Phase I study of paclitaxel, TS-1 and cisplatin in patients with advanced gastric cancer (OGSG 0703)

Kishimoto T[1)], Imamura H[1)], Kimura Y[2)], Tsuzinaka T[3)], Imano M[4)], Tokunaga Y[5)], Matsuoka M[6)], Shimokawa T[7)], Kurokawa Y[3)] ,Furukawa H[1)]

1) Sakai Municipal Hospital, Osaka, Japan, 2) NTT West Osaka Hospital, Osaka, Japan, 3) National Osaka Medical Center, Osaka, Japan, 4) Kinki University Hospital, Osaka, Japan, 5) Osaka kitateisin Hospital, Osaka, Japan, 6) Dongo Hospital, Nara, Japan, 7) Yamanashi University, Yamanashi, Japan

Osaka Gastrointestinal Cancer Chemotherapy Study Group

Background

- TS-1/CDDP combination therapy is a standard regimen for patients (pts) with advanced gastric cancer (AGC) in Japan[1)].
- The docetaxel, cisplatin, and fluorouracil (DCF) regimen demonstrated a survival advantage over the cisplatin and fluorouracil (CF) regimen [2)], however, the increased of severe adverse events such as febrile neutropenia (9%) and the inconvenience of continuous intravenous infusion limit the use of this regimen.
- Phase I/II study of DTX/CDDP/TS-1 (DCS) [3~5)] and phase I/II study of PTX/CDDP/TS-1 (PCS) [6,7)] combination therapy in Japan showed favorable efficacy and feasibility, however, these regimens require hospitalization.
- On the basis of these results, we planned a phase I study to evaluate a triplet regimen adding paclitaxel (PTX) to TS1/CDDP combination therapy on an outpatient basis with AGC.

Objective

To determine the maximum tolerated dose (MTD) and the recommended dose (RD) of PTX/TS-1/CDDP combination therapy on an outpatient basis with AGC

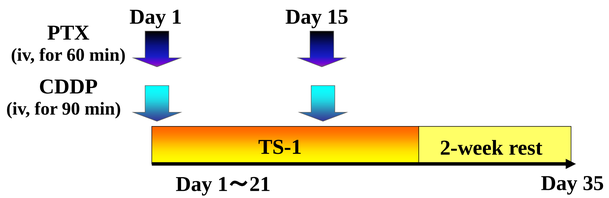
Inclusion criteria

(1) Histologically confirmed gastric cancer
(2) At least one evaluable lesion
(3) No previous chemotherapy and radiotherapy for advanced or recurrent cancer
(4) Age：20-75
(5) Performance status (ECOG)： 0-1
(6) Life expectancy ≥ 3 months
(7) Adequate organ function
　i） WBC：4000-12000/mm3　ii） Neu：≥ 2000/mm3　iii） Hemoglobin：≥ 8.0g/dL
　iv） PLT：≥ 10x104/mm3　v） T.B：≤1.5mg/dL　vi）GOT･GPT：＜100IU/L
　vii） Creatinine：≤ 1. 2mg/dL　viii） Ccr：≥ 60mL/min
(8) Tolerance of oral feeding (oral administration)
(9) Written informed consent

Exclusion criteria

(1) Gastrointestinal active bleeding
(2) Unable to intake anticancer drug because of gastrointestinal stenosis
(3) Experience of severe drug hypersensitivity
(4) Massive ascites or pleural effusion that needs treatment
(5) Severe medical conditions
(6) Liver cirrhosis and icterus
(7) Mental disorder that needs treatment with antipsychotic drug
(8) Symptom of brain metastasis
(9) Other concurrent active malignancy
(10) Pregnant woman, breast-feeding woman, possibility or the will to be pregnant
(11) Judged to be ineligible according to the attending physician

Treatment schedule of PTX/TS- 1/CDDP



Dosage and number of patients

Level	TS-1 (mg/m²/day)	CDDP (mg/m²)	PTX (mg/m²)
0	80	30	40
1	80	30	50
2	80	30	60
3	80	30	70
4	80	30	80

Dose escalation schedule

Number of DLT	Schedule
0/3cases	Progress to next dose level
1/3cases	Addition of up to 3 pts. at the same dose level
≥2/3cases	Defined as the MTD, no more patients are added
1/6cases	Progress to next dose level
≥2/6cases	Defined as the MTD, no more patients are added

Definitions of dose limiting toxicity (DLT)

- DLTs are defined according to NCI-CTCAE version 3.0 and included the following：

(1) Grade 4 leukopenia or neutropenia
(2) Grade 3 or 4 neutropenia lasting for 4 days or more with fever (body temperature ≥ 38℃)
(3) Grade 4 thrombocytopenia
(4) Grade 3 or 4 non-hematological toxicity (except for nausea and vomiting)
(5) Cannot administrate CDDP and PTX of day15 to day22 as a result of adverse events
(6) Cannot administrate TS-1 for 7 days or more as a result of adverse events
(7) Treatment delay of 7 days or more as a result of adverse events

Determination of recommened dose (RD)

(1) DLTs are assessed during the first course of treatment
(2) RD is set as one dosage level below the MTD
(3) RD is reviewed by the protocol committee unless MTD is achieved at level 4

Patients characteristics

Gender	Male/Female	13/5
Age (years)	Median /Range	61/34-74
PS	0/1	13/5
Histology	Intestinal/Diffuse	7/11
Metastatic sites	LN/Peritoneum/Liver/Other	15/6/5/2

Adverse events

Adverse events	50mg/m² PTX n=3				60mg/m² PTX n=3				70mg/m² PTX n=6				80mg/m² PTX n=6			
	G1	G2	G3	G4	G1	G2	G3	G4	G1	G2	G3	G4	G1	G2	G3	G4
Leukocytopenia	1	2			1				2	2	2			3	1	
Neutropenia	1	1	1		1					1	2	1(DLT)		1	2	
Anemia	2		1		2				1	4			3	1	1	
Thrombocytopenia	1				1				1				2			
Febrile neutropenia											1(DLT)				1(DLT)	
AST/ALT elevation					1				3							
Hypoalbuminemia	1				1				2	1				1	1	
Hypokalemia									1							
Hyponatremia									4							
Anorexia	1	2			1	2			3					3		
Nausea	1		1						1				1	1		
Vomiting	1	1			2	1			1				1			
Diarrhea	1	1							1				1			
Fatigue		2				2								1	1	
Alopecia	1				1								1			
Allergic reaction									3							
Sensory neuropathy	2								1							
Stomatitis	1															
Fever																
Rash									1							

Summary of DLT

Level	PTX (mg/m²)	Number of DLT
1	50	0/3 cases
2	60	0/3 cases
3	70	1/6 cases (G3 Febrile neutropenia, G4 Neutropenia)
4	80	1/6 cases (G3 Febrile neutropenia)

MTD was not achieved at level 4, however, grade 3 of hyponatremia and hypokalemia in 2 of 6 pts. occurred during the second treatment course at level 4. Accordingly, the protocol committee defined level 4 as the MTD, and determined level 3 as the RD.

Response (RECIST)

Dose level	Assessable patients	Response				Response Rate (%)	Disease control rate (%)
		CR	PR	SD	PD		
1	3	0	2	1	0	66.7	100
2	2	0	1	1	0	50	100
3	4	0	3	1	0	75	100
4	5	0	1	4	0	20	100
total	14	0	7	7	0	50	100

Conclusion

- The RD of PTX/TS1/CDDP combination therapy on an outpatient basis with AGC was PTX 70mg/m² and CDDP 30mg/m² on day 1,15 and TS-1 80mg/m² on days 1-21 of every 35-day cycle.
- This regimen is feasible with a favorable toxicity profile.
- Multicenter phase II study at the RD obtained in this study is ongoing.

References

1) Koizumi W, Narahara H, Hara T, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 2008; 9: 215-221
2) Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 study group. J Clin Oncol 2006; 24:4991-4997
3) Takayama T, Sato Y, Sagawa T, et al. Phase I study of S-1, docetaxel and cisplatin combination chemotherapy in patients with unresectable metastatic gastric cancer. British Journal of Cancer 2007; 97:851-856
4) Nakayama N, Koizumi W, Sasaki T, et al. Phase II study of combination therapy with docetaxel, cisplatin, and S-1(DCS) for advanced gastric cancer: (KDOG 0601). J Clin Oncol 2009; 27:15s (suppl; abstr 4555)
5) Sato Y, Takayama T, Sagawa T, et al. Phase II study of S-1, docetaxel and cisplatin combination chemotherapy in patients with unresectable metastatic gastric cancer. Cancer Chemother Pharmacol. 2009 Dec 30.
6) Iwase H, Shimada M, Tsuzuki T, et al. A phase I study of S-1 administration and a 24-h infusion of cisplatin plus paclitaxel in patients with advanced gastric cancer. Anticancer research 2006; 26:1605-1610
7) Iwase H, Tsuzuki T, Shimada M, et al. Multicenter phase II study of triple combination with S-1 and cisplatin (CDDP) plus paclitaxel (TXL) in patients with advanced gastric cancer. J Clin Oncol 2008; 26:15s, (suppl; abstr 4539)