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ORIGINAL ARTICLE

S-1 Versus S-1 Plus Cisplatin as First-line Treatment for Metastatic Gastric Cancer

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ABSTRACT

Objective: *To compare S-1 with S-1 plus cisplatin (SP) as first-line treatment for metastatic gastric cancer.*

Methods: *Records of patients with metastatic gastric cancer who received either the S-1 or SP regimen as first-line treatment for metastatic gastric cancer between January 2013 and December 2014 in Queen Mary Hospital were retrospectively reviewed. Baseline characteristics, overall response rate, median progression-free survival (PFS), overall survival (OS), and toxicity of the two groups were compared.*

Results: *During the study period, 17 patients received S-1 and 13 patients received SP. The median patient ages were 69 and 57 years, respectively. In the S-1 group, more patients were aged ≥70 years (47.1% vs. 7.7%, p = 0.02), fewer patients underwent surgical resection of primary tumours (23.5% vs. 53.8%, p = 0.09), more patients required initial dose reduction (70.6% vs. 15.4%, p = 0.001), and fewer patients received subsequent chemotherapy (5.9% vs. 30.8%, p = 0.07) compared with the SP group. The S-1 group had a lower response rate (11.8% vs. 46.2%, p = 0.049). Nonetheless, S-1 and SP groups were comparable for clinical benefit rate (47.1% vs. 77.0%, p = 0.14), median PFS (34.5 weeks vs. 28.8 weeks, p = 0.72), median OS (46.4 weeks vs. 52.7 weeks, p = 0.18), and 30-day mortality (11.8% vs. 7.7%, p = 1.00). There was a trend of improved OS in the SP group (hazard ratio = 1.84, 95% confidence interval = 0.74-4.55, p = 0.185). The two groups were also comparable for the rate of grade 3/4 neutropaenia (17.7% vs. 38.5%, p = 0.24) and grade 3/4 diarrhoea (5.9% vs. 30.8%, p = 0.14). There was no treatment-related death.*

Conclusion: *Both S-1 and SP regimens are effective and safe as first-line treatment for metastatic gastric cancer. A dose-adjusted S-1 regimen is a viable option for patients with advanced age and marginal performance status.*

Key Words: *Cisplatin; Neoplasm metastasis; S 1 (combination); Stomach neoplasms*

中文摘要

比較S-1與S-1加順鉑作為轉移性胃癌的一線治療

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目的：比較S-1與S-1加順鉑（SP）作為轉移性胃癌的一線治療。

方法：回顧分析2013年1月至2014年12月間在瑪麗醫院接受S-1或SP方案作為轉移性胃癌的一線治療的患者紀錄。比較兩組的基線特徵、總體反應率、中位無進展生存期（PFS）、總生存期（OS）和毒性。

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結果：17例患者接受S-1，13例患者接受SP。患者年齡中位數分別為69歲和57歲。在S-1組中，與SP組比較較多患者年齡≥70歲（47.1%對7.7%，p = 0.02），較少患者接受原發腫瘤切除（23.5%對53.8%，p = 0.09），較多患者需要減少初始劑量（70.6%對15.4%，p = 0.001），和較少患者接受後續化療（5.9%對30.8%，p = 0.07）。S-1組的反應率較低（11.8%對46.2%，p = 0.049）。儘管如此，S-1和SP兩組有相當的臨床獲益率（47.1%對77.0%，p = 0.14），中位PFS（34.5週對28.8週，p = 0.72），中位OS（46.4週對52.7週，p = 0.18），30天死亡率（11.8%對7.7%，p = 1.00）。SP組有改善OS的趨勢（風險比 = 1.84，95%置信區間 = 0.74-4.55，p = 0.185）。兩組有相當的3 / 4級中性粒細胞減少率（17.7%對38.5%，p = 0.24）和3 / 4級腹瀉率（5.9%對30.8%，p = 0.14）。沒有患者出現治療相關的死亡。

結論：S-1和SP方案作為轉移性胃癌的一線治療是有效和安全的。經過劑量調整的S-1方案對於高齡和邊緣狀態的患者是可行的選擇。

INTRODUCTION

Gastric cancer is the fifth most common cancer and the third most common cause of cancer death in the world.[1] Its new cases in East Asia account for half of the global disease burden.[1] The age-standardised incidence of gastric cancer is highest in East Asia at 35.4 and 13.8 per 100,000 men and women, respectively.[1] In patients with metastatic gastric cancer, systemic chemotherapy has shown to improve survival, symptom control, and quality of life.[2-5] Combination chemotherapy is superior to fluoropyrimidine monotherapy in terms of overall survival (OS).[2] Nonetheless, the advantage of triplet over doublet chemotherapy remains controversial. Cisplatin plus 5-fluorouracil (5-FU) is the most commonly used regimen.[6-8] In the United Kingdom, the triplet regimen of epirubicin, cisplatin plus 5-FU (ECF) is superior to the doublet regimen of cisplatin plus 5-FU (PF), but this is not confirmed by other studies.[9-11] In the V325 study, PF plus docetaxel improved progression-free survival (PFS) and OS, but its toxicity profile was a major concern and thus the regimen has not been accepted as standard treatment worldwide.[12-14] A doublet regimen of platinum plus fluoropyrimidine remains the standard of care for metastatic gastric cancer. In the ML17032 study, cisplatin plus capecitabine was not inferior to PF in PFS.[3] In the REAL-2 study, epirubicin, oxaliplatin plus capecitabine (EOX) was comparable with ECF in terms of response rate and survival.[4,15]

S-1 is an oral fluoropyrimidine that combines tegafur with two modulators: 5-chloro-2, 4-dihydroxypyridine (to maintain the plasma concentration of 5-FU) and potassium oxonate (to reduce the metabolite that causes gastrointestinal toxicity).[5] In phase II studies of S-1 alone, the response rate was 45% and the 2-year survival was 17%.[16,17] In the phase III SPIRITS trial, S-1 plus cisplatin (SP) was superior to S-1 alone in improving PFS and OS but had a higher incidence of grade 3/4 toxicity.[5] In the phase III FLAGS trial, SP was comparable to PF in terms of PFS and OS but had an improved toxicity profile.[18] In North Americans, OS was higher in those who received SP compared with PF. However, in Europeans and Latin Americans, OS was comparable or lower in those who received SP compared with PF.[18] In Hong Kong, S-1–containing regimens have been increasingly used. This study aimed to compare S-1 with SP as first-line treatment for metastatic gastric cancer.

METHODS

The study was approved by the Institutional Review Board of the University of Hong Kong / Hospital Authority Hong Kong West Cluster (reference number: UW 16-523) and conducted in compliance with the Declaration of Helsinki.

Patients with metastatic gastric cancer who received either the S-1 or SP regimen as first-line treatment for metastatic gastric cancer between January 2013 and December 2014 in Queen Mary Hospital were retrospectively reviewed.

For the S-1 regimen, 40-60 mg of S-1 was given orally twice daily for 4 consecutive weeks, followed by a 2-week rest period, in a 6-weekly cycle. For the SP regimen, 40-60 mg of S-1 was given orally twice daily for 3 consecutive weeks, and 60 mg/m^2 of cisplatin was given intravenously on day 8, followed by a 2-week rest period, in a 5-weekly cycle. The initial dose was reduced by one dose when patients were aged >70 years or had a creatinine clearance of 30-50 ml/min. S-1 was omitted if the creatinine clearance was <30 ml/min.

The overall response rate was evaluated according to the Response Evaluation Criteria in Solid Tumors version 1.1. The median PFS and OS were estimated using the Kaplan-Meier method. Toxicity was reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Variables of the two groups were compared using the Fisher's exact test or Chi-square test. The median PFS and OS of the two groups were compared by the log-rank test and hazard ratio by the Cox proportional hazard method.

RESULTS

During the study period, 17 patients received S-1 and 13 patients received SP. The median patient age was 69 and 57 years, respectively. The most common site of the primary tumour was the gastric fundus (n=11), followed by the gastric body (n=10), pylorus (n=7), and linitis plastica (n=2). The most common site of metastasis was the lymph node (n=16), followed by peritoneum (n=15), liver (n=7), and bone (n=5) [Table 1].

The two groups were comparable in terms of performance status (measured by Eastern Cooperative Oncology Group score), histology, primary site, metastatic site, cycles received, and follow-up duration. In the S-1 group, more patients were aged ≥70 years (47.1% vs. 7.7%, p = 0.02), fewer patients underwent surgical resection of primary tumours (23.5% vs. 53.8%, p = 0.09), more patients required initial dose reduction (70.6% vs. 15.4%, p = 0.001), and fewer patients received subsequent chemotherapy (5.9% vs. 30.8%, p = 0.07).

The S-1 group had a lower response rate (11.8% vs. 46.2%, p = 0.049). Nonetheless, S-1 and SP groups were comparable for clinical benefit rate (47.1% vs. 77.0%, p = 0.14), median PFS (34.5 weeks vs. 28.8 weeks, p = 0.72), median OS (46.4 weeks vs. 52.7 weeks, p = 0.18) [Figure], and 30-day mortality (11.8% vs. 7.7%, p = 1.00). There was a trend of improved OS in the SP group (hazard ratio = 1.84, 95% confidence interval = 0.74-4.55, p = 0.185). The two groups were comparable for rate of grade 3/4 neutropaenia (17.7% vs. 38.5%, p = 0.24) and grade 3/4 diarrhoea (5.9% vs. 30.8%, p = 0.14). There was no treatment-related death.

DISCUSSION

The PFS and OS of the S-1 and SP regimens were comparable and the response rate was consistent with that reported in other phase II / III trials.[5,16] There was

Table 1. Patient characteristics and outcome.*

Characteristic / outcome	S-1 alone (n = 17)	S-1 plus cisplatin (n = 13)	p Value
Sex			0.79
Female	6 (35.3)	4 (30.8)	
Male	11 (64.7)	9 (69.2)	
Age (years)			0.02
<70	9 (52.9)	12 (92.3)	
≥70	8 (47.1)	1 (7.7)	
Eastern Cooperative Oncology Group score			0.50
0	1 (5.9)	2 (15.4)	
1	12 (70.6)	10 (76.9)	
2	2 (11.8)	1 (7.7)	
3	2 (11.8)	0	
Histology			0.177
Diffuse type	9 (52.9)	10 (76.9)	
Intestinal type	8 (47.1)	3 (23.1)	
Primary site			0.35
Fundus	6 (35.3)	5 (38.5)	
Body	6 (35.3)	4 (30.8)	
Pylorus	5 (29.4)	2 (15.4)	
Linitis plastica	0	2 (15.4)	
Resection of primary tumour	4 (23.5)	7 (53.8)	0.09
Metastatic site			
Lymph node	11 (64.7)	5 (38.5)	0.27
Peritoneum	8 (47.1)	7 (53.8)	1.00
Liver	4 (23.5)	3 (23.1)	1.00
Bone	1 (5.9)	4 (30.8)	0.14
Lung	3 (17.6)	0	0.24
Ovary	1 (5.9)	0	1.00
Cycle delay	9 (52.9)	7 (53.8)	0.96
Dose reduction due to advanced age or baseline renal impairment	12 (70.6)	2 (15.4)	0.001
Dose reduction due to treatment toxicity	2 (11.8)	1 (7.7)	0.60
No. of cycles received	3	4	0.22
Follow-up duration (weeks)	46 (3-109)	52 (8-126)	0.41
Subsequent chemotherapy	1 (5.9)	4 (30.8)	0.07
Response rate (%)			
Complete	11.8	30.8	0.36
Partial	0	15.4	0.18
Overall	11.8	46.2	0.049
Clinical benefit rate (%)	47.1	77.0	0.14
Progression-free survival (weeks)	34.5	28.8	0.72
Overall survival (weeks)	46.4	52.7	0.18
Haematological toxicity			
Neutropaenia	7 (41.2)	10 (76.9)	0.28
Grade 3	2 (11.8)	3 (23.1)	
Grade 4	1 (5.9)	2 (15.4)	
Anaemia	16 (94.1)	9 (69.2)	0.94
Grade 3	4 (23.5)	1 (7.7)	
Grade 4	1 (5.9)	1 (7.7)	
Thrombocytopaenia	9 (52.9)	10 (76.9)	0.38
Grade 3	0	0	
Grade 4	1 (5.9)	0	
Non-haematological toxicity			
Renal toxicity	4 (23.5)	3 (23.1)	0.46
Grade 3	0	0	
Grade 4	0	0	
Vomiting	3 (17.6)	3 (23.1)	0.51
Grade 3	1 (5.9)	0	
Grade 4	0	0	
Diarrhoea	5 (29.4)	8 (61.5)	0.24
Grade 3	1 (5.9)	4 (30.8)	
Grade 4	0	0	
Hand-foot skin reaction	6 (35.3)	4 (30.8)	0.43
Grade 3	0	0	
Grade 4	0	0	
30-day mortality	2 (11.8)	1 (7.7)	1.00

* Data are presented as no. (%) of patients, median, or median (range)

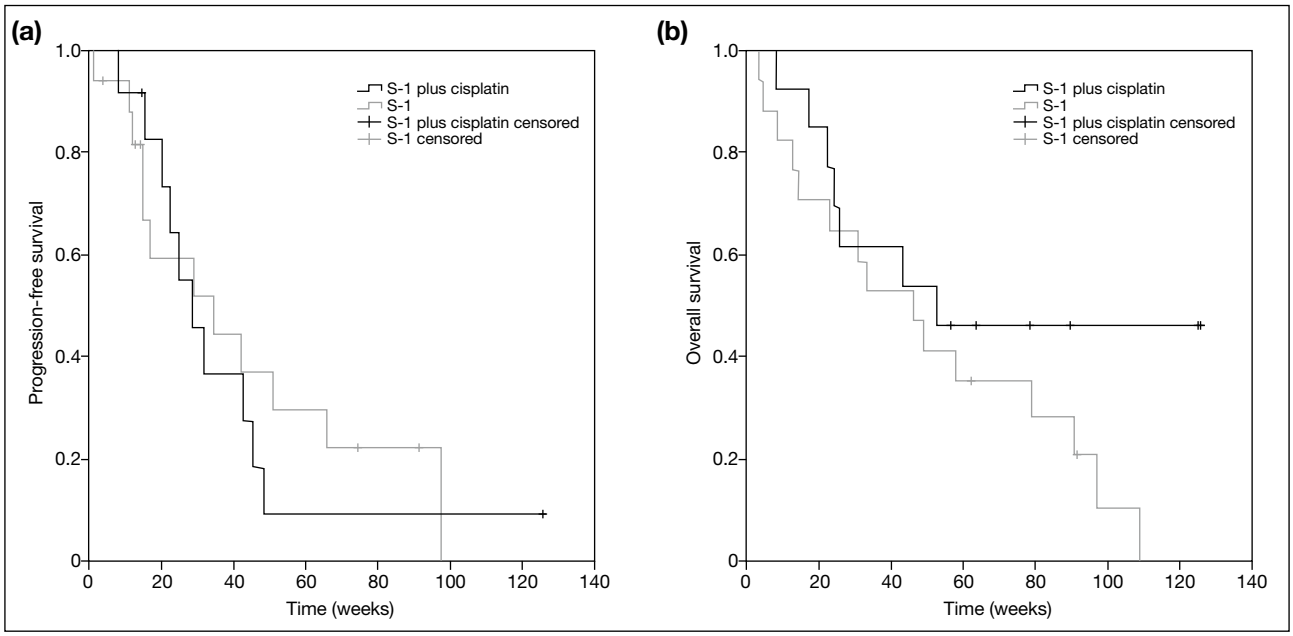

Figure. Kaplan-Meier curve for (a) progression-free survival and (b) overall survival of the S-1 and S-1 plus cisplatin groups.

Table 2. Comparison of the FLAGS trial and ML17032 trial.

Variable	FLAGS trial (n=1053)[18]	ML17032 trial (n=316)[3]
Geographical region	24 countries	Korea
Regimen compared	SP vs. PF	PX vs. PF
Median (range) patient age (years)	59 (18-85)	56 (22-74)
Eastern Cooperative Oncology Group score	0-1	0-1
Primary site	Stomach and gastro-oesophageal junction	Stomach
>1 site of metastasis (% of patients)	64.8	70.6 (PX), 57.7 (PF)
Median overall survival (months)	8.6 vs. 7.9	10.5 vs. 9.3
Grade 3/4 neutropaenia (%)	32.3 vs. 63.6	16 vs. 19

Abbreviations: SP = S1 + cisplatin; PX = cisplatin + capecitabine; and PF = cisplatin + 5-fluorouracil.

a trend of improved OS in the SP group, probably because fewer patients were aged ≥70 years, more patients underwent surgical resection of primary tumours, fewer patients required initial dose reduction, and more patients received subsequent chemotherapy. Both regimens were well tolerated; grade 3/4 treatment-related toxicity was infrequent, 30-day mortality was low, and there was no treatment-related death. This is consistent with the results of a phase III trial.[18] Toxicity was consistently less with the S-1 combination regimen than the 5-FU and cisplatin combination regimen.[5,18]

With limited progress in prolonging the survival of metastatic gastric cancer patients, treatment regimens should be least toxic and most convenient for patients. The time spent in hospital for infusion of 5-FU can be substituted with S-1 oral tablets.[19] In the ML17032 study, cisplatin plus capecitabine was not inferior to cisplatin plus 5-FU in terms of PFS.[3] In the phase-III SPIRITS trial, SP achieved improved PFS and OS compared with S-1.[5] In the phase-III FLAGS trial, SP and cisplatin plus 5-FU were comparable in terms of PFS and OS but had an improved safety profile.[18] Replacement of 5-FU by S-1 or capecitabine improved the OS by approximately 1 month and reduced the rate of grade 3/4 haematological toxicity (Table 2).[3,18] Nonetheless, there are limitations in cross-trial comparisons. The standard dose of cisplatin in the cisplatin plus 5-FU regimen was 80 to 100 mg/m^2, whereas that used in the S-1 regimen was 60 mg/m^2. The lower dose of cisplatin potentially reduced renal toxicity and severe vomiting, and did not adversely affect survival outcome.

In a meta-analysis, both S1-based and capecitabine-based chemotherapy as first-line treatment for

metastatic gastric cancer were comparable for response rate, time-to-tumour progression, OS, and toxicity profile, with fewer hand-foot-skin reactions.[20] Nonetheless, most studies included were small phase-II studies with limited information on quality of life. In the phase-II XParTS II study, comparable outcome was also demonstrated, but subgroup analysis showed superiority of SP for PFS in patients with diffuse-type gastric cancer (hazard ratio = 0.42, 95% confidence interval = 0.20-0.86, p = 0.015).[21]

This study had several limitations. The size of the two groups was small and the follow-up was short. This limits the statistical power to detect differences in survival. There was selection bias intrinsic to the retrospective study. In the S-1 group, more patients were older and required initial dose reduction, and fewer patients underwent surgical resection of primary tumours and received subsequent chemotherapy. This probably reflects the choice of S-1 monotherapy by oncologists.

CONCLUSION

Both S-1 and SP regimens are effective and safe as first-line treatment for metastatic gastric cancer. A dose-adjusted S-1 regimen is a viable option for patients with advanced age and marginal performance status.

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