Surgery Alone, Adjuvant Tegafur/gimeracil/octeracil (S-1), or Platinum-based Chemotherapies For Resectable Gastric Cancer: Real-world Experience and A Propensity Score Matching Analysis

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Abstract

Background: Adjuvant chemotherapy has changed the paradigm in resectable gastric cancer. S-1 is an oral chemotherapeutic with promising efficacy in Asia. However, comparisons with close observation or platinum-based doublets post D2 gastrectomy have been less reported.

Methods: We retrospectively evaluated patients with D2-dissected stage IB-III gastric cancer who received S-1 (S-1, n=64), platinum-based doublets (P, n=95) and operation with close observation (OBS, n=110) from Jan 2013 to Oct 2018. A propensity score matching was used to compare for recurrence-free (RFS) and overall survivals (OS). Adverse reactions, dosage, and associated factors for S-1 are also discussed.

Results: In a median follow-up of 42.5 months, Group S-1 had a comparable survival to that of P and OBS. (median RFS/OS: S-1 vs. P, 24.4/37.4 vs. 39.1/62.1 months, HR=1.12/1.22, $p=0.667/0.514$; S-1 vs. OBS, 23.6/37.4 vs. 24.0/64.6 months, HR=1.17/1.23, $p=0.554/0.499$). However, in patients with N2-3 or stage IIIB/IIIC disease, P significantly improved survival as compared with S-1. Conversely, S-1 was comparable to P and superior to OBS in stage IB-IIIA or N0-1 disease. S-1 was well-tolerated with a relative dose intensity of 73.6%, a median duration of 8.3 months and associated with less adverse reactions as compared with P. In the subgroup analysis, P was favored in stage III, N2-3 or T3-4 disease whereas patients with *Helicobacter Pylori* infection had a better survival when treated with S-1.

Conclusions: Adjuvant S-1 correlated with comparable survival rates but fewer adverse reactions as compared with platinum-based doublets. Patients with low to moderate risk of recurrence and *Helicobacter pylori* infection derived benefits from S-1 while platinum-based doublets were favored in advanced cases. The study provides additional information about adjuvant S-1 in patients with selected risk of recurrence.

Background

Among all primary gastrointestinal malignancies globally, gastric cancer is highly prevalent and ranks as the 3rd most deadly cancer.[1] The incidence of gastric cancer varies with distinctive geographic and ethnic distributions, where countries in Eastern/Central Asia, Latin America, and Eastern Europe are commonly affected.[2] Despite emerging improvements in early detection and curative treatment, nearly two thirds of high-risk patients still encounter a recurrence or progression of the disease.[3] Therefore, adjuvant or perioperative chemotherapies have been intensively investigated in recent years to reduce distant metastasis. [4–6] Interestingly, the Eastern and Western world share different perspectives of the same disease, in that the former tends to have patients diagnosed earlier, have more lymph nodes dissected, have biologically favorable tumors, and receive more adjuvant chemotherapies and fewer concurrent chemoradiotherapies (CCRT).[7] However, given aggressive salvage therapies, patients with recurrent or advanced gastric cancer still have a dismal outcome with survival barely exceeding more than one year.[8]

S-1, or TS-1, is an orally available chemotherapeutic composed of tegafur (a prodrug of fluorouracil, 5-FU), gimeracil (preventing dihydropyrimidine dehydrogenase-mediated degradation of 5-FU), and oteracil (reducing the toxic effects of 5-FU).[9] It is well-tolerated without serious adverse reactions, easily implemented in an outpatient setting, and currently approved for gastric, lung, breast, and biliary tract cancers in several

European and Asian countries but not in the United States.[10] S-1 is a key drug replacing the 5-FU backbone and has been incorporated with various chemotherapeutic partners in the treatment of advanced or metastatic gastric cancer in Japanese patients.[11–13] In addition, S-1-based adjuvant therapies, either as mono- or combinatorial regimens, have been confirmed to have efficacy in patients with gastric cancer who have received curative gastrectomy and adequate lymph node dissection (D2 or above) in phase III studies.[14, 15] Ongoing studies are investigating neoadjuvant or perioperative chemotherapies containing S-1 as promising options for patients with borderline resectable, locally advanced, or high-risk gastric cancer.[16]

Although S-1 has extended the therapeutic options in adjuvant therapy for gastric cancer, most of the published studies have incorporated patients from Northeast Asia. The extrapolation of the results to other Asian or non-Asian countries remains undetermined. Conversely, genetic and ethnic polymorphisms contribute to differences in drug metabolism, interactions, and dose-limiting toxicities. Pharmacokinetic studies revealed a significantly lower tolerable dose of S-1 in Caucasian patients.[17] In addition, real-world experiences outside of clinical trial settings have been less reported, in which the efficacy of S-1 is potentially confounded by compliance, availability, and undesirable adverse events. In the absence of a universal consensus related to the effective use of adjuvant chemotherapies for resectable gastric cancer, conventional regimens vary across countries. In general, platinum-based doublets, such as cisplatin or oxaliplatin plus a fluoropyrimidine, are widely recommended in the international guidelines.[18] Therefore, a comparison of the efficacy and tolerability of S-1 monotherapy with other adjuvant chemotherapies for patients with resectable gastric cancer warrants further studies, notably real-world experiences in daily clinical practice.

In the present study, we retrospectively evaluated patients with resectable gastric cancer who had received adjuvant S-1 monotherapy post D2 gastrectomy. Patients who received surgery alone or adjuvant platinum-based doublet chemotherapies were enrolled for the purpose of detailed comparisons. Characteristics and survival outcomes were assessed. Also, we reviewed the adverse events and associated factors for S-1 other than platinum-based regimens as selected by physicians. Owing to the differences in baseline disease severity and the nature of retrospective observations, propensity score matching was conducted to enhance between-group comparability. A landscape of recent S-1-based adjuvant or perioperative therapies for gastric cancer was reviewed as well.

Materials And Methods

Patients

We included 269 eligible Han Chinese patients with resectable gastric (cardia, fundus, body, antrum, and pylorus) or gastroesophageal junction (GEJ) (Siewert type III tumor) cancer from Jan 2013 to Oct 2018. All patients had an initial American Joint Committee on Cancer (AJCC) pathological staging of IB to III or a re-staging of IB to III disease post neoadjuvant therapies. Stage IB patients were excluded if they had T1 disease only or had no high-risk features for recurrence, such as poor differentiation of the tumor, lymphovascular or perineural invasions.[19] Patients were treated and evaluated at National Cheng Kung University Hospital and its affiliated branches in Taiwan, with an average volume of radical gastrectomy of 90 cases per year. Eligible patients were required to have received radical gastrectomy (laparotomic, laparoscopic or robotic) plus perigastric and celiac axial lymph node dissection (D2) in R0 resection without residual tumors. Adjuvant

chemotherapies were defined as oral or intravenous administration of any single or combinatorial chemotherapeutics within 12 weeks post-operatively for at least two cycles or for 6 consecutive weeks. Eligible chemotherapeutics included S-1 (TTY Biopharm, Taiwan), 5-FU, leucovorin, cisplatin, oxaliplatin, and capecitabine, which were selected based on the physician's clinical judgment. Other additional antineoplastic adjuvant therapies, such as immune checkpoint inhibitors or targeted therapeutics, did not preclude patients from enrollment. Patients were allocated according to the chosen adjuvant chemotherapies as S-1 (Group S-1) or platinum-based doublets (Group P). Those who received close observation with active surveillance without adjuvant therapies were deemed as surgery alone (observation, Group OBS). Patients were excluded if they had carcinoma *in situ*, initial metastatic or recurrent diseases, adenocarcinoma of unspecified primary sites, secondary cancer with gastric invasion, gastric or GEJ squamous cell carcinoma, small cell carcinoma, lymphoma, or neuroendocrine carcinoma.

Clinical evaluations

Clinical and pathological features, including demographic characteristics, biochemical markers, *Helicobacter pylori* (*H. pylori*) infection, human epidermal growth factor receptor-2 (HER2) status, and treatment outcomes were evaluated based on written or electronic medical records. Chemotherapy-related adverse events were retrospectively retrieved from documented materials and graded according to the Common Toxicity Criteria of the National Cancer Institute (CTCAE) version 4.0. Routine or on-demand esophagogastroduodenoscopy, imaging studies (computed tomography or magnetic resonance imaging), and biopsied or cytological examinations were arranged according to the local practice guidelines and incorporated as the detection of disease recurrence or progression. Recurrence-free survival (RFS) was defined by the date of diagnosis to first documented recurrence or progression of the disease, physician-initiated subsequent therapy, or the death of the patient due to any cause. Overall survival (OS) was defined by the date of diagnosis to the death of the patient due to any cause.

Statistical analysis

We presented the clinical and pathological features in descriptive analyses as percentages. Continuous variables were compared using a Student's t-test or a one-way analysis of variance (ANOVA) plus a post-hoc Tuckey honestly significant difference (Tuckey's HSD) test, whereas categorical variables were compared using a Chi-squared test or Fisher's exact test.

The variables that did not meet the parametric assumptions were evaluated using non-parametric methods. Propensity scores (PPS) were calculated using a multivariate logistic regression adjusted for the following covariates: age, sex, performance status, AJCC stage, lymph node (N) stage, histology classification, lymphovascular invasion (LVI), and serum CEA level. We conducted PPS matching using the nearest neighbor method at a ratio of 1:1 with a caliper of 0.25 to reduce selection bias. If the standardized mean differences are less than 10%, the covariates are considered balanced between the two groups. In addition, we calculated RFS and OS using a Kaplan-Meier survival estimation and compared it with the results of the log-rank test. Uni- and multivariate binary logistic regression analyses were conducted to elucidate independent associated

factors related to selecting S-1-based adjuvant chemotherapy. Statistical significance was prespecified by $p < 0.05$. We used GraphPad Prism 7.0® (GraphPad software, CA, US), SAS 9.4® (SAS Institute Inc., NC, US) and R® 3.5.1 for data management and graphics.

Results

Patient enrollment and baseline characteristics

The flow diagram of the study is shown in Fig. 1. A total of 465 patients were screened for enrollment from Jan 2013 to Oct 2018. We excluded 126 patients who were not eligible for the study. Another 70 patients were excluded due to the absence of high-risk features, inadequate lymph node dissection, and adjuvant CCRT. Finally, 269 eligible patients were included in the study. The patient and tumor characteristics are shown in Table 1. Among the included patients, 110 received curative gastrectomy without adjuvant therapies (Group OBS); 64 had S-1 (Group S-1), and 95 had platinum-based doublet (Group P) adjuvant chemotherapies. The distributions of sex, *H. pylori* infection, HER2 status, baseline performance status, GEJ tumors, and serum cancer antigen 19 – 9 (CA19-9) levels were similar among the three groups. The median ages were similar in patients who received adjuvant chemotherapies, but patients who received surgery alone were significantly older (S-1 vs. P vs. OBS, 65.2 vs. 60.3 vs. 73.3 years). More patients had early stages of the disease, notably stage IB/II, T1-2 or N0 disease, in the Group OBS as compared with Group S-1 or P (OBS: stage IB/II, 58.2%; T1-2 58.2%; N0, 53.6%; all $p < 0.001$ when compared with S-1 or P). Similarly, Group S-1 had more stage IB/II and N0 patients as compared with Group P (S-1 vs. P: stage IB/II, 48.4% vs. 23.2%, $p = 0.002$; N0, 21.9% vs. 4.2%, $p = 0.001$). Lymphovascular invasion (LVI) was more evident in Group S-1 and P as compared with OBS, and the former two had no significant between-group differences (OBS vs. S-1 vs. P: 39.1% vs. 65.6% vs. 77.9%; $p < 0.001$ when OBS was compared with S1 or P; $p = 0.088$ in S1 vs. P). Lauren histology classification of the tumors were generally balanced, with the exception of more diffuse type tumors in Group P as compared with OBS or S1 (OBS vs. S-1 vs. P: 30.9% vs. 43.8% vs. 51.6%; $p = 0.009$ in OBS vs. P). The median serum CEA was higher in Group P as compared with S-1 or OBS (OBS vs. S-1 vs. P: 2.1 vs. 1.8 vs. 2.8 ng/mL; $p = 0.007$ via a Kruskal-Wallis test). A total of 8 patients in the study had received neoadjuvant therapies prior to surgery, where 3 had triplet; 1 had doublet; 2 had immune checkpoint inhibitors and chemotherapies, and 1 had CCRT.

Table 1
Patient characteristics

Group	OBS		S-1		P				
	Operation alone (n = 110)		S-1 (n = 64)		Platinum-based doublets (n = 95)		<i>p</i>		
							OBS vs. S-1	OBS vs. P	S-1 vs. P
Age, median (IQR)	73.3	(63.2–81.2)	65.2	(52.0–70.7)	60.3	(52.5–68.0)	< 0.001*	< 0.001*	0.066
Male, n (%)	63	(57.3)	32	(50.0)	58	(61.1)	0.353	0.264	0.224
AJCC stage, n (%)							0.321	< 0.001*	0.002*
IB/II	64	(58.2)	31	(48.4)	22	(23.2)			
IIIA	14		13		14				
IIIB/IIIC	32		20		59				
pT stage, n (%)									
T1/2	64	(58.2)	13	(20.3)	18	(18.9)	< 0.001*	< 0.001*	0.992
T3	34		32		38				
T4	12		19		39				
pN stage, n (%)							< 0.001*	< 0.001*	0.001*
N0	59	(53.6)	14	(21.9)	4	(4.2)			
N1/2	42		36		40				
N3	9		14		51				
ECOG ≥ 2, n (%)	13	(11.8)	4	(6.3)	8	(8.4)	0.233	0.424	0.840
HER2-positive, n (%)	15	(13.6)	4	(6.3)	9	(9.5)	0.132	0.355	0.665
HER2-therapy ^a , n	0		2						
Tumor at GEJ, n (%)	7	(6.3)	3	(4.7)	9	(9.5)	0.647	0.408	0.415
Lauren histology, n (%)							0.195	0.009*	0.600
Intestinal	57	(51.8)	25	(39.1)	32	(33.7)			
Diffuse	34	(30.9)	28	(43.8)	49	(51.6)			
Mixed	16		10		14				

Group	OBS		S-1		P				
Others ^b	3		1		0				
Borrmann classification, n (%)							0.190	< 0.001	0.058
Infiltrative	54	(49.1)	38	(59.4)	70	(73.7)			
Non-infiltrative	56		26		25				
LVI (+), n (%)	43	(39.1)	42	(65.6)	74	(77.9)	< 0.001*	< 0.001*	0.088
H. pylori infection, n (%)	21	(19.1)	13	(20.3)	28	(29.5)	0.845	0.082	0.267
Median CEA, ng/mL (IQR)	2.1	(1.3–3.4)	1.8	(1.3–2.6)	2.8	(1.5–4.8)	0.143	0.027*	0.002*
Median CA19-9, U/mL (IQR)	12.6	(8.4–26.0)	13.7	(6.4–24.1)	12.7	(6.8–32.5)	0.669		
Neoadjuvant therapies ^c , n (%)	0		3	(4.7)	5	(5.3)	-	-	0.836
Adjuvant chemotherapy, n									
S-1	-		63		-				
S-1/nivolumab	-		1		-				
PFL	-		-		43				
XELOX/FOLFOX	-		-		46				
Others ^d	-		-		6		-	-	-
a. Defined as any frontline or subsequent HER2-directed therapies in patients with HER2-positive disease. Group OBS, XELOX/trastuzumab (n = 1); Group P, XELOX/trastuzumab (n = 1) and lapatinib (n = 1).									
b. Group OBS, lymphoepithelioma (n = 3); Group S-1, adenocarcinoma with neuroendocrine differentiation (n = 1).									
c. Group S-1, DCF (n = 1) and FLOT (n = 2); Group P, pembrolizumab/cisplatin (n = 1), pembrolizumab/cisplatin/capecitabine (n = 1), ECF (n = 1), XELOX (n = 1) and 5-FU/cisplatin-based CCRT (n = 1).									
d. Pembrolizumab/cisplatin/capecitabine (n = 4), pembrolizumab/cisplatin (n = 1) and ECF (n = 1)									
IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; GEJ, gastroesophageal junction; LVI, lymphovascular invasion; CCRT, concurrent chemoradiotherapy; PFL, cisplatin/fluorouracil/leucovorin; XELOX, capecitabine/oxaliplatin; FOLFOX, oxaliplatin/fluorouracil/leucovorin; DCF, docetaxel/cisplatin/fluorouracil; FLOT, docetaxel/oxaliplatin/fluorouracil/leucovorin; ECF, epirubicin/cisplatin/ fluorouracil.									

PPS matching and post-match characteristics

Two independent matched results are demonstrated in Table 2. A total of 61 and 58 patients were matched in the analysis 1 (S-1 vs. P) and 2 (S-1 vs. OBS), respectively. Both post-match analyses revealed well-balanced characteristics in terms of age, sex, performance status, stage (disease, T, or N stage), and histology classification, with the exception of marginal disproportions in stage IB/II disease in analysis 1 and serum CEA in analysis 2. In Group S-1, all patients had S-1 monotherapy as adjuvant chemotherapy. In Group P, 29/61 patients had cisplatin/5-FU/leucovorin (PFL); 30/61 patients had oxaliplatin-based doublets, and 2/61 patients had pembrolizumab/cisplatin/capecitabine as the selected adjuvant chemotherapies.

Table 2
Post matching characteristics

	Analysis 1 (1:1)					Analysis 2 (1:1)				
Group	S-1		P-based			S-1		OBS		
	S-1 (n = 61)		Platinum- based (n = 61)		<i>p</i>	S-1 (n = 58)		Surgery alone (n = 58)		<i>p</i>
Age, median (IQR)	65.0	(55.9–75.3)	61.8	(55.5–69.4)	0.544	65.5	(57.8–76.0)	70.1	(60.6–76.2)	0.143
Male, n (%)	31	(51.7)	33	(54.1)	0.784	29	(50.0)	31	(53.4)	0.999
Disease stage, n (%)	0.470					0.370				
IB/II	25	(40.1)	19	(31.1)		31	(53.4)	33	(56.9)	
IIIA	13		13			9		13		
IIIB/IIIC	23		29			18		12		
pT stage, n (%)	0.825					0.999				
T1/2	12	(19.7)	14	(23.0)		13	(22.4)	13	(22.4)	
T3/4	49		47			45		45		
pN stage, n (%)	0.499					0.980				
N0	11	(18.0)	7	(11.5)		14	(24.1)	16	(27.6)	
N1/2	36		36			32		31		
N3	14		18			12		11		
ECOG ≥ 2, n (%)	4	(6.6)	5	(8.2)	0.729	4	(6.9)	8	(13.8)	0.222
HER2-positive, n (%)	4	(6.6)	5	(8.2)	0.729	3	(5.2)	6	(10.3)	0.298
Tumor at GEJ, n (%)	2	(3.3)	3	(4.9)	0.995	3	(5.2)	3	(5.2)	0.999
Lauren histology type, n (%)	0.509					0.287				
Intestinal	24	(39.3)	23	(37.7)		23	(39.7)	28	(48.3)	
Diffuse	26	(42.6)	31	(50.8)		25	(43.1)	19	(32.8)	
Mixed	10		7			9		10		
a. Adenocarcinoma with neuroendocrine differentiation (n = 1)										
b. Pembrolizumab/cisplatin/capecitabine (n = 2)										

Analysis 1 (1:1)					Analysis 2 (1:1)				
Others ^a	1		0			1		0	
Borrmann classification, n (%)					0.253				0.699
Infiltrative	37	(60.7)	43	(70.5)		38	(65.5)	36	(62.1)
Non-infiltrative	24		18			20		22	
LVI (+), n (%)	42	(68.9)	49	(80.3)	0.145	31	(53.4)	36	(62.1)
Median CEA ng/mL, (IQR)	1.9	(1.2–2.7)	1.9	(1.2–3.1)	0.535	1.9	(1.3–2.6)	2.1	(1.5–4.4)
H. pylori infection, n (%)	12	(19.7)	16	(26.2)	0.389	13	(22.4)	10	(17.2)
Adjuvant chemotherapy, n (%)									
S-1	61		-			58		-	
PFL	-		29			-		-	
XELOX/FOLFOX	-		30			-		-	
Others ^b	-		2			-		-	
a. Adenocarcinoma with neuroendocrine differentiation (n = 1)									
b. Pembrolizumab/cisplatin/capecitabine (n = 2)									

Survival: S-1 vs. platinum-based doublets

All patients were evaluated in a median follow-up time of 42.5 months. In analysis 1, patients who received adjuvant S-1 had a trend of shorter RFS and OS as compared with platinum-based doublets but it did not reach statistical significance (median RFS/OS: S-1 vs. P, 24.4/37.4 vs. 39.1/62.1 months, HR = 1.12/1.22, $p = 0.667/0.514$; Fig. 2A and 2B). Stratified by the N stage, the patients in Group P had significantly better RFS and OS in N2-3 disease as compared with Group S-1 (median RFS/OS: S-1 vs. P, 19.3/27.8 vs. 28.5/56.0 months, HR = 2.04/2.29, $p = 0.010/0.007$; Fig. 2C and 2D). However, the survival differences were not evident in terms of N0-1 disease (5-year RFS/OS rates: S-1 vs. P, 66.5%/67.1% vs. 60.0%/71.0%, HR = 0.65/0.57, $p = 0.458/0.479$; Fig. 2E and 2F). Stratified by staging, patients with stage IB to IIIA disease had comparable RFS and OS (5-year RFS/OS rates: S-1 vs. P, 62.3%/66.3% vs. 52.8%/71.3%, HR = 0.73/0.60, $p = 0.431/0.371$; Supplementary 1A and 1B). However, platinum-based doublets were associated with significantly prolonged survival rates in patients with stage IIIB/IIIC disease (median RFS/OS: S-1 vs. P, 12.8/27.0 vs. 28.5/55.6 months, HR = 2.87/2.89, $p = 0.001/0.002$; Supplementary 1C and 1D). We did not observe significant survival differences based on the S-1, oxaliplatin, or cisplatin-based chemotherapy in the matched population (median

RFS: S-1 vs. oxaliplatin vs. cisplatin, 24.4 vs. 24.7 vs. 54.3 months; all $p \geq 0.05$ between groups; Supplementary 1E) (median OS: S-1 vs. oxaliplatin vs. cisplatin, 37.4 vs. 55.67 vs. 64.2 months; all $p \geq 0.05$ between groups; Supplementary 1F).

Survival: S-1 vs. OBS

In analysis 2, Group S-1 had a comparable survival outcome to that of OBS (median RFS/OS: S-1 vs. OBS, 23.6/37.4 vs. 24.0/64.6 months, HR = 1.17/1.23, $p = 0.554/0.499$; Fig. 3A and 3B). Conversely, patients with N0-1 disease in Group S-1 had a significantly better RFS and OS (median RFS/OS: S-1 vs. OBS, undefined/37.4 vs. undefined/61.0 months, HR = 0.41/0.27, $p = 0.038/0.024$; Fig. 3C and 3D), but the survival advantage disappeared in N2-3 disease as compared with OBS (median RFS/OS: S-1 vs. OBS, 16.1/27.8 vs. 16.2/28.9 months, HR = 1.10/1.03, $p = 0.778/0.948$; Fig. 3E and 3F). Stratified by staging, stage IB to IIIA patients in Group S-1 had a longer RFS and OS (5-yr RFS/OS rates: S-1 vs. OBS, 71.0%/65.4% vs. 50.1%/56.9%, HR = 0.41/1.03, $p = 0.041/0.032$; Supplementary 2A and 2B). However, dismal survival outcomes were observed in the stage IIIB and IIIC patients, irrespective of whether they received adjuvant S-1 or not (median RFS/OS: S-1 vs. OBS, 12.8/21.0 vs. 11.8/25.9 months, HR = 0.95/1.09, $p = 0.871/0.841$; Supplementary 2C and 2D).

Adverse events and dosage intensity

We present the adverse events and the grading in Table 3 for the total number of evaluable patients (S-1 monotherapy, $n = 61$; platinum-based doublets, $n = 84$). There were no deaths attributable to the adjuvant chemotherapies. Anemia was the most common adverse event in all patients and was significantly higher in the platinum-based doublets as compared with S-1 (grade III/IV anemia: S-1 vs. combination therapy, 4.9% vs. 9.5%, $p = 0.028$). Grade III/IV thrombocytopenia, renal insufficiency, and neutropenia were prevalent in the platinum-based doublets (thrombocytopenia, 17.9%; renal insufficiency, 4.8%; neutropenia, 3.6%). Scattered cases of severe diarrhea, anorexia, mucositis, and palmar plantar erythrodysesthesia were also observed in patients who received platinum-based doublets. In the S-1 group, except for a few cases with grade III/IV hepatitis ($n = 2$), thrombocytopenia ($n = 1$), and neutropenia ($n = 1$), there were no additional warning toxicities reported. One patient developed S-1-related grade III drug eruptions that were relieved after discontinuation and supportive care. The average dose intensity of S-1 was 40.9 ± 13.6 mg in patients with a body surface area (BSA) $< 1.25 \text{ m}^2$, 47.4 ± 13.4 mg with a BSA from 1.25 to 1.50 m^2 , and 58.5 ± 12.4 mg with a BSA $> 1.50 \text{ m}^2$ per day, which were lower than the suggested dose from the published studies, with an average relative intensity of 73.6% (Supplement 3). 10.9% of the patients required a dose reduction due to intolerable toxicity. The median duration of S-1 was 8.3 months, respectively.

Table 3
Adverse events, according to the treatment

Events	S-1 (n = 61)				Platinum-based doublets (n = 84) ^a				p ^b
	Total, n	Grade I/II, n	Grade III/IV, n	Grade III/IV, (%)	Total, n	Grade I/II, n	Grade III/IV, n	Grade III/IV, (%)	
Any events	90	82	8	-	212	173	39	-	-
Anemia	22	19	3	4.9	47	39	8	9.5	0.028*
Thrombocytopenia	7	6	1	1.6	36	21	15	17.9	< 0.001*
Neutropenia	3	2	1	1.6	12	9	3	3.6	0.121
Renal insufficiency	5	5	0	0	17	13	4	4.8	0.046*
Hepatitis	13	11	2	3.3	15	13	2	2.3	0.759
Anorexia	22	22	0	0	37	33	4	4.8	0.427
Diarrhea	9	9	0	0	8	7	1	1.2	0.481
Vomiting	6	6	0	0	29	29	0	0	0.001*
Mucositis	1	1	0	0	4	3	1	1.2	0.398
PPE	0	0	0	0	6	5	1	1.2	-
Skin eruptions	2	1	1	1.6	1	0	1	1.2	0.573
a. XELOX (n = 41), PFL (n = 38) and FOLFOX (n = 5).									
b. Comparisons with incidence of all events.									
PPE, palmar plantar erythrodysesthesia									

Subgroup analysis

The subgroup analyses for RFS and OS are shown in Fig. 4 using forest plotting. In the total population, we did not observe significant differences among those treated with adjuvant S-1 or platinum-based doublets. In the subgroups, patients with stage III, T3-4, or N2-3 disease had a longer RFS on platinum-based doublets. Female gender, stage III or N2-3 disease were associated with favorable OS when treated with platinum-based doublets. To the contrary, *H. pylori* infection correlated with a survival benefit in patients who received S-1.

Factors associated with adjuvant S-1

We evaluated the factors associated with selecting adjuvant S-1 versus platinum-based doublets using a binary logistic regression, and the results are shown in Table 4. We observed that low serum CEA, N0-2 disease, increased patient age, low serum CA19-9, and early stages were associated factors in the univariate regression. Following multivariate adjustments, low serum CEA, N0-2 disease, and increased patient age were significant factors for adjuvant S-1 rather than platinum-based doublets.

Table 4
Associated factors for the selection of adjuvant S-1

	Univariate regression				Multivariate regression		
	n	OR	95% CI	p	OR	95% CI	p
CEA	40	1.00	2.11–13.79	< 0.001*	3.93	1.44–10.7	0.008*
≥5 ng/mL	119	5.39					
<5 ng/mL							
N stage	65	1.00	1.60–7.09	0.001*	2.16	1.02–5.01	0.044*
N3	75	3.36	3.13–33.20	< 0.001*	5.48	1.21–24.90	0.028*
N1-2	19	10.2					
N0							
Age, increased by 1 year	159	1.03	0.99–1.05	0.058	1.04	1.01–1.07	0.041*
CA199	23	1.00	1.21–11.61	0.022*	2.82	0.77–10.42	0.118
≥47 IU/mL	136	3.75					
<47 IU/mL							
AJCC stage	107	1.00	1.66–6.60	0.001*	1.74	0.69–4.41	0.241
III	52	3.31					
I/II							
Gender	90	1.00	0.83–2.97	0.169			
Male	69	1.57					
Female							
<i>H. pylori</i> infection	41	1.00	0.77–3.48	0.197			
Presence	118	1.64					
Absence							
LVI	118	1.00	0.78–3.28	0.198			
Presence	41	1.60					
Absence							

OR, odds ratio

	Univariate regression				Multivariate regression		
	n	OR	95% CI	p	OR	95% CI	p
Lauren classification	55	1.00	0.36–1.47	0.381			
Intestinal	77	0.73	0.39–2.59	0.991			
Diffuse	27	1.01					
Mixed							
T stage	31	1.17	0.50–2.74	0.725			
T1-2	70	0.68	0.27–1.66	0.391			
T3	58						
T4							
Tumor differentiation	44	1.00	0.37–1.50	0.409			
Well/Moderate	115	0.74					
Poor							
ECOG	147	1.00	0.40–4.79	0.613			
<2	12	1.38					
≥2							
HER2 status	13	1.00	0.43–2.85	0.829			
Positive	146	1.11					
Negative							
Borrmann classification	41	1.00	0.52–2.22	0.852			
Non-infiltrative	118	1.07					
Infiltrative							
OR, odds ratio							

Discussion

Adjuvant S-1 has extended the therapeutic options in stage II and III gastric cancer patients who have received D2 gastrectomy, notably in Asia.[18] The present study provides additional information on S-1 versus conventional platinum-based chemotherapies based on real-world practice. Our results indicated that patients with early stages of the disease had comparable outcomes on adjuvant S-1 as compared with platinum-based doublets. Conversely, S-1 monotherapy was associated with fewer adverse reactions and better tolerability. In an era prompting aggressive adjuvant therapies for high-risk diseases, curative gastrectomy alone is no longer being considered as a standard of care. Sakuramoto *et al.* proposed that adjuvant S-1 is

superior to D2 gastrectomy alone in stage II and III gastric cancer in terms of both recurrence-free and overall survival.[14, 20] In the CLASSIC study, adjuvant capecitabine/oxaliplatin (XELOX) significantly improved survival outcomes as compared with surgery only at the cost of more adverse events.[21] In patients with a particularly high risk of recurrence, the role of more aggressive therapies has been intensively investigated. The ARTIST-2 trial evaluated the role of adjuvant S-1/oxaliplatin (SOX), SOX plus CCRT (SOXRT), and S-1 monotherapy in lymph node-positive patients, where it was concluded that S-1-based doublets, irrespective of whether the patient underwent radiotherapy or not, were superior to S-1 in terms of disease-free survival and met the prespecified endpoint early.[22] Yoshida *et al.* also reported the therapeutic efficacy of docetaxel/S-1 in stage III, $\geq T2$ or lymph node-positive patients versus S-1, with a significantly higher incidence of grade III to IV treatment-related toxicities.[15] Other combinations, such as oxaliplatin or cisplatin plus S-1, have been considered to be feasible options but were found to be relatively more toxic than S-1 monotherapy.[11, 23–25] Our results suggest that adjuvant S-1 is well-tolerated and comparable in efficacy to other combinatorial regimens in patients with moderate to low risk of recurrence. Although the results of intensive protocols are promising, selecting an optimal adjuvant chemotherapy remains a difficult task that requires a balance between the therapeutic benefits and toxicity.

Despite the fact that we did not discover a significant difference between adjuvant S-1 versus platinum-based doublets in the total population, subgroups of patients still shared distinctive outcomes. Patients with *H. pylori* infection had more favorable survival when treated with S-1. *H. pylori* played an unclear role as a prognostic factor in patients with gastric cancer.[26, 27] However, Nishizuka *et al.* reported that *H. pylori*-infected patients had superior survival rates when treated with adjuvant S-1, which was compatible with our results.[28] Host antitumor immunity may be enhanced by *H. pylori* infection and fluoropyrimidine-mediated eradication of myeloid-derived suppressor cells, which may contribute to a survival advantage.[29] Furthermore, we noticed that the survival outcomes in stage IB-IIIa or N0-1 disease were better with S-1, whereas platinum-based doublets led to additional benefits in the more advanced diseases. In the ACTS-GC study, the therapeutic efficacy of S-1 was less evident in patients with stage III, T3-4 disease, or more than 3 involved lymph nodes.[20] A retrospective analysis indicated that patients with stage IIIC, N3 disease, or a lymph node ratio (LNR) > 0.25 did better with adjuvant XELOX rather than with S-1.[30] Hsieh *et al.* also suggested that stage III or LNR > 0.21 are significant prognostic factors in patients receiving S-1 versus non-S-1 doublet chemotherapies.[31] Similarly, in the JACCRO-GC-07 trial, despite the fact that docetaxel/S-1 was superior to S-1 monotherapy in the primary analysis, the benefit disappeared in patients with N0-1 disease.[15] Our results, in line with the published reports, indicated a definitive role of adjuvant S-1 in patients with selected risk of recurrence post curative surgery.

Good tolerance and limited warning toxicities with adjuvant S-1 was observed in the present study. We found only a few cases of grade III to IV events, such as anemia, hepatitis, and skin eruptions in contrast to a higher risk of anemia, thrombocytopenia, neutropenia, and renal insufficiency with the use of platinum-based doublets. In addition, a low demand of dose reduction (10.9%) was noticed, despite the fact that the patients were potentially under-dosed (73.6% as compared with reference trials) in a real-world practice environment. Kim *et al.* reported a dose of S-1 at 40 mg/m² twice daily in D1-28 every 6 weeks for one year and concluded that 46.3% of the patients required a dose modification, and 16.1% discontinued treatment due to persistent toxicity.[32] Yamatsuji *et al.* compared a 4-week administration period followed by two weeks of rest (4-w/2-

w) with a two week administration period followed by one week of rest (2-w/1-w) and revealed that the latter had a higher completion rate, higher relative dose intensity, and similar toxicities.[33] In addition, the optimal dosage of S-1 is potentially confounded by ethnicity. Yang *et al.* revealed that S-1 at a dose of 35 mg/m² twice daily was better tolerated in Asian patients in combination with oxaliplatin.[34] However, another pharmacokinetic study revealed a poor tolerance in a Western population, and the dose was reduced to 25 mg/m² twice daily.[17] The discrepancy is partially derived from the pharmacogenetic polymorphisms of cytochrome P 2A6 (CYP2A6), which contribute to a distinctive S-1 elimination efficiency.[35] Further studies are required to determine the patient-tailored optimal dosage of S-1, both in mono- or combinatorial therapies.

We found that physicians preferred S-1 as adjuvant chemotherapy in patients with low CEA, N0-2 disease, and increased age. Lee *et al.* suggested that S-1 is more likely to be selected as adjuvant chemotherapy for patients over 65 years of age, whereas XELOX was selected for patients with stage III disease, corresponding to our results.[36] Terashima *et al.* evaluated the tumor gene expression profiles of 102 patients who received adjuvant chemotherapies via a DNA microarray and found that the cluster of differentially expressed genes that favored S-1 was enriched with immune-related genes.[37] Together, these results highlight physician preferences and potential selection biomarkers for those who may derive benefits from S-1 containing adjuvant therapies. Recently, perioperative chemotherapies have gained awareness for the efficacy on locally-advanced or high-risk patients with resectable or borderline resectable gastric cancer. Various combinations of fluoropyrimidines, platinum, anthracyclines, or taxanes have been adopted to improve the resectability, surgical outcome, and long-term survival, as well as to reduce recurrence.[4–6, 21, 38, 39] The addition of S-1 to these agents is being intensively investigated.[40–42] Furthermore, the results are promising in the combination of S-1, nivolumab, oxaliplatin, and capecitabine in advanced or recurrent gastric cancer.[43] More clinical studies are required to delineate the role of S-1, both in the frontline or adjuvant setting and in the treatment of gastric cancer.

The strength of the present study is the real-world information of S-1 outside of clinical trial settings, which is more closely related to actual clinical scenarios. In addition, we incorporated PPS matching to exclude baseline heterogeneity and enhance between-group comparability. Third, we provided the dosages and adverse reactions for S-1 in comparison with other combinatorial regimens. However, there are some limitations to this study. It is a retrospective analysis that cannot address prospective consequential imputations. Also, we included patients who received S-1 monotherapy in the absence of S-1-based combinations, which have gradually become the standard of care in high-risk populations. In addition, despite the efforts we made to control for differences of patients via PPS matching, we still were unable to eradicate possible exclusion bias and undetermined imbalances. Lastly, the patients were collected from a single institution, and the case number was not significantly large enough to have an excellent statistical power. Overall, the study still provided information concerning adjuvant S-1 in the treatment of resectable gastric cancer and a comparison with close observation and platinum-based doublets.

Conclusion

In the present study, patients with D2-resected stage IB-III gastric cancer who received adjuvant S-1 had comparable survival rates and fewer adverse reactions as compared with those receiving platinum-based

doublets. Patients with low to moderate risk of recurrence and *H. pylori* infection derived more benefits from S-1, while platinum-based doublets were found to be superior in advanced diseases. S-1 was relatively under-dosed and was found to be selected by physicians based on serum CEA, lymph node status, and patient age. More prospective studies are required to delineate the optimal selection of patients who may benefit from S-1 or S-1-based combinations in gastric cancer.

List Of Abbreviations

S-1, tegafur/gimeracil/octeracil; OBS, observation; RFS, recurrence-free; OS, overall survivals; CCRT, concurrent chemoradiotherapies; GEJ, gastroesophageal junction; AJCC, American Joint Committee on Cancer; *H. pylori*, *Helicobacter pylori*; CTCAE, Common Toxicity Criteria of the National Cancer Institute; ANOVA, analysis of variance; PPS, propensity scores; CA19-9, cancer antigen 19-9; LVI, lymphovascular invasion; PFL, cisplatin/5-FU/leucovorin; LNR, lymph node ratio; CYP, cytochrome P.

Declarations

Ethics approval and consent to participate

This is a retrospective observational study including patients with standard medical care. All analyzed information had received a valid de-identification process. Therefore, the informed consent is waived as approved by the Institutional Review Board (IRB) at National Cheng Kung University Hospital, Tainan, Taiwan. The study is approved by the registry serial number B-ER-109-184 in accordance with the Declaration of Helsinki and its amendments.

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are available from Cancer Registry of the Electronic Medical Records in National Cheng Kung University Hospital but restrictions apply to the availability of these data, which were used under specific permission for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Clinical Research Center, National Cheng Kung University Hospital, Tainan, Taiwan. em74820@mail.hosp.ncku.edu.tw. No. 138, Sheng-Li Road, Tainan 70403, Taiwan. Tel: +886-6-235-3535 ext. 4817.

Competing interests

The authors have no conflicts of interest to declare.

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Authors' contributions

Chih-Chieh Yen is the first author of the study and was responsible for writing the manuscript and data management. Yan-Shen Shan is the second author, who provided critical advice and suggestions for revisions. Ting-Kai Liao, Yin-Jui Chao, Hsuan-Yi Huang and I-Ting Liu are the third group of authors, who contributed to the writing of the manuscript. Chia-Jui Yen is the corresponding author who initiated the study design and investigations.

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Figures

Figure 1

Flow diagram of the study a. Concomitant malignancies other than gastric cancer (n=6), metastatic carcinoma not confined to gastric origin (n=3), and esophageal carcinoma with gastric invasion (n=2). CCRT, concurrent chemoradiotherapy; LN, lymph node; PPS, propensity score.

Figure 2

Survival: S-1 vs. platinum-based doublets RFS and OS by adjuvant chemotherapy (A-B), lymph node stage of N2-3 (C-D), and N0-1 (E-F). LN, lymph node stage; HR, hazard ratio; CI, confidence interval. Log-rank test, $p < 0.05$ as statistically significant and shown as *.

Figure 3

Survival: S-1 vs. close observation RFS and OS by adjuvant S-1 or OBS (A-B), lymph node stage of N0-1 (C-D), and N2-3 (E-F). Log-rank test, $p < 0.05$ as statistically significant and shown as *.

Figure 4

Subgroup analysis p for interaction< 0.05 as statistically significant and shown as *

Supplementary Files

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