Randomized phase II study of CPT-11 versus PTX versus each combination chemotherapy with S-1 in patients with advanced gastric cancer refractory to S-1 or S-1 plus platinum (OGSG 0701)

Masahiro Gotoh[1] ,Hiroshi Imamura[2], Tomono Kawase[3], , Yutaka Kimura[3], Shugo Ueda[4], Jin Matsuyama[5], Kazuhiro Nishikawa[6], Naotoshi Sugimoto[7], Junya Fujita[8], Takao Tamura[9], Takayuki Kii[1], Taroh Satoh[11], Yukinori Kurokawa[11], Daisuke Sakai[11], Toshio Shimokawa[12], Toshimasa Tsujinaka[13], Hiroshi Furukawa[14]

[1]Osaka Medical College Hospital, Takatsuki, Japan; [2]Toyonaka Municipal Hospital, Toyonaka, Japan; [3] Sakai City Hospital, Sakai, Japan; [4]Kitano Hospital ,Osaka, Japan; [5]Yao Municipal Hospital, Yao, Japan; [6]Osaka General Medical Center, Osaka, Japan; [7]Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan; [8]NTT West Osaka Hospital, Osaka, Japan; [9]Kinki University Faculty of Medicine, Ikoma, Japan; [10]Yamagata Prefectural Central Hospital, Yamagata, Japan; [11]Osaka University Graduate School of Medicine, Osaka, Japan; [12]Yamanashi University, Kofu, Japan; [13]Kaizuka City Hospital, Kaizuka, Japan; [14]Kinki University Faculty of Medicine, Sayama, Japan

Abstract

Background: S-1 plus platinum (SP) is recognized as standard first-line chemotherapy for advanced gastric cancer (AGC) and S-1 monotherapy is recognized as standard adjuvant chemotherapy for locally AGC in Japan. Taxane or CPT-11 are two main options and a retrospective analysis has reported that S-1 combination chemotherapy extended overall survival as second-line chemotherapy for AGC that was resistant to first-line S1-based chemotherapy. However, second-line chemotherapy for AGC is not established. Thus, this prospective multicenter phase II study was carried out to examine efficacy and safety comparing CPT-11, PTX, and each combination chemotherapy with S-1 refractory to S-1 or SP.

Methods: Patients with AGC after first-line chemotherapy with S-1 or SP, or patients during adjuvant chemotherapy or within 26 weeks after adjuvant chemotherapy completion with S-1 who confirmed disease progression by imaging technique were eligible. Patients were randomly divided into four groups by treatment as follows; Group A: CPT-11 150 mg/m^2, day1, q14days, Group B: PTX 80 mg/m^2, day1, 8, 15, q28days, Group C1: CPT-11 80 mg/m^2, day1, 8, S-1 80 mg/m^2, day1-21, q35days, Group C2: PTX 50 mg/m^2, day1, 15, S-1 80 mg/m^2, day1-14, q21days. Primary endpoint was overall survival (OS), and secondary endpoints were progression free survival (PFS), response rate and safety.

Results: From July 2008 to March 2012, 127 patients were enrolled. Median OS was 11.3/11.3/14.6/10.5 months(M) (Group A/B/C1/C2), 11.8 M in Group A+C1 and 11.1 M in Group B+C2 (p=0.922, HR: 0.981 [0.679-1.419]), and 11.3 M in Group A+B and 11.1 M in Group C1+C2 (p=0.808, HR: 0.952 [0.643-1.412]), respectively. Median PFS was 3.0/4.4/3.8/3.5 M (Group A/B/C1/C2), 3.6 M in Group A+C1 and 4.1 M in Group B+C2 (p=0.035, HR:0.674 [0.468-0.972]), and 3.7 M in Group A+B and 3.7 M in Group C1+C2 (p=0.931, HR: 1.017 [0.643-1.412]) , respectively.

The most common grade 3 or 4 adverse events (Group A/B/C1/C2, %), were leukopenia (12/7/5/0), neutropenia (29/16/24/24), anemia (7/9/14/14), anorexia (10/2/14/10), nausea (7/2/10/5), diarrhea (5/0/10/0), and fatigue (5/2/10/5). Conclusions: The difference in OS between CPT-11 and PTX, and the efficacy of S-1 sequential therapy were not observed in second-line chemotherapy for AGC refractory to S-1 or SP.

Background

- S-1 plus cisplatin (SP) is recognized as standard first-line chemotherapy for advanced gastric cancer (AGC)[1] and S-1 monotherapy is recognized as standard adjuvant chemotherapy for locally AGC in Japan[2,3].
- Taxane or CPT-11 are two main options and a retrospective analysis has reported that S-1 combination chemotherapy extended overall survival as second-line chemotherapy for AGC that was resistant to first-line S1-based chemotherapy[4].
- However, second-line chemotherapy for AGC is not established.

Study Design

gastric cancer
- Refractory to S-1 or S-1+platinum as first-line chemotherapy or adjuvant chemotherapy with S-1
- Adequate oral intake
- 20-74 y.o
- PS 0-2

R — N=120

Group A: CPT
CPT-11 150 mg/m^2 day1, q14days

Group B: PTX
PTX 80 mg/m^2, day1, 8, 15, q28days

Group C1: S-1+CPT
CPT-11 80 mg/m^2, day1, 8 S-1 80 mg/m^2, day1-21, q35days

Group C2: S-1+PTX
PTX 50 mg/m^2, day1, 15 S-1 80 mg/m^2, day1-14, q21days

Stratifications
- Metastatic or recurrent /adjuvant
- PS 0-1/2
- Peritoneal metastasis ＋/－
- Institution

Objective & Endpoints

- Objective

  To examine efficacy and safety comparing CPT-11, PTX, and each combination chemotherapy with S-1 refractory to S-1 or SP

- Endpoints
  - ✓ Primary endpoint - Overall Survival (OS)
  - ✓ Secondary endpoints - progression free survival (PFS)
  - safety
  - response rate (RR) (Under follow-up, immature)

Statistical Considerations

- Sample size n=120
  - ✓40 patients/each Group A and Group B
  - ✓20 patients/each Group C1 and Group C2
- Expected median OS: 7 months, threshold median OS: 4 months
- Enrollment: 5 years, Follow-up: 2 years
- 1-sided α=0.1, a power of 80%
- Intension-to-treat basis

Main Inclusion Criteria

- Histologically confirmed gastric cancer
- disease progression confirmed by imaging technique during first-line chemotherapy with S-1 or SP or during adjuvant chemotherapy or within 26 weeks after adjuvant chemotherapy completion with S-1
- ECOG performance status 0-2
- Age 20-74
- No severe organ dysfunction
- Written informed consent

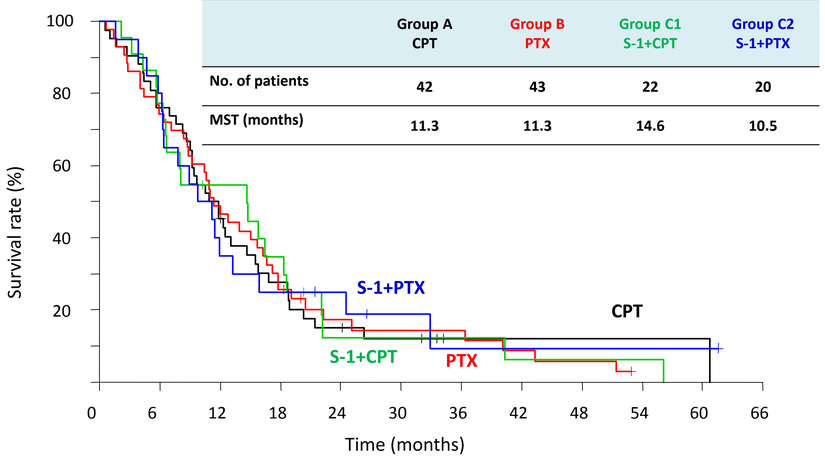
Patient Characteristics

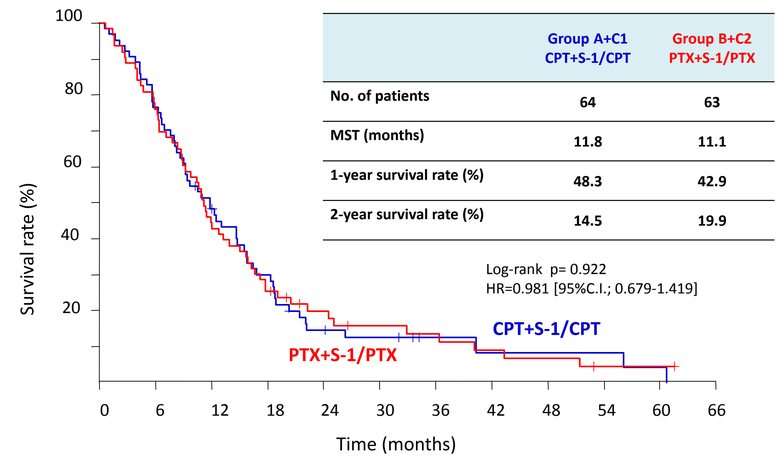
	Group A CPT (n=42)	Group B PTX (n=43)	Group C1 S-1+CPT (n=22)	Group C2 S-1+PTX (n=20)
Sex Male/Female	30/12	35/8	15/7	12/8
Age, years Median(range)	65 (44-74)	65 (31-74)	67 (47-73)	63 (37-74)
ECOG PS 0-1/2	42/0	41/2	21/1	20/0
Histology Intestinal/Diffuse/Unknown	24/18/0	25/17/1	11/10/1	12/8/0
Prior gastrectomy Yes/No	22/20	21/22	13/9	13/7
Peritoneal metastasis Yes/No	15/27	15/28	7/15	4/16
No. of metastasis sites 0-1/≥2	28/14	31/12	19/3	16/4

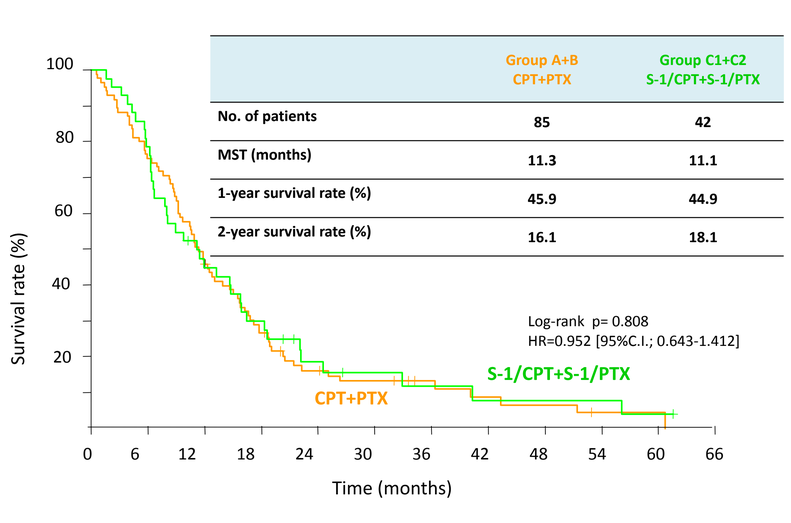
Adverse Events

Adverse Events	CPT (n=42) All n (%)	CPT (n=42) ≥ G3 n (%)	PTX (n=43) All n (%)	PTX (n=43) ≥ G3 n (%)	S-1+CPT (n=21) All n (%)	S-1+CPT (n=21) ≥ G3 n (%)	S-1+PTX (n=21) All n (%)	S-1+PTX (n=21) ≥ G3 n (%)
Leukocytopenia	25 (59.5)	5 (12.0)	18 (41.9)	3 (7.0)	13 (61.9)	1 (4.8)	12 (57.1)	0 (0)
Neutropenia	30 (71.4)	12 (28.6)	19 (44.2)	7 (16.3)	14 (66.7)	5 (23.8)	13 (61.9)	5(23.8)
Hemoglobin	36 (85.7)	3 (7.1)	32 (74.4)	4 (9.3)	16 (76.2)	3 (14.3)	19 (90.5)	3 (14.3)
Thrombocytopenia	14 (33.3)	2 (4.8)	9 (20.9)	1 (2.3)	5 (23.8)	0 (0)	4 (19.0)	1 (4.8)
Febrile neutoropenia	0 (0)	0 (0)	5 (11.6)	5 (11.6)	0 (0)	0 (0)	0 (0)	0 (0)
Bilirubin	9 (21.4)	0 (0)	5 (11.6)	0 (0)	7 (33.3)	0 (0)	5 (23.8)	1 (4.8)
AST	9 (21.4)	1 (2.4)	13 (30.2)	2 (4.7)	5 (23.8)	0 (0)	7 (33.3)	0 (0)
ALT	8 (19.0)	1 (2.4)	10 (23.3)	1 (2.3)	5 (23.8)	0 (0)	4 (19.0)	0 (0)
Nausea	16 (38.0)	3 (7.1)	11 (25.6)	1 (2.3)	12 (57.1)	2 (9.5)	8 (38.1)	1 (4.8)
Vomiting	10 (23.8)	2 (4.8)	3 (7.0)	1 (2.3)	4 (19.0)	0 (0)	3 (14.3)	0 (0)
Anorexia	27 (64.3)	4 (9.5)	19 (44.2)	1 (2.3)	13 (61.9)	3 (14.3)	14 (66.7)	2 (9.5)
Diarrhea	17 (40.5)	2 (4.8)	5 (11.6)	0 (0)	14 (66.7)	2 (9.5)	7 (33.3)	0 (0)
Neuropathy	1 (2.4)	0 (0)	27 (62.8)	0 (0)	1 (4.8)	0 (0)	8 (38.1)	0 (0)
Fatigue	27 (64.3)	2 (4.8)	23 (53.5)	1 (2.3)	13 (61.9)	2 (9.5)	14 (66.7)	1 (4.8)

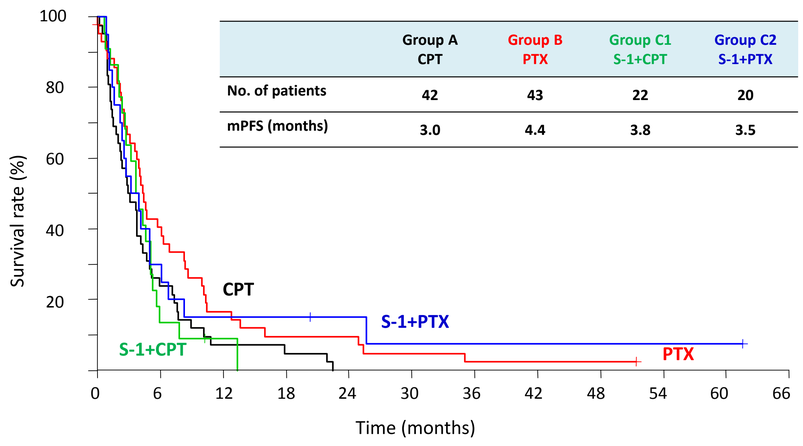
Overall Survival

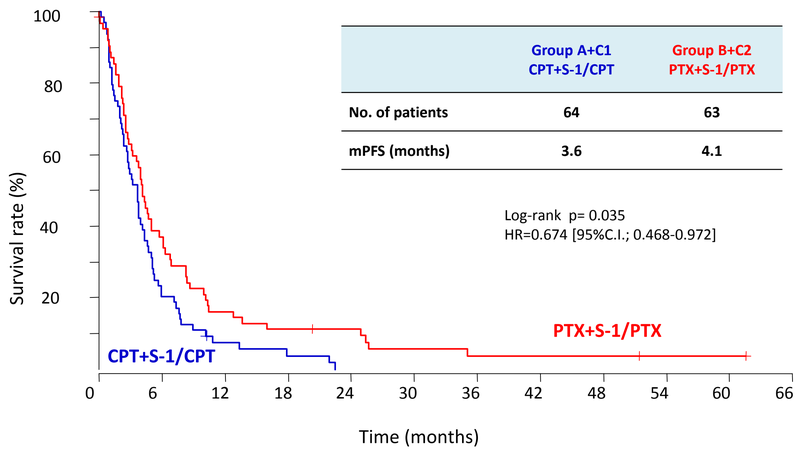


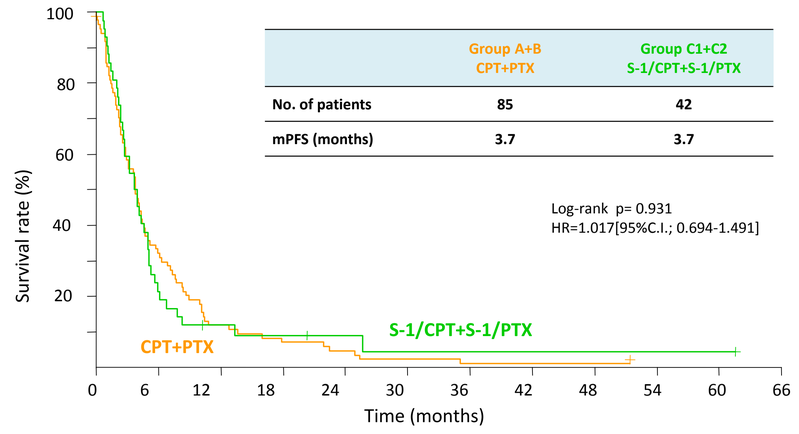




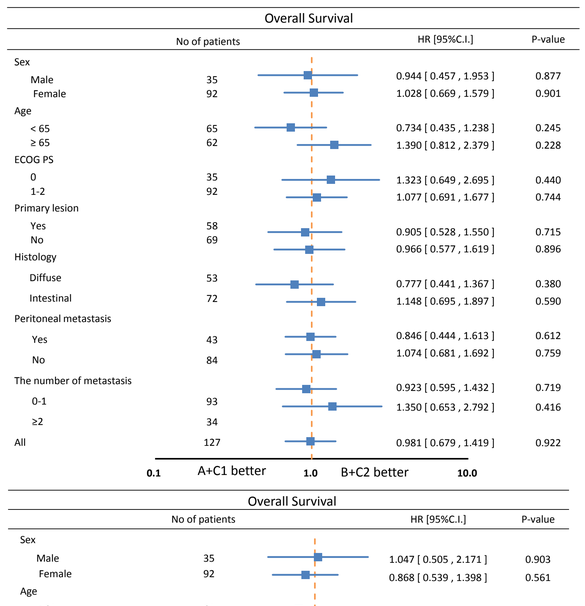
Progression-free Survival

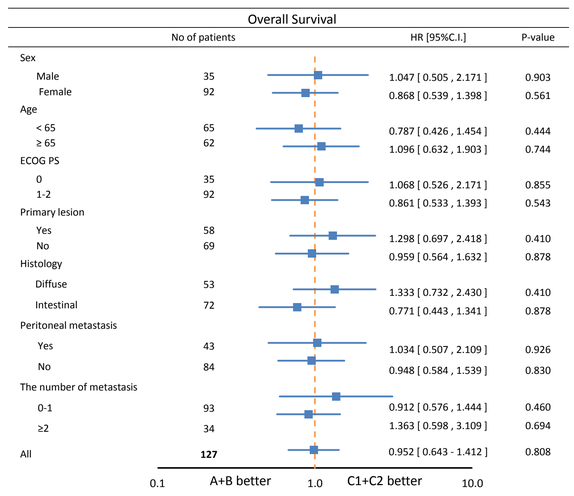






Subgroup Analysis





Conclusion

- The difference in OS between CPT-11 and PTX, and the efficacy of S-1 sequential therapy were not observed in second-line chemotherapy for advanced gastric cancer refractory to S-1 or SP.

References

1. W. Koizumi et al. Lancet Oncol. 2008 9 (3):215-21.
2. S. Sakuramoto et al. N Engl J Med. 2007 357 1810-20.
3. M. Sasako et al. J Clin Oncol. 2011 29 (33) 4387-93
4. N. Sugimoto et al. Gan To Kagaku Ryoho. 2009 36 (3): 417-24