Randomized phase II trial of S-1 plus irinotecan versus S-1 plus paclitaxel as first-line treatment for advanced gastric cancer (OGSG0402)

K. Fujitani, H. Takiuchi, N. Sugimoto, H. Imamura, S. Iijima, M. Imano, Y. Kimura, T. Shimokawa, Y. Kurokawa, T. Tsujinaka, H. Furukawa

Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG), Osaka, Japan

Background

- JCOG 9205 (Ohtsu A et al; J Clin Oncol 21:54-59, 2003)

5FU alone as reference arm

	5FU	5FU+ CDDP	UFT + MMC
No. of pts	105	105	70
Response rate	11%	34%	9%
Median PFS (M)	1.9	3.9	2.4
MST (M)	7.1	7.3	6.0

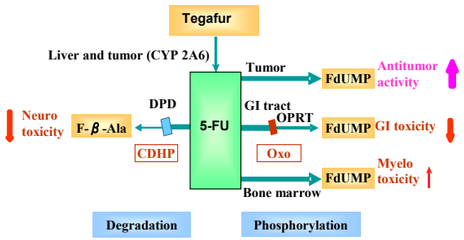
- JCOG 9912 (Boku N et al; ASCO 2007; LBA 4513)

S-1's non-inferiority to 5FU

	5FU	S-1	CPT + CDDP
No. of pts	234	234	236
Response rate	9%	28%	38%
PFS (M)	2.9	4.2	4.8
MST (M)	10.8	11.4	12.3

S-1

– S-1 is an oral agent containing tegafur, gimeracil (CDHP) and oteracil potassium (Oxo) at a molar ratio of 1:0.4:1.



– Phase I/II study of S1 plus irinotecan (OGSG 0002)

CPT-11 bi-weekly, iv — 80 mg/m² — S-1(p.o.) 80 mg/m²/day x 3 wks — 2-wk rest

<Efficacy>

Response rate	47.8 (27.4-68.2) %
1-year survival	52.9 %
MST	394 days

Standard dose of S-1

Body surface area	Daily dose (equivalent to tegafur)
< 1.25m²	40mg x 2
1.25 - < 1.50m²	50mg x 2
1.50m² ≤	60mg x 2

<Adverse events> (Grade 3 or higher)

Hematological toxicity		Non-hematological toxicity	
Leukopenia	4.3 %	Diarrhea	4.3 %
Neutropenia	8.7 %	Anorexia	4.3 %
Anemia	8.7 %	Nausea/Vomiting	4.3 %

(Takiuchi H et al; Jpn J Clin Oncol 35: 520-5, 2005. Uedo N et al; Oncology 73: 65-71, 2007.)

– Phase I/II study of S1 plus paclitaxel (OGSG 0105)

Paclitaxel weekly, iv — 50 mg/m² — S-1(p.o.) 80 mg/m²/day x 2 wks — 1-wk rest

<Efficacy>

Response rate	48.3 (30.1-66.5) %
1-year survival	57.6 %
MST	13.9 M

Standard dose of S-1

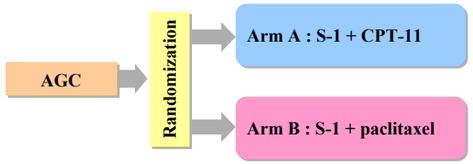
Body surface area	Daily dose (equivalent to tegafur)
< 1.25m²	40mg x 2
1.25 - < 1.50m²	50mg x 2
1.50m² ≤	60mg x 2

<Adverse events> (Grade 3 or higher)

Hematological toxicity		Non-hematological toxicity	
Leukopenia	0 %	Diarrhea	3.4 %
Neutropenia	3.4 %	Anorexia	0 %
Anemia	0 %	Nausea/Vomiting	0 %

(Fujitani K et al; Oncology 69: 414-20, 2005. Narahara H et al; Oncology 74: 37-41, 2008.)

Study design



Factors adjusted for allocation

(1) Unresectable advanced / recurrent with adjuvant chemotherapy / recurrent without adjuvant chemotherapy
(2) PS 0/1/2

Objectives

- To evaluate the efficacy and safety of S-1 plus irinotecan and S-1 plus paclitaxel as first-line treatments against AGC with an aim of choosing the optimal regimen for a subsequent phase III trial
- Primary endpoint
  - Overall response rate (ORR)
- Secondary endpoints
  - Progression-free survival (PFS)
  - Overall survival (OS)
  - Safety

Statistical considerations

Sample size: 50 pts in each arm
determined to reject the ORR of 30% under the expectation of 50% with a power of 80% and a two-sided α of 5%

Planned accrual & follow-up: 2 years & 3 years

Actual accrual: 102 pts from 13 institutions
12/15/2005 - 11/14/2007

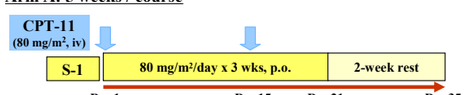
Latest analysis: 1/8/2010

Eligibility criteria

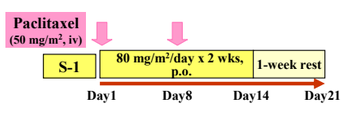
- Histologically proven unresectable advanced or recurrent gastric cancer with measurable lesions
- No prior chemotherapy except adjuvant CTX completed 4 weeks or more before entry
- PS of 2 or less on the ECOG scale
- Aged 20-75 years
- Tolerance of oral feeding
- Life expectancy of at least 3 months
- Adequate organ function
- Written informed consent

Treatment schedule

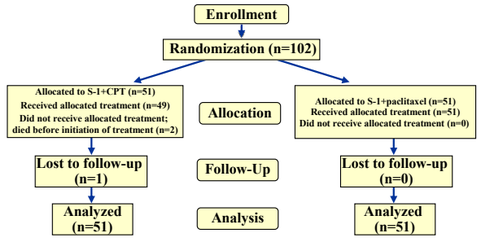
- Arm A: 5 weeks / course



- Arm B: 3 weeks / course



Patient disposition



Patient characteristics

	S-1+CPT (n=51)	S-1+paclitaxel (n=51)
Gender (male/female)	38/13	38/13
Age median (range)	64 (25-75)	62 (30-75)
PS (0/1/2)	41/8/2	39/12/0
Histology (intestinal/diffuse/others)	28/22/1	33/16/2
Primary lesions (+/-)	37/14	37/14
Advanced/recurrent	40/11	40/11
Recurrent pts after adjuvant chemotherapy (+/-)	3/8	1/10

Number of treatment courses

	No. of pts	Total no. of courses	Median (range)
S-1+CPT	48	237	4 (1-16)
S-1+ paclitaxel	51	319	5 (1-40)

Reasons for discontinuation (S-1+CPT/S-1+paclitaxel) :

•Progressive disease	70 (33/37) pts
•Adverse events	11 (4/7) pts
•Patient withdrawal	7 (4/3) pts
•Doctor's decision	1 (1/0) pt
•Others	8 (5/3) pts

Anti-tumor effect

RECIST

	No. of pts	Response CR	PR	SD	PD	NE	Response rate (%) (95%CI)	Chi-square test (p-value)
S-1+CPT	51	2	15	17	8	9	33.3% (20.8-47.9)	0.841
S-1+ paclitaxel	51	1	15	18	11	6	31.4% (19.1-45.9)	

- ORR was determined by extra-mural review
- Tumor lesions were assessed every other month after initiation of treatment
- Null hypotheses (ORR≤30%) were not rejected in both arms (S-1+CPT-11: p=0.65, S-1+paclitaxel: p=0.88)

best ORR

	No. of pts	Response CR	PR	SD	PD	NE	Response rate (%) (95%CI)	Chi-square test (p-value)
S-1+CPT	51	2	17	21	6	5	37.3% (24.1-51.9)	1.000
S-1+ paclitaxel	51	2	16	22	6	5	35.3% (22.4-49.9)	

- ORR was determined by extra-mural review
- For assessment of best ORR, determination of CR or PR did not require confirmation performed at least 4 weeks later
- Tumor lesions were assessed every other month after initiation of treatment

Adverse events

hematological toxicity

	S-1+CPT(n=48) G3/4 (≥G3)	S-1+paclitaxel (n=51) G3/4 (≥G3)
Leukopenia	7/0 (15%)	0/0 (0%)
Neutropenia	8/1 (19%)	1/0 (2%)
Anemia	6/0 (13%)	2/1 (6%)
Thrombocytopenia	0/0 (0%)	0/1 (2%)
Infection/febrile neutropenia	1/0 (2%)	0/0 (0%)

NCI-CTC version 2.0.

* No treatment-related deaths (TRDs) occurred during the study

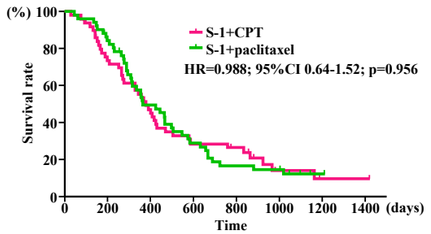
non-hematological toxicity

	S-1+CPT (n=48) G3/4 (≥G3)	S-1+paclitaxel (n=51) G3/4 (≥G3)
Diarrhea	3/0 (6%)	1/0 (2%)
Nausea/Vomiting	2/0 (4%)	3/0 (6%)
Fatigue	2/0 (4%)	1/0 (2%)
Stomatitis	1/0 (2%)	0/0 (0%)
Anorexia	6/0 (13%)	5/0 (10%)
Creatinine	0/0 (0%)	0/0 (0%)
T-Bil	1/0 (2%)	1/0 (2%)
AST (GOT)	0/0 (0%)	1/0 (2%)
ALT (GPT)	0/0 (0%)	2/0 (4%)

NCI-CTC version 2.0.

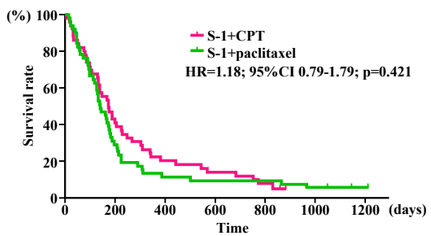
* One grade 4 cerebral infarction occurred 7 days after the completion of the 3rd course of treatment in the S-1 + CPT arm

Overall Survival



	Events	MST (95% CI)	1-year OS (95% CI)
S-1+CPT -11 (n=50)	41	379 days (280 – 507 days)	53.1% (40.9 – 69.1 %)
S-1+paclitaxel (n=51)	43	364 days (311 - 549 days)	49.4 % (37.2 – 65.6 %)

Progression Free Survival



	Events	median PFS (95% CI)	1-year PFS (95% CI)
S-1+CPT-11 (n=50)	46	173 days (134 - 247 days)	22.6 % (13.5 – 38.0 %)
S-1+paclitaxel (n=51)	48	141 days (126 - 181 days)	13.7 % (6.9 – 27.3 %)

Discussion

Study	Regimen	Pts	Best ORR (%)	PFS (M)	OS (M)	p-value (OS)
OGSG0402	S-1+CPT	51	37.3	5.7	12.5	0.956
	S-1+paclitaxel	51	35.3	4.6	12.0	
GC0301/TOP-002[1] (2008)	S-1+CPT	155	41.5	5.0	12.8	0.233
	S-1	160	26.9	3.4	10.5	
SPIRITS[2] (2007)	S-1+CDDP	148	54.0	6.0	13.0	0.037
	S-1	150	31.1	4.0	11.0	
JCOG 9912[3] (2007)	S-1	234	28	4.2	11.4	0.034 (1-sided)
	5FU	234	9	2.9	10.8	
	CPT+CDDP	236	38	4.8	12.3	0.055

1) Imamura H et al; ASCO-GI 2008; LBA 5
2) Narahara H et al; ASCO 2007; LBA4514
3) Boku N et al; ASCO 2007; LBA4513

Conclusions

Both S-1+CPT and S-1+paclitaxel showed equally longer survival and superior tolerance in patients with AGC.
Although predicted ORR of 50% was not achieved by either regimen, both regimens may become one of the options as first line treatment for AGC.

Participating Institutions

Osaka Medical Center for Cancer and Cardiovascular Diseases
Sakai Municipal Hospital
National Hospital Organization Osaka National Hospital
Minoh City Hospital
Osaka Medical College Hospital
Kinki University School of Medicine
NTT West Osaka Hospital
Kansai Medical University Takii Hospital
Osaka City University Hospital
Kinki Central Hospital of Mutual Aid Association of Public School Teachers
Kumamoto Regional Medical Center
Osaka Seamen's Insurance Hospital
Osaka Saiseikai-Nakatsu Hospital

• Consulting statistician : T. Shimokawa, Yamanashi University

Abstract

Introduction: S1-based regimens are commonly used for advanced gastric cancer (AGC) in Japan. Both S1 plus irinotecan (SI) and S1 plus paclitaxel (SP) have shown an overall response rate (ORR) of 48% in respective phase II trials. This randomized phase II trial compared the efficacy and safety of these two S1-based regimens as first-line treatment for AGC.

Methods: Patients with previously untreated, locally advanced and/or metastatic measurable gastric adenocarcinoma, a performance status of ≤ 2, and adequate organ function were randomly assigned to receive S-1 (80 mg/m²/day) for 21 consecutive days plus irinotecan (80 mg/m²) on days 1 and 15, repeated every 5 weeks for the SI arm, or the same dose of S1 for 14 consecutive days plus paclitaxel (50 mg/m²) on days 1 and day 8, repeated every 3 weeks for the SP arm. Both treatments were continued until disease progression or intolerable toxicity occurred. The follow-up time was 2.0 year. Study endpoints included ORR as primary, progression free survival (PFS), overall survival (OS), and toxicity.

Results: One hundred and two patients were enrolled from December 2005 to November 2007. The evaluable patients were 101 (SI/SP, 50/51), and patients characteristics were well balanced between the two arms. At the end of trial, 84 events (83%) had been observed. Median survival time (MST) of SI arm was 379 days (95%CI: 280-470) and that of SP arm was 364 days (95%CI: 311-549), with no significant difference (log-rank test p=0.89; HR=0.97). The 1-year survival was 52.3% for the SI arm and 49.2% for the SP arm. PFS of SI arm was 173 days (95%CI: 134-228) and that of SP arm was 141 days (95%CI: 126-179), with no significant difference (log-rank test p=0.37; HR=1.28). ORR on RECIST was 33.3% (95% CI, 20.8% to 47.9%) for the SI arm and 31.4% (95% CI, 19.1% to 45.9%) for the SP arm, with no significant difference between the two. No treatment-related deaths occurred during the study. Both arms were well tolerated although grade 3/4 neutropenia (19% vs. 2%) and anemia (13% vs. 6%) were more frequent in the SI arm.

Conclusions: Both regimens showed equally longer survival and superior tolerance in patients with AGC. Although predicted ORR of 50% was not achieved by either regimen, both regimens may become one of the options as first line treatment for AGC.