irinotecan	21	44	2.6	4.0
	BSC	19	5	-	2.4
Kang *et al*.[52]	SLC (docetaxel or irinotecan)+BSC	133	-	5.6	5.3
	BSC	69	-	-	3.8
WJOG4007[53]	Weekly paclitaxel	108	20.9	3.6	9.5
	Irinotecan	111	13.6	2.3	8.4

TTP, time to progression; OS, overall survival; AIO, Arbeitsgemeinschaft Internistische Onkologie; BSC, best supportive care; SLC, salvage chemotherapy.

line chemotherapy was shown to be effective in the treatment of advanced stomach cancer if the performance status and the compliance of the patient were guaranteed. In a recent phase III trial, weekly paclitaxel (wPTX) was compared with irinotecan (CPT-11), and the results did not show the superiority of irinotecan.[53] Therefore, the study suggested that wPTX could be used as a control regimen of second-line chemotherapy in advanced gastric cancer.

There is no standard regimen for second-line chemotherapy. NCCN guidelines recommend that a combination therapy of fluoropyrimidine and cisplatin with trastuzumab can be used when the first-line therapy does not use trastuzumab (category 2A) or a chemotherapy regimen with paclitaxel, docetaxel, and inirotecan or inirotecan alone (category 2B). In Korea, a second-line combination therapy based on paclitaxel, docetaxel, or inirotecan has been used in patients with advanced or recurrent gastric cancer. There are clinical phase III trials that are currently under investigation to study the effectiveness of second-line chemotherapy using targeted agents such as everolimus, ramucirumab, and gefitinib.

CONCLUSIONS

Several studies of targeted therapies for treating gastric cancer have been released. Due to the different natural courses of disease and treatment techniques for gastric cancer in Eastern and Western countries, appropriate individualization of the course of treatment is necessary.

Adjuvant chemotherapy for stomach cancer that was administered after extended D2 lymph node dissections (D2) was found to improve the OS of patients. A current trend favors new combinations of drugs such as oxaliplatin, capecitabine, S-1, taxane, and irinotecan as palliative chemotherapy. Second-line palliative chemotherapy in patients with previously treated advanced gastric cancer was shown to improve OS and relieve symptoms with minimal mortality and morbidity compared to BSC when performance status and compliance of the patient are guaranteed. Trastuzumab has demonstrated clinical utility in patients with HER2 overexpressing gastric cancer. Different molecular targeted therapies have been actively investigated in gastric cancer treatment and these studies will identify the roles of these agents.

CONFLICTS OF INTEREST

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

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