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REVIEW

The role of S-1 in the treatment of gastric cancer

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Abstract: Gastric cancer is a lethal disease and continues to be the second leading cause of cancer death worldwide. Surgical resection remains the main treatment for early stages with complete resection having the potential for a cure. Recent data suggest that surgery alone is inferior to surgery plus some form of adjunctive therapy. Unfortunately, most patients with gastric cancer are diagnosed in advanced stages, rendering palliative systemic therapy as the only choice of treatment. The most common chemotherapy combination as a first-line treatment in advanced gastric cancer (AGC) includes a platinum compound, a fluoroporyrimidine and a taxane (in the United States) or an antracycline (in Europe). Fluoropyrimidines have been the backbone in the chemotherapy regimens for the treatment of gastric cancer. There has been considerable interest in oral fluoropyrimidines. S-1 is a fourth-generation oral fluoropyrimidine that combines tegafur, which is a prodrug of 5-fluorouracil (5-FU), and two biochemical modulators: (1) 5-chloro-2,4-dihydroxypyridine, a powerful but reversible inhibitor of dihydropyrimidine dehydrogenase that prevents 5-FU degradation, and (2) potassium oxonate, which reduces gastrointestinal (GI) toxicity by inhibition of 5-FU phosphorylation in the GI mucosa. S-1 has produced an advantage in the postoperative setting in a large Phase III trial and has also been evaluated as a preoperative chemotherapy in gastric cancer, but in the preoperative setting, there are no completed Phase III clinical trials. Nonetheless, S-1 is considered, as a single agent, as the standard of care in Japan for the adjuvant treatment of resected gastric cancer and in combination with cisplatin in the advanced setting based on level 1 evidence in Phase III trials. S-1 is now widely available and has been approved in 27 European countries as a first-line treatment for AGC. S-1 is generally well tolerated with a low toxicity profile. It is a novel agent that provides a convenient and safe advantage over intravenous fluoropyrimidine in AGC.

Keywords: tegafur, Ftorafur, FT, 5-FU, advanced gastric cancer

Introduction

Throughout the world, nearly one million new cases of gastric cancer are diagnosed every year, with the highest incidence in East Asia, South America, and Eastern Europe. Gastric cancer continues to be a lethal disease, with over 70% of new cases and deaths occurring in developing countries.[1] The incidence of gastric cancer has decreased in the United States over the past decades, but an estimated 21,000 new cases were diagnosed in and 10,570 deaths occurred in 2010.[2] The median age at diagnosis is 70 years of age, though 37% of the patients diagnosed with gastric cancer are between the ages of 20 and 60 years.[2] Risk factors include diets rich in salt or smoked foods, smoking, *Helicobacter pylori* infection, atrophic gastritis, blood type A, prior gastric surgery, and socioeconomic status (high socioeconomic group increases the risk of proximal

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cancer and low socioeconomic status results in an increase in distal cancers).[3] A paradoxical rise has been noted in the incidence of esophageal adenocarcinoma and gastroesophageal junction tumors in the United States compared with the incidence of distal gastric cancer.[4] This might be explained by the increase in obesity and tobacco use, and moreover, the eradication of *Helicobacter pylori* infection might increase the risk of gastroesophageal reflux disease.[5] Several familial syndromes have also been associated with a predisposition to gastric cancer: hereditary nonpolyposis colorectal cancer/Lynch syndrome, E-cadherin mutation, familial adenomatous polyposis, and Peutz-Jeghers syndrome.[6] Gastric cancer is usually asymptomatic or causes nonspecific symptoms like abdominal pain, bloating, nausea, and weight loss. By the time symptoms arise, the disease might be already in advanced stages. In general, survival rates are poor, and this can be attributed to the combination of the absence of effective screening programs, limited awareness of the disease, the slow development of newer and improved treatments, and the underlying aggressiveness of this tumor that contributes to higher relapse rates and hence to the overall low survival. Surgical resection remains the major contributor to cure in relatively early stages, and complete (R0) resection is essential for cure; however, more than half of the tumors recur.[7] Therefore, newer therapies are urgently needed that can prevent reoccurrence and also prolong survival in the advanced setting.

The prognosis is dismal for patients with advanced disease, and the median overall survival for patients undergoing chemotherapy treatment is approximately 9 months. In Western countries, the treatment for advanced gastric cancer (AGC) includes a platinum compound (oxaliplatin or cisplatin), an intravenous or oral fluoropyrimidine (5-fluorouracil [5-FU] or capecitabine), and a taxane (docetaxel)[8] or an antracycline[9] (epirubicin). Molecular-targeted therapy has made its advancement in the treatment of AGC; trastuzumab (a humanized immunoglobulin G monoclonal antibody against human epidermal growth factor receptor 2) has been approved in combination with chemotherapy for the treatment of patients with AGC whose tumors overexpress erbB2 protein.[10]

The fluoropyrimidine 5-FU, an antimetabolite initially synthesized by Heidelberger in the 1950s,[11] continues to be the backbone in the chemotherapy regimens for gastrointestinal (GI) malignancies including gastric cancer. An ideal treatment should be safe, suitable and effective; chemotherapy is evolving towards safer and patient-friendly regimens with the goal of improved efficacy. Until recently, the primary mode of administration of 5-FU has been intravenously, but its infusion requires an indwelling catheter and a portable pump that patients carry for many days, which is quite inconvenient, and these catheters can be associated with increased morbidity.[12] Oral fluoropyrimidines have been in development for 30 years with the aim of increasing tumor cytotoxicity, reducing side effects, and offering a convenient alternative to the patient. S-1 is a fourth-generation oral fluoropyrimidine that combines a 5-FU prodrug tegafur (Ftorafur® [FT], Jinan Yunjia chemical Co, Jinan, China) and two 5-FU-modulating enzymes: 5-chloro-2,4-dihydroxypyridine (CDHP, gimeracil) and potassium oxonate (Oxo) in a molar ratio of 1:0.4:1.[13] S-1 is novel because it enhances 5-FU tumor concentration and decreases GI toxicity due to the action of both CDHP and Oxo, respectively.[14] S-1 is approved in Japan as a single agent for the treatment of gastric cancer in the adjuvant setting and in combination with other chemotherapy agents for the treatment of AGC in East Asia and Europe. Described in this review are the pharmacokinetics, the mechanism of action, and the clinical evidence that led to the approval of S-1 in Japan and Europe.

S-1 (TS-1/Teysuno™)

S-1, developed in Japan and manufactured by Taiho Pharma (Princeton, NJ), is an example of advanced drug engineering because it combines the 5-FU prodrug FT with CDHP, a competitive reversible DPD inhibitor that prolongs the half-life of 5-FU, and Oxo, a phosphoribosyltransferase inhibitor that prevents the phosphorylation of 5-FU in the digestive tract, therefore mitigating its GI toxicity.[13,15] It was designed to provide continuous 5-FU plasma exposure comparable to the intravenous infusion. The concept of a new therapeutic drug with high anticancer activity and less adverse effects that can substitute the conventional treatment was conceived by Kobayashi in 1969 and subsequently crystalized to an oral form by Shirasaka in 1991.[16] Since then, S-1 has been approved for the treatment of gastric cancer, head and neck, colorectal, nonsmall cell lung, breast, pancreatic, and biliary tract cancers in East Asia and for the treatment of AGC in combination with cisplatin in 27 European countries.

FT, the 5-FU prodrug, is absorbed in the small intestine and converted to 5-FU through the liver microsomal P-450 metabolizing enzyme system (CYP2A6). The main mechanism of 5-FU activation is conversion to fluorouridine monophosphate (FUMP). 5-FU is metabolized to three active metabolites: 5-fluoro-2′-deoxyuridine-5′-monophosphate, which inhibits thymidine synthesis through noncompetitive inhibition

of thymidylate synthase (TS) preventing DNA synthesis, 5-fluorouridine-5′-triphosphate, which is incorporated into the RNA causing alteration of its metabolism, and 5-fluoro-2′deoxyuridine-5′-triphosphate, which integrates into the DNA suppressing its synthesis.[12]

Most of the 5-FU is degraded (85%) by dihydropyrimidine dehydrogenase (DPD), leading to the formation of α-fluoro-β-alanine (FBAL).[12,17,18] CDHP inhibits DPD, thus allowing higher concentrations of 5-FU to enter the anabolic pathway and enhancing its therapeutic effect. Additionally, the inhibition of DPD leads to a decreased amount of FBAL formation, which results in less neurotoxicity.[12,17,19] The final component of the S-1 formulation (Oxo) inhibits orotate phosphoribosyltransferase in the GI mucosa, which prevents the formation of FUMP, decreasing GI toxicity.[14,20]

Phase I trials have studied the pharmacokinetics and pharmacodynamics of this component. The median time to maximum plasma concentration (T_{max}) of S-1 after 40–60 mg per dose is 2–3 hours for FT and approximately 3.5 hours for 5-FU in the Asian population. Blood levels of 5-FU are effectively maintained over 24 hours with twice daily dosing.[18] In European and US populations, S-1 administered in a single dose of 50 mg/m^2 or 25–30 mg/m^2 twice daily at least 1 hour before or 1 hour after a meal achieved median T_{max} values of 0.5–1.5 hours for FT and 2–3 hours for 5-FU.[21–23] These studies also recognized GI toxicities to be the more prominent toxicities from S-1 in Western patients, like diarrhea, nausea, vomiting, and hyperbilirubinemia, whereas hematological toxicities are more prevalent in Japanese patients. Other side effects include fatigue, anorexia, stomatitis, and hand-foot syndrome.[21–24] The maximum tolerated dose was established at 80 mg/m^2 in two divided doses for Japanese population and 25 mg/m^2 twice a day for Caucasian population.[25,26]

This inter-ethnic variability of S-1 pharmacokinetics and pharmacodynamics has been attributed to differences in the CYP2A6 genotypes. Studies have demonstrated high frequency of allelic variants CYP2A6*4, *7, and *9 in East Asians than in Caucasians, which might be associated with reduced enzymatic activity and decreased activation of FT.[27,28] On the contrary, higher FT metabolism is seen in Caucasians due to higher CYP2A6 activity; however, Chuah et al[29] established similar 5-FU exposure between these two ethnic groups. These findings were explained by higher CDHP exposure in Asians, resulting in increased DPD inhibition and slower catabolism of 5-FU, despite having low CYP2A6 activity, while Caucasians had higher CYP2A6 activity but faster 5-FU clearance. The difference in toxicities could not be explained by differences in 5-FU exposure, since they were similar. A potential explanation might be inter-ethnic variabilities of thymidylate synthase promoter enhancer region polymorphisms, which are more frequently seen in Asians or in Caucasians on a higher folate diet. Further evaluation is warranted in order to explain these discrepancies.

The use of S-1 in the treatment of gastric cancer

Clinical studies of S-1 in the neoadjuvant setting

Perioperative treatment has been recommended for the treatment of gastric cancer for patients with advanced T and N stages in order to improve resectability and outcomes. Perioperative chemotherapy has been demonstrated to be more effective in resectable gastric cancer than surgery alone. The first study to demonstrate improvement in overall survival (OS) for patients with localized gastric cancer including gastroesophageal junction (GEJ) adenocarcinoma was the MAGIC (MRC Adjuvant Gastric Infusional Chemotherapy) trial.[30] In this study, patients were randomized to receive pre- and post-chemotherapy, followed by surgery versus surgery alone. Patients in the chemotherapy group received chemotherapy for 3–6 weeks (total of three cycles) before surgery and another three cycles, 6–12 weeks after surgery. The chemotherapy regimen consisted of ECF (epirubicin 50 mg/m^2, cisplatin 60 mg/m^2 on day 1, and 5-FU 200 mg/m^2/d for 21 days). The 5-year survival data showed an advantage for the chemotherapy group (36%) compared with the surgery-alone group (23%). Median survival was 24 months in the chemotherapy group compared with 20 months in the surgery-alone group (hazard ratio [HR], 0.75; $P = 0.009$). Progression-free survival was also significantly prolonged; however, the mortality rate was 6% in both arms, and within the perioperative chemotherapy arm only 55% of the patients initiated post-surgery chemotherapy and 42% completed it. Recently, the results of a Phase III trial, from the Federation Nationale des Centres de Lutte Contre le Cancer ACCORD07-FFCD 9703, were reported; 224 patients with resectable adenocarcinoma of the lower esophagus, GEJ, or stomach were randomly assigned to receive chemotherapy for two or three cycles (cisplatin and continuous infusion of fluorouracil) and three or four postoperative cycles of the same regimen versus surgery alone.[31] This trial demonstrated a significantly increased curative resection rate, disease free survival (DFS), and OS between perioperative chemotherapy and surgery (CS) versus surgery (S) alone in favor of the multimodality group (OS 5-year rate, 38% (CS) versus 24% (S); HR for death, 0.69; 95% confidence interval [CI], 0.50–0.95;

$P = 0.02$; DFS 5-year rate, 34% versus 19%; HR, 0.65; CI, 0.48–0.89; $P = 0.003$). These are the only two studies that have demonstrated this advancement in survival with the use of perioperative treatment in Western patients. Several other regimens have demonstrated response rate (RR) of 34%–69% for initially unresectable cases,[32–34] with associated adverse effects. Therefore, initial performance status might be considered for an effective neoadjuvant treatment.

There are few studies evaluating the efficacy of S-1 for neoadjuvant treatment, and these studies are only limited to the Asian population. Two Japanese retrospective analyses of S-1 in combination with cisplatin as neoadjuvant treatment in locally advanced disease achieved a RR of 44%–79%.[35,36] An initial pilot study of S-1 for neoadjuvant treatment showed excellent results and promising effects on survival for patients with resectable gastric cancer.[37] Therefore, the Japan Clinical Oncology Group (JCOG) conducted a Phase II trial of S-1 as a single agent for neoadjuvant chemotherapy in patients with resectable scirrhous gastric cancer.[38] S-1 was administered at a dose of 100–120 mg daily for 28 days every 6 weeks for a total of two courses, followed by radical surgery. Fifty-five patients were included and 46 patients underwent resection. The survival rate was better than that of the historical control; however, the survival rate did not reach the expected rate (2-year survival 59%–60%, $P = 0.245$). The S-1 group did not reach the survival rate required to design a Phase III trial. A chemotherapy combination using S-1 plus cisplatin has shown more promising data; the Phase II study of preoperative chemotherapy (CX) with S-1 and cisplatin followed by gastrectomy for clinically resectable type 4 and large type 3 gastric cancer (JCOG 0210) was conducted by the JCOG[39] (Table 1). A total of 50 patients were enrolled in this study. Patients received two cycles of induction chemotherapy (cisplatin 60 mg/m^2 on day 8 plus S-1 at a dose of 80–120 mg orally from day 1–21) every 28 days. Gastrectomy with D2/3 dissection was performed 3–5 weeks after chemotherapy. A total of 36 patients (73%) received two cycles of CX and R0 resection. Pathological response was seen in 24 patients (48), and the 1-year survival was 70%. Because of the superiority of this combination, the JCOG has already started a Phase III trial to confirm the effectiveness of neoadjuvant chemotherapy using S-1 and cisplatin followed by surgery against extended surgery in patients with scirrhous or large type 3 gastric cancers. Furthermore, the survival results from the Phase II study of preoperative chemotherapy with S-1 and cisplatin followed by D3 gastrectomy for gastric cancer with extensive lymph node metastases demonstrated a 3-year OS of 58.8% (95% CI, 44.1%–70.9%) in 51 eligible patients. This multimodality treatment is promising in patients with locoregional disease and extensive node metastases.[40]

Li and Chen have also evaluated the combination of S-1 and oxaliplatin in a Phase II trial.[41] In this trial 66 patients with AGC were enrolled. 32 patients received S-1 orally at a dose of 80 mg/m^2 for 14 days and oxaliplatin 130 mg/m^2 on day 1 every 3 weeks; the other 34 patients were in the control group. After neoadjuvant treatment, 32 patients underwent surgical resection, and 78.1% received D2 lymph node dissection. The R0 resection rate was 81.3% versus 73.5% in the control group ($P = 0.040$). Grade 3/4 anemia and neutropenia was observed in 6.4% of patients and GI toxicities like nausea, anorexia, and liver dysfunction were observed in 12.5%, 5.4%, and 9.7% respectively. It was concluded from this study that S-1 plus oxaliplatin (SOX regimen) as a neoadjuvant treatment was associated with high efficacy, acceptable side effects and increase rate of D2 dissection and R0 resection.

A prospective randomized Phase II trial (COMPASS) comparing neoadjuvant chemotherapy of two or four cycles of paclitaxel plus cisplatin or S-1 plus cisplatin followed by surgery in locally advanced gastric cancer is currently accruing. The results are not available yet. The purpose of this study is to select the most promising neoadjuvant regimen for a Phase III study. Most of the remaining reports have been case reports where S-1 in combination with cisplatin has demonstrated marked response and in some cases complete pathological response (CR). The role of S-1 in the neoadjuvant setting remains to be established in validated large clinical trials.

Evidence of benefit from S-1 as a postoperative adjuvant treatment

Few studies for adjuvant treatment have been performed after curative resection of gastric cancer; yet the definition from

Table 1 Phase II clinical trials with S-1 in preoperative setting

Study	Number of patients	Treatment	Pathology RR	OS
JCOG 0210[39]	50	S-1 + cisplatin followed by D2/D3 gastrectomy	48.0%	3 year = 26%
JCOG 0002[38]	55	S-1 followed by gastrectomy	32.6%	2 year = 60%
JCOG 0405[40]	53	S-1 + cisplatin followed by D3 gastrectomy	51.0%	3 year = 58%
COMPASS[42]	Currently accruing			

Abbreviations: RR, response rate; OS, overall survival.

curative resection differs between Western countries and Japan. In Western countries, the standard curative resection comprises gastrectomy plus D1 lymphadenectomy (lymph node dissection of right and left cardiac lymph nodes, lesser curvature lymph nodes, left gastric lymph nodes, and supra/infrapyloric lymph nodes). In Japan the standard operation for gastric cancer includes gastrectomy plus D2 lymphadenectomy (D1 lymphadenectomy plus lymph node dissection of common hepatic, celiac, splenic, and splenic hilar lymph nodes).[43] Final results from the Dutch trial failed to demonstrate survival benefit of D2 dissection over D1 dissection; moreover, the hospital mortality was higher in the D2 operation arm,[44] which is the reason why D1 dissection is the standard of care in the US. The intergroup 0116 (INT-0116) reported the results of a randomized trial of postoperative adjuvant chemoradiotherapy for gastric carcinoma versus observation.[45] Median survival in the surgery-only and chemoradiation groups was 27 and 36 months, respectively ($P = 0.005$). Although this study has been criticized due to the limited or inadequate node dissection (D0 or D1), it has established adjuvant chemoradiation as the standard of care for patients with adenocarcinoma of the stomach who have undergone curative resection and have not received preoperative treatment. However, the Japanese Gastric Association does not recommend this adjuvant treatment due to the poor lymph node dissection performed by Macdonald et al.[45] Several studies in postoperative treatment after gastric resection were also conducted in Japan: the JCOG 8801[46] failed to demonstrate a survival benefit for patients treated with adjuvant therapy. In addition to this study, the JCOG 9206-1,[47] JCOG9206-2,[48] and NSAS-GC[46] (National Surgical Adjuvant Study Group for Gastric Cancer) evaluated adjuvant chemotherapy after D2 dissection. In the JCOG 8801 and JCOG 9206-1 trials, survival rates were 85.8% and 91.2% in the adjuvant treatment group versus 82.9% and 86.1% in the control groups; however, no survival benefit was demonstrated with surgery alone. The final analysis of the NSAS-GC trial, where adjuvant chemotherapy with UFT (uracil + FT) was evaluated, revealed a survival benefit for postoperative adjuvant therapy with UFT. The large Phase III trial that demonstrated that adjuvant chemotherapy with S-1 for a total of 12 months significantly improves the survival after D2 curative gastrectomy for patients with stage II and III gastric cancer was reported by Sakuramoto et al[49] in the ACTS-GC trial (the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer) (Table 2). Between 2001 and 2004, 1059 patients were randomly assigned to receive surgery followed by S-1 or to receive surgery only. S-1 was started 6 weeks after surgery and continued for a total of 12 months. The treatment consisted of S-1 at a dose of 80 mg/m^2 daily for a total of 4 weeks, every 6 weeks. The HR for death in the S-1 group compared with surgery alone was 0.65 (95% CI, 0.53–0.81; $P = 0.003$). The 5-year overall survival for S-1 was 71.7% and 61.1% in the surgery only group (hazard ratio 0.669; 95% CI, 0.540 to 0.828). Five-year OS of each stage (stage II, IIIA, and IIIB) in the S-1 group was 84.2%, 67.1%, and 50.2% compared with 71.3%, 57.3%, and 44.1% in the surgery-only group, respectively.[50] Based on the results of this study, adjuvant S-1 chemotherapy after D2 surgery has been established as standard of care in Japan.

Feasibility studies of adjuvant chemotherapy with S-1 and either cisplatin[51] or docetaxel[52] have been performed, with favorable results, and these combinations have been proposed for future Phase III trials.

Clinical trials of S-1 for advanced unresectable gastric cancer

The majority of patients present with advanced disease rendering a poor prognosis. Chemotherapy in the palliative setting improves survival; although, a balance between toxicity versus benefit should be assessed before treatment is administered. Two regimens are considered as standard for first-line treatment in AGC in Western countries: docetaxel + cisplatin + 5-FU (DCF)[8] being the most commonly used combination chemotherapy in the United States, and epirubin + cisplatin or oxaliplatin + 5-FU or capecitabine[9] in Europe. Targeted therapies have emerged for the treatment of AGC with improvement in survival, having trastuzumab level 1 evidence; this is especially effective in tumors that overexpress erbB2 protein.[10] The need of more active cytotoxic agents or targeted agents

Table 2 Results of randomized controlled trial in adjuvant setting for gastric cancer

Study	Number of patients	Treatment	% LN dissection	OS	*P* value
INT 0116[45]	275/281	Surgery only versus surgery + postoperative 5-FU + RT (45 Gy)	D0 = 54% D1 = 36%	41/50%	0.005
MAGIC Trial[30]	250/253	Surgery only versus preoperative ECF + surgery postoperative ECF	D1 = 20% D2 = 41%	29.5/36.3%	0.009
ACTS-GC[49]	530/529	Surgery only versus surgery + postoperative S-1	D2 = 94.7%/D3 = 5.3%	70.1%/80.1%	0.003

Abbreviations: ECF, epirubicin + cisplatin + 5-FU; 5-FU, 5-fluorouracil; RT, radiotherapy; LN, lymph node; OS, overall survival.

that improve survival in AGC is unquestionable; however, refurbishing current treatment might pose an advantage in safety and toxicity benefits. The oral fluoropyrimidines offer a convenience in treatment schedule, improvement in patient quality of life, and a manageable toxicity profile.

Capecitabine is an oral fluoropyrimidine, a prodrug of 5-FU, which is approved in the USA for the treatment of metastatic breast, colorectal, and stage III colon cancer. It is also widely used for AGC in several countries and North America; however, it has not been approved in the USA for this indication. The efficacy and safety between S-1 and capecitabine has not been reported.

S-1 has shown activity in AGC in several phase II and III studies. Early phase II studies demonstrated a response rate of 31.6%, 44%, and 49% as single agent.[53–55] S-1 in combination with cisplatin showed RR of 51% (95% CI, 35%–67%) with a median time to progression of 4.8 months (95% CI, 3.8–6.1 months).[56]

Boku et al reported a randomized Phase III trial comparing 5-FU alone, irinotecan plus cisplatin (CP), and S-1 alone in AGC under the Gastrointestinal Oncology Study Group/Japan Clinical Oncology Group (Table 3).[57] S-1 showed noninferiority compared with 5-FU, while CP did not show superiority over 5-FU alone. In the Phase III study by Koizumi et al,[58] a total of 305 patients were enrolled and randomly assigned to S-1 plus cisplatin or S-1 alone (SPIRITS: S-1 plus cisplatin versus S-1 alone for first-line treatment of AGC). Median overall survival was significantly longer in patients that received S-1 plus cisplatin (13 months) than in those who received S-1 alone (11 months; HR 0.77). S-1 plus cisplatin has been recognized as a first-line treatment for AGC in Asia. Results from the multicenter Phase III comparison of cisplatin/S-1 (CS) with cisplatin/infusional fluorouracil (CF) in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial[59] showed different results to the ones reported in the SPIRITS trial. Patients were randomly assigned either to the traditional 5-FU plus cisplatin (5-FU 1000 mg/m^2/24 hours for 120 hours and cisplatin at 100 mg/m^2 intravenously (IV) on day 1) or S-1 plus cisplatin (S-1 25 mg/m^2 twice a day and cisplatin at 75 mg/m^2 IV on day 1). The median overall survival was 8.6 months in the cisplatin and S-1 group versus 7.9 months in the cisplatin and 5-FU group (HR 0.92; 95% CI, 0.80–1.05; $P = 0.20$). In this trial, treatment-related deaths were significantly more common in the CF arm (4.9%) than in the CS arm (2.5%). Neutropenia, thrombocytopenia, and leucopenia were more frequent in the CF than in the CS arm (14.4% versus 5.0%; $P < 0.01$). Nonhematologic adverse events like stomatitis, mucosal inflammation, electrolyte imbalances, and renal-related events were also significantly more frequent in the CF arms than in the CS arm.

Another Phase III trial conducted in Japan compared the efficacy and safety of irinotecan plus S-1 (IRI-S) versus S-1 monotherapy in patients with advanced or recurrent gastric cancer.[60] The median survival time with IRI-S versus S-1 monotherapy was 12.8 versus 10.5 months ($P = 0.233$). The response rate was significantly higher for IRI-S than for S-1 monotherapy (41.5% versus 26.9%, $P = 0.035$). Although IRI-S achieved longer median survival than S-1 monotherapy with good tolerance, it did not show significant superiority in this study. Lately, the results from a prospective randomized multinational trial, where combination of S-1 plus docetaxel versus S-1 alone in patients with AGC, has been reported.[61] S-1 (40 mg/m^2) was administered twice daily for 14 days every 21 days, plus docetaxel (DOC 40 mg/m^2) IV on day 1.

Table 3 Phase III clinical trials with S-1 in advanced gastric cancer

Study	Number of patients	Regimen	RR, %	RFS (median)	OS (median)	HR/ *P* value
JCOG9912[57]	234	5-FU	9%	2.9 months	10.8 months	
	234	S-1	28%	4.2 months	11.4 months	$P = 0.034$
	236	CPT-11/CDDP	38%	4.8 months	12.3 months	$P = 0.055$
SPIRITS[58]	150	S-1	31%	4.0 months	11.0 months	HR = 0.77
	148	S-1/CDDP	54%	6.0 months	13.0 months	$P = 0.037$
FLAGS[59]	527	S-1 + CDDP	29.1%	4.8 months	8.6 months	$P = 0.20$
	526	CDDP + 5FU	31.9%	5.5 months	7.9 months	
GCO301/TOP002[60]	160	S-1	27%	3.6 months	10.5 months	HR = 0.86
	155	S-1/CPT-11	42%	4.5 months	12.8 months	$P = 0.23$
START JACCRO	323	S-1	18.4%	4.2 months	11.1 months	HR = 0.88
GC-03[61]	316	S-1/DOC	30.3%	5.4 months	13.0 months	$P = 0.14$

Abbreviations: 5-FU, 5-fluourouracil; CPT-11, irinotecan; DOC, docetaxel; CDDP, cisplatin; HR, hazard ratio; RR, response rate; RFS, relapse free survival; OS, overall survival.

In the second group, patients received S-1 at the same dose for 28 days, followed by 14 days rest. S-1/DOC did not meet primary endpoint of OS, but the OS in the nonmeasurable group and the time to treatment progression of the S-1/DOC was significantly superior to that of the S-1 alone.

To investigate the noninferiority of S-1 plus oxaliplatin to S-1 plus cisplatin, a randomized Phase III study comparing S-1 plus oxaliplatin with S-1 plus cisplatin as first-line therapy for advanced or recurrent gastric cancer is being planned.

Conclusion

Despite worldwide efforts to improve the treatment of gastric cancer, survival remains dismal. While the focus of today's research in the majority of malignancies as well as gastric cancer is on targeted therapy, it is also important to improve safety of current treatments.

S-1 is a novel oral fluoropyrimidine that has shown activity in the treatment of gastric cancer, and results from Phase III trials in AGC have demonstrated that S-1 in combination with chemotherapies is noninferior to conventional 5-FU, with the benefit of convenience and reduced toxicity. We can say that the role of S-1 in gastric cancer is a more suitable alternative that can substitute IV 5-FU. Also, S-1 is a promising agent in the neoadjuvant and adjuvant settings; nevertheless, it is necessary to accumulate evidence and data from large Phase III clinical trials before S-1 can be approved in the USA.

Future direction

Our evolving understanding of intrinsic factors in tumor biology and molecular pathways, as well as the interaction of the tumor microenvironment, might help us differentiate which tumors are more likely to respond to certain treatments and targeted approaches. S-1 can be considered in combination with targeted therapy for future clinical trials.

Disclosure

The authors report no conflicts of interest in this work.

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