Phase II trial of S-1 for elderly patients over 75 years with advanced gastric cancer as first-line treatment : OGSG0404

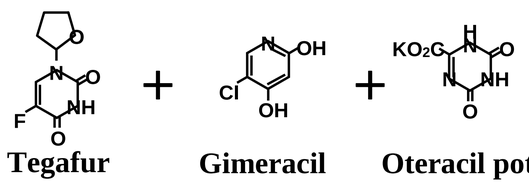
M. Gotoh[1], H. Takiuchi[1], H. Imamura[2], Y. Kimura[2], T.Morimoto[2], M. Imano[2], S.Iijima[2], K.Yamashita[2], M.Matsuoka[2], K.Maruyama[2], H. Furukawa[2]

[1]Cancer Chemotherapy Center,Osaka Medical College, Osaka, Japan.

[2]Osaka Gastrointestinal Cancer Chemotherapy Study Group: OGSG

Background (1)

- S-1 (TS-1®)
  - S-1, an oral agent containing tegafur, gimeracil (CDHP) and oteracil potassium (Oxo) at a molar ratio 1: 0.4: 1, showed the high response rate (>40%) for advanced gastric cancer. (Eur J Cancer 1998, Oncology 2000)



Tegafur Gimeracil Oteracil potassium

Background (2)

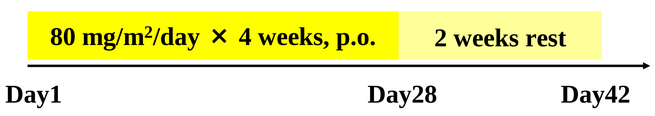
- In Japan, S1-based regimens are commonly used for advanced gastric cancer (AGC) because the usefulness of S-1-based treatment as first-line for AGC has been demonstrated. (Lancet Oncology 2008, ASCO2009 #4514)
- However, because over 75 years patients (pts) were excluded from this trial, the significance of S-1 based chemotherapy for elderly AGC pts is unclear.

Objectives

- To evaluated the efficacy and safety of S-1 monotherapy in elderly patients over 75 years of age with unresectable advanced or recurrent gastric cancer.
- **Primary endpoint**
  - Overall response rate (ORR)
- **Secondary endpoints**
  - Safety
  - Overall survival (OS)
  - Progression-free survival (PFS)
  - Time to treatment failure (TTF)

Treatment schedule

- A course of treatment consisted of 4 weeks administration followed by 2 weeks rest period, and the patients received repeated courses.
- S-1 monotherapy : 6 weeks/course



Determination of Starting dose

- The starting dose was determined by body surface area (BSA) and Creatinine clearance (Ccr).

BSA (m^2)	Ccr (mL/min)			
	≧80	80-50	50-30	≦30
≧1.5	120 mg/day	100 mg/day	80 mg/day	Do not administer
1.25 - 1.5	100 mg/day	80 mg/day	50 mg/day	
≦1.25	80 mg/day	50 mg/day	40 mg/day	

- To avoid the adverse event, adjusted dosages lower than standard criteria.

Statistical considerations

- **Sample Size**: 35 pts
  - determined to reject the ORR of 11% under the expectation of 30% with a power of 80% and an one-sided α of 5%
- **Planned accrual & follow-up**: 4 yrs & 2 yrs
- **Actual accrual**: 35 pts from 9 institutions

  11/5/2004 – 6/17/2008

Eligibility criteria

- Histologically proven unresectable advanced or recurrent gastric cancer with measurable lesions
- No prior chemotherapy except adjuvant CTX completed 6 months or more before entry
- PS of 2 or less on the ECOG scale
- Age over 75 years old
- Tolerance of oral feeding
- Life expectancy of at least 3 months
- Adequate organ function
- Written informed consent

Patient characteristics

Charactaristics	No. of pts (n=35)
Gender (male/female)	21 / 14
Age median (range)	78 (75-86)
PS (0/1/2)	19 / 12 / 4
Advanced / recurrent	22 / 13
Primary lesions (+/-)	15 / 20
Histology (intestinal/diffuse/others)	24 / 10 / 1
Complications (+/-)	10 / 25
Initial Dose (mg) (120/100/80/50/40)	1 / 14 / 11 / 7 / 2

Anti-tumor effect : Response rate

No. of patients	Response					RR (%) (95%CI)	p-value (two-side)	DCR (%) (95%CI)
	CR	PR	SD	PD	NE			
35	0	5	15	10	5	14.3% (4.8-30.3)	P=0.584	57.1% (40.7-73.5)

- ORR was determined by extra-mural review
- Evaluation based on Japanese Classification of Gastric Carcinoma (13th edition)
- Null hypotheses (ORR<11%) were not rejected

Adverse events : hematological

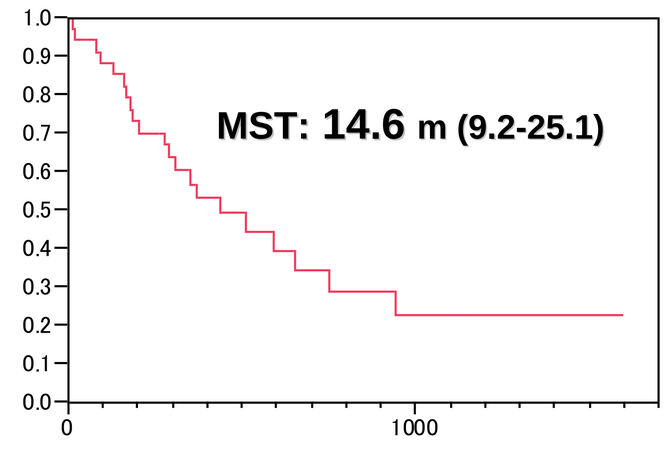
	NCI-CTC version 2.0				Frequency (%)	
	1	2	3	4	All	≧G3
Leukopenia	3	1	0	0	11.8	0
Neutropenia	2	1	1	0	11.8	2.9
Anemia	10	11	1	0	64.7	2.9
Thrombocytopenia	6	1	0	0	20.6	0

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

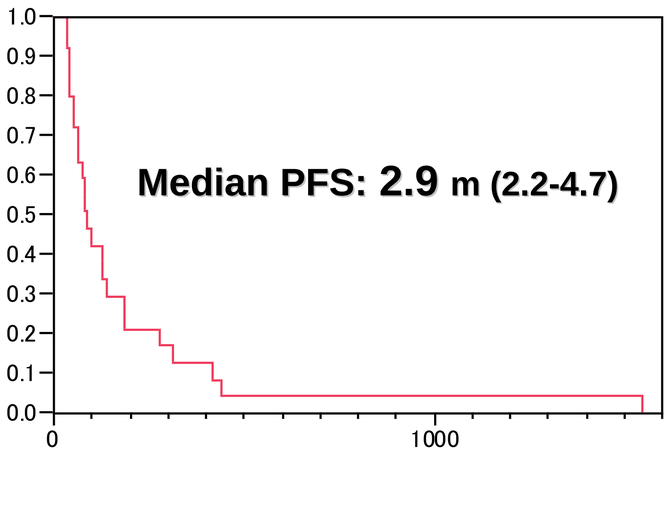
Adverse events : non-hematological

	NCI-CTC version 2.0				Frequency (%)	
	1	2	3	4	All	≧G3
ALT/AST	0	0	1	0	2.9	2.9
T-Bil	2	1	0	0	8.8	0
Nausea/Vomiting	4	1	0	0	14.7	0
Anorexia	10	5	1	0	47.1	2.9
Fatigue	3	0	2	0	14.7	5.9
Stomatitis	1	1	0	0	5.9	0
Diarrhea	3	1	0	0	11.8	0

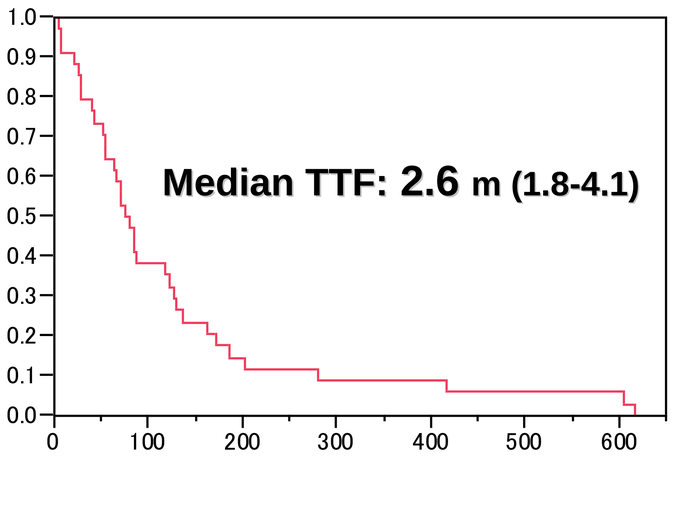
Overall survival (OS)



Progression-free survival (PFS)



Time to treatment failure (TTF)



Summary

- ORR of S-1 monotherapy was 14.3% for elderly patients with AGC.
- Safety profile were well tolerated and there was no Grade 4 toxicity.
- The median TTF, PFS and OS of this regimen was 2.6 months, 2.9 months and 14.6 months, respectively.

Discussion

- Although the median PFS was short, MST was longer than previous Phase III trials.
- It is necessary to examine which treatment selected after first-line treatment.
- Because adjusted starting dose was low, it was possible that the treatment effect of S-1 monotherapy not enough.

Results of S-1 monotherapy in Japanese trials

study	OGSG0404	TCOG	JCOG9912	SPIRITS
Phase	II	II	III	III
Age	≧75	≧75	20-75	20-74
RR (%)	14.3	21.2	28	31
TTF (Mo)	2.6	3.2	4.0	3.9
PFS (Mo)	2.9	3.9	4.2	4.0
OS (Mo)	14.6	15.7	11.4	11.0

Conclusions

- Predicted ORR was not achieved by this regimen.
- S-1 monotherapy was effective in terms of OS and safety in elderly patients with unresectable and advanced or recurrent gastric cancer.
- S-1 monotherapy is well tolerated and useful for elderly patients with AGC.