Phase II study of weekly paclitaxel as third-line chemotherapy for advanced or recurrent gastric cancer : OGSG0602

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Background 1

- The median survival time (MST) was longer than 1 year in randomized phase III studies for advanced or recurrent gastric cancer (GC) conducted in Japan.
- In Japanese phase III trial (SPIRITS trial) of first-line chemotherapy by S-1 with cisplatin, the MST and the progression free survival (PFS) showed 13.0 and 6.0 months.
- Although the PFS of first-line chemotherapy has improved, many patients receive for second-line or later therapies with new agents such as paclitaxel or docetaxel after first-line treatment. It may contribute greatly to prolong overall survival.

Objective

This study evaluated the efficacy and safety of weekly paclitaxel as third line chemotherapy in patients with S-1- and CPT-11-Refractory GC.

Conclusion

- A weekly regimen of paclitaxel was well tolerated and achieved a good disease control rate, and acceptable TTF relatively for advanced or recurrent GC.

Background 2

- Recently, the randomized phase III trial as second-line chemotherapy in patients with refractory GC was reported in annual meeting of ASCO 2009, CPT-11 showed superior than best supportive care for MST.
- In OGSG0504 trial, CPT-11 with cisplatin as second-line chemotherapy in patients with S-1-refractory GC showed 28.6% for RR, 71.4% for DCR, 5.5 months for PFS, 14.6 months for MST.
- However, there isn't any trial as third-line chemotherapy in patients with refractory GC except case study.

Methods

patients with S-1-, CPT-11-Refractory GC
PS 0-2
↓
Registration
↓
Paclitaxel: 80mg/m^2 day 1, 8, 15, q4wks

Primary Endpoint : feasibility
Secondary Endpoint : safety
overall survival
progression free survival

Treatment Schedule

	1	8	15	22
Plan A : Paclitaxel(80 mg/m^2)	↓	↓	↓	
Plan B : Paclitaxel(80 mg/m^2)	↓	↓		
Plan C : Paclitaxel(80 mg/m^2)	↓		↓	

The standard treatment schedule is day1, 8 and 15 of a cycle for 4 weeks like the plan A, if possible.
It is feasible to skip only once like the plan B or C.

Statistical plan and analysis

● Primary Endpoint:
Feasibility (The treatment schedule is day1, 8 and 15 of a cycle for 4 weeks, if possible. It is feasible to skip only once.)

● Secondary Endpoints:
1. Safety : adverse events (percentage and grade)
2. Overall survival (OS)
3. Progression free survival (PFS)
4. Time to treatment failure (TTF)
5. Relative dose intensity (RDI)

The criteria for eligibility

1. histologically proven advanced or recurrent GC
2. had received with prior two regimens including S-1 and irinotecan, excluding paclitaxel and docetaxel
3. age >20
4. ECOG performance status (PS) 0-2
5. adequate organ function

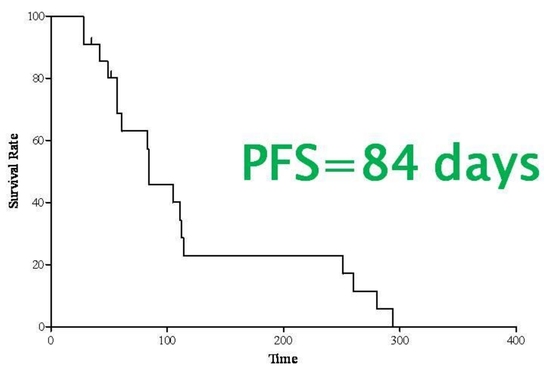
Leukocyte	≥3,000/mm^3
Neutrophil	≥1,500/mm^3
platelet	≥100,000/mm^3
Hb	≥8.0g/dL
AST、ALT	Within normal limit x 2.5
Total Bilirubin	≤1.5mg/dL
creatinine	≤1.5mg/dL
Electrocardiogram	Within normal limit

6. informed consent received
7. advisable having measurable lesion

Baseline characteristics of the patients

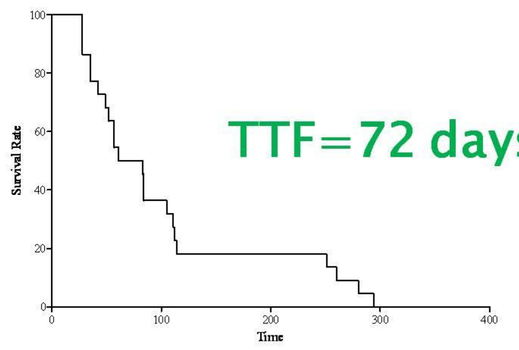
➢Age (median)	54-82(65)	➢1st-line regimen	
➢Gender (M / F)	18 / 4	S-1	16
		S-1+CDDP	2
➢PS (0/1/2)	3 / 18 / 1	S-1+CPT-11	1
		S-1+L-OHP	1
➢Primary tumor site (present / absent)	12 / 10	5-FU+CDDP	1
➢no. of metastatic site (1/2/3)	15 / 5 / 2	➢2nd-line regimen	
		CPT-11	12
➢Histological type		CPT-11+CDDP	5
pap	1	CPT-11+S-1	3
tub	12	CPT-11+MMC	2
sig	1		
por	8		

Progression free survival



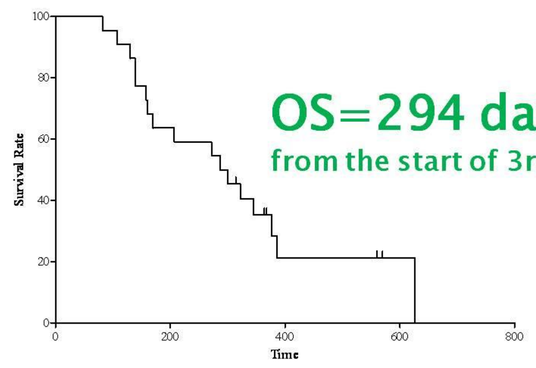
PFS=84 days

Time to Progression



TTF=72 days

Overall survival



OS=294 days
from the start of 3rd line

Response

n	22
CR	0
PR	3
SD	14
PD	3
NE	2

RR(response rate)=14%

DCR(disease control rate)
PR+SD=77%

percentage of Adverse Events

	Gr.1	Gr.2	Gr.3	Gr.4	≥Gr.3(%)
Leukopenia	5	23	5	0	5
Neutropenia	23	23	18	0	18
Thrombocytopenia	0	0	0	0	0
Hb	23	36	14	0	14
Nausea	32	14	5	-	5
Vomiting	9	14	5	0	5
Appetite loss	36	14	9	0	9
Diarrhea	27	5	0	0	0
Febrile neutropenia	-	-	5	0	5
General fatigue	41	23	5	0	5

No death within 30 days from last chemotherapy

CTCAE ver.3

Other reports of 2nd line

	n	regimen	RR	MST(M)	
CPT-11 base					
Boku	15	CPT-11+CDDP	27%		JCO 1999
Ajani	32	CPT-11+CDDP	31%	5.0	Oncology 2002
Hizuka	12	CPT-11+PTX	33%		JASMO 2003
Hamaguchi	45	CPT-11+MMC	29%	10.2	ASCO 2004
Kim	64	CPT-11+5-FU/LV	21%	9.1	ESMO 2004
Taxane系					
Arai	35	PTX	23%	6.9	ASCO 2003
Park	43	DTX+CDDP	17%	5.8	Am JCO 2004
Jo	154	DTX	14%	7.2	Jpn JCO 2007

Phase II study of weekly paclitaxel as thirrd line chemotherapy for advanced or recurrent gastric cancer. (OGSG0602)

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Background： The median survival time was longer than 1 year in randomized phase III studies for advanced or recurrent gastric cancer (GC) recently conducted in Japan. Although progression free survival of first-line chemotherapy has improved, many patients receive for second-line or later therapies with new agents such as paclitaxel or docetaxel after first-line treatment. It may contribute greatly to prolong overall survival. This study evaluated the efficacy and safety of weekly paclitaxel as thirrd line chemotherapy in patients with advanced or recurrent GC.

Material and methods： The criteria for eligibility were histologically proven advanced or recurrent GC, had given with prior two regimens including S-1 and irinotecan, age ≥20, performance status(PS) 0-2, adequate organ function, and informed consent received paclitaxel 80mg/m2 on day1, 8 and 15 of a cycle for 4 weeks until progression. Primary endpoint is feasibility and secondary endpoints are safety, overall survival, progression free survival (PFS), time to treatment failure (TTF) and relative dose intensity in this study.

Results： A total of 22 patients, 18 males and 4 females with a median age of 60 years old(54-82), 2/19/1 in PS 0/1/2 were enrolled between Dec. 2006 and Sep. 2008. All patients had received first line chemotherapy including S-1 and second line including irinotecan. Patients received median of 4 (range 1-12) cycles of treatment. Reasons for discontinuation were progression in 18 and withdrawal in 4. Grade 3 adversed events included neutropenia in 3(14 %), anemia in 1(4%), appetite loss in 1(4%). Overall response rate was 14%, disease control(PR+SD) rate was 77%, median TTF was 79 days, median PFS was 78 days, median overall survival don't reach.

Conclusions： A weekly regimen of paclitaxel was well tolerated and achieved a good disease control rate, and acceptable TTF relatively for advanced or recurrent GC. Although follow-up is ongoing on survival.