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Phase I/II study of weekly Taxol (TXL) plus CPT-11 for patients with advanced or recurrent gastric cancer (AGC/RGC)

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Abstract

Background: A new combination chemotherapy with weekly TXL and CPT-11 for patients with AGC/RGC was investigated in a multicenter phase I/II study.
Methods：Eligibility criteria included the following; pathologically confirmed AGC/RGC, measurable lesions, with or without prior therapy, 20 to 75 years old, PS0-1, normal organ functions and written IC. TXL was administrated on days 1 and 8 and the dose was escalated by 10 mg/m^2 from the starting dose of 50 mg/m^2 in the phase I study. CPT-11 was administered in the same manner. The doses of these drugs were alternately escalated by 10 mg/m^2. A single course lasted for 3 weeks.

Results: During the phase I study, which was conducted from 1/2002 to 2/2003, 1 out of 6 patients developed DLT in step I and 3 out of 5 patients did so in step II. The recommended doses were therefore determined to be 50 mg/m^2 (TXL) and 50 mg/m^2 (CPT-11), i.e., the doses for step 1. A total of 21 patients were registered for the phase II study from 2/2004 to 5/2005 and 27 patients who satisfied the entry criteria were enrolled in the phase II study. The 27 patients characterics were as follows; median age 64 (53to74), M/F 21/6, histological type differentiated/undifferentiated 16/11, absence/presence of prior chemotherapy 17/10. The patients received an average of 4.37 courses (1－19) of chemotherapy. As adverse events, hematological toxicity of grade 3 or worse was observed in 9 patients (33.3%) (leucopenia:14.8%, anemia:14.8%) and non-hematological toxicity was seen in 1 patients (7.4%). These adverse events were all tolerable and treatable. Efficacy was assessed by RECIST criteria: 2 patients achieved CR, 6 achieved PR, 11 showed SD, 6 had PD. and 2 showed NE. The response rate was 29.6 % and the MST was 417 days. The response rate to the combination as initial treatment was 35.3 % and that as 2nd -line therapy was 20 %.

Conclusion: This new combination chemotherapy is considered useful for AGC/RGC because adverse reactions are mild and the response rate is 29.6%. Moreover, it is helpful for improving QOL as one of the modalities for treatment of AGC/RGC because of the ease of its use on an outpatient basis for patients who cannot take oral antineoplastic agents and those who are refractory to other forms of chemotherapy

Introduction

Mortality due to gastric cancer in Japan has recently been decreasing because of an improvement in early diagnosis and a decrease in the incidence of this cancer. However, it still remains a common malignancy. Whether chemotherapy can extend the survival of patients with unresectable advanced gastric cancer/recurrent gastric cancer is unknown, but the results of a number of studies making a comparison with best supportive care have indicated that chemotherapy is effective for the extending the survival of patients with AGC/RGC.

TXL (paclitaxel) was developed by Bristol-Myers Squibb and is an anticancer drug with a new chemical structure derived from 10-deacetyl baccatin III, a precursor without cytotoxicity that is extracted from the needles and twigs of Taxus baccata.

After TXL was approved in the USA, it was originally administered as a 24-hour infusion. However, this administration method restricted the activities of patients and caused various clinical problems, so a three-hour infusion method was subsequently developed. Studies were then conducted in various countries to reduce the infusion time from three hours to one hour, and the safety of a one-hour infusion method has been confirmed. Studies on weekly administration have also been conducted, and the one-hour infusion method and weekly administration method have come to be widely used for chemotherapy of outpatients. Premedication to prevent hypersensitivity to TXL is usually done at 12-14 hours before administration of the drug, but a new method of premedication 30 minutes before TXL administration has also been approved.

CPT-11 (irinotecan HCl) was developed by Yakult Honsha Co., Ltd. in 1983 as an anticancer drug with a new mechanism of action: topoisomerase I inhibition. It was synthesized from camptothecin, an alkaloid found in plants such as Camptotheca acuminata originating from China. Irinotecan is a prodrug that is converted to its active metabolite (SN-38) by carboxyesterase in the liver.

In a Phase II clinical study, Boku *et al.* treated metastatic gastric cancer with a combination of CPT-11 (70 mg/m^2, days 1 and 15) plus CDDP (80 mg/m^2, day 1), and they obtained good results (a response rate of 48% (21/44) and a median survival time of 309 days). The Osaka Gastrointestinal Chemotherapy Study Group (OGSG) also confirmed in its OGSG0001 study that the combination of CPT-11 and CDDP achieved high response rates.

Combination therapy with TXL and CPT-11 for gastric cancer has not been studied, although it has been assessed for other cancers. Asai *et al.* conducted a Phase I clinical study in lung cancer patients using a fixed TXL dose and escalating CPT-11 dose. They reported that TXL at 135 mg/m^2 (day 8) plus CPT-11 at 60 mg/m^2 (days 1 and 8) every 3 weeks were the maximum tolerance doses (MTD), with a response rate of 38.5% when G-CSF was not administered. They also reported that concomitant TXL administration caused the AUCs of CPT-11 and SN-38 to increase significantly.

It was also confirmed by this study that there were no differences in the pharmacokinetics of CPT-11 and SN-38, even when the order of administration of TXL and CPT-11 was changed. In another study of small-cell lung cancer, the recommended weekly doses of TXL and CPT-11 were 50 mg/m^2 and 60 mg/m^2, respectively.

Taking into consideration the fact that TXL and CPT-11 have different mechanisms of action, that the response rates of advanced gastric cancer achieved with TXL and CPT-11 were both approximately 20%, and that combination therapy with the two drugs achieved good results for other cancers, we have planned Phases I and II clinical studies in order to investigate the optimum doses of these drugs for combination therapy.

Aim

The studies will be conducted in patients with advanced/recurrent gastric cancer. A Phase I clinical study will be conducted in order to investigate the efficacy and safety of combination therapy with TXL and CPT-11 and to estimate their optimum doses for this regimen, while a Phase II clinical study (open study) will be conducted in order to investigate the efficacy and safety of combination therapy based on the doses obtained in the Phase I clinical study.

Method

Eligibility criteria

- histologically gastric carcinoma(AGC/RGC)
- clinically measurable or evaluable disease
- any prior therapies were accepted
  exclude of treatments within 4weeks
- age : 20< , <75
- Performance status : 0-1 (JSCO)
- life expectancy > 12 weeks
- without high disorder of many organs
  WBC:4000< , <12000 Cre:<1.5 etc.
- Informed consent

Treatment regimen

			1st course			2nd course	
		day	1	8		22	29
TXL	X mg/m^2	div/60-90min	↓	↓		↓	↓
CPT-11	Y mg/m^2	div/60-90min	↓	↓		↓	↓

phase I : 1 more course

phase II : 2 more course

phase I study

	TXL	CPT-11	
level 1	50	50	mg/m^2
level 2	**60**	**50**	
level 3	60	60	
level 4	70	60	

*Definitions of DLT

Grade 4 leucopenia , neutropenia , thrombocytopenia

Grade 3 non-hematologic toxicity except nausea and vomiting

Administration of course 1 was skipped due to adverse effects

Administration on day 1 of course 2 was delayed due to adverse effects.

* Schedule for dose levels

1) Administration to 3 patients at the same dose level
2) Occurence of dose-limiting toxicity (DLT) by the scheduled date (day 22) for starting course 2 is assessed.
Whether or not to proceed to the next dose level is determined according to the following criteria.

Criteria for proceeding to the next dose level

Schedule for dose levels

Numbers of DLT	Schedule
0 / 3 case	Progress to next dose level
1 / 3 case	Addition of upto 3pts at the same dose
≧ 2 case	No more patients are added

Recommended dose assumed under one level of MTD.

Result

phase I study

All registerd patients n=11

	TXL	CPT-11	
Level 1 (3+3pt.)	**50**	**50**	**mg/m^2**
Level 2 (3+2pt.)	**60**	**50**	

Day 1.8 d.i.v.

Appearance of DLT

	primary	addition	total
Level 1 (6pt.)	**1/3**	**0/3**	**1/6**
Level 2 (5pt.)	**1/3**	**2/2**	**3/5**

Accordingly, Level 1 was defined as recommended dose.

phase II study

*Treatment regimen

			1st course		2nd course	
day			1	8	22	29
TXL	50mg/m²	div/60-90min	↓	↓	↓	↓
CPT-11	50 mg/m²	div/60-90min	↓	↓	↓	↓

phase II : 2 more course

*characteristics of patients n=27

male/female		21/6
median age		64 y.o. (53-74)
PS	0	16
	1	11
primary/recurrent		15/12
histology		
diff./undiff.		16/11
site of disease		
stomach		15
liver		9
lymphnode		23
prior chemotherapy		
no/yes		17/10

***cycles of treatments**

N=27

1 course	**:**	**4**
2	**:**	**5**
3	**:**	**3**
4	**:**	**7**
5 =<	**:**	**8**

Average : 4.37 course

***toxicity**

	NCI CTC			
	1-2	3	4	3+4 %
myelosuppression				
anemia	22	3	1	14.8%
leucopenia	14	4	0	14.8%
neutropenia	7	3	1	14.8%
thrombocytopenia	0	0	0	0%

	NCI CTC			
	1-2	3	4	3+4%
Digestive disorder				
diarrhea	5	1		3.7%
abdominal pain	2	1		3.7%
nausea/emessis	6	1		3.7%
appetite loss	11	1	1	7.4%
Others				
alopecia	11	0		0%
etc	1	0		0%

*Response Information on 27 patients

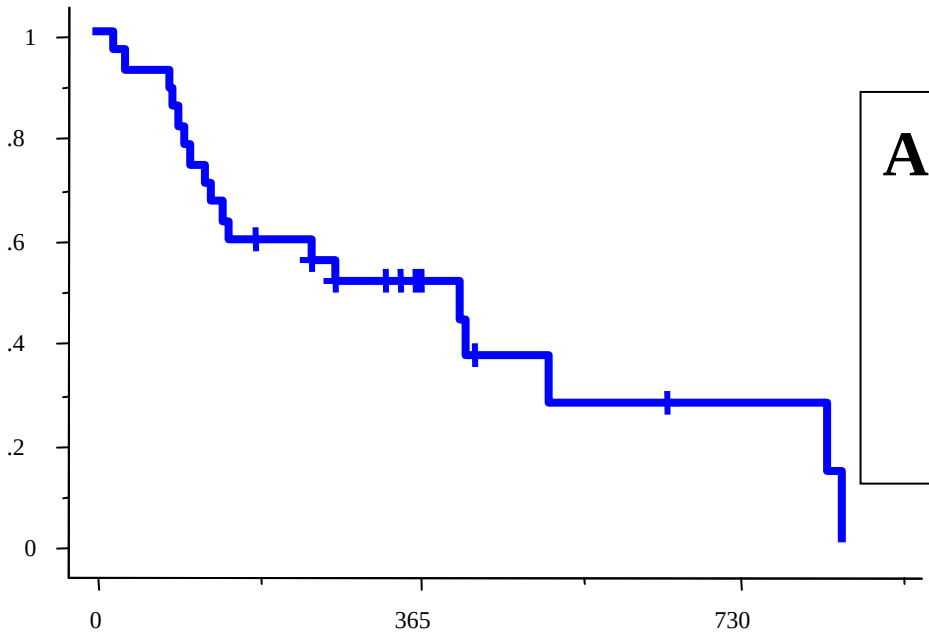
Assessable for objective response 25/27

CR	**2**
PR	**6**
SD	**11**
PD	**6**
NE	**2**

Overall response rate : 8/ 27 = 29.6 %

Survival time of all cases (27patients)

Follow up time : median 529days



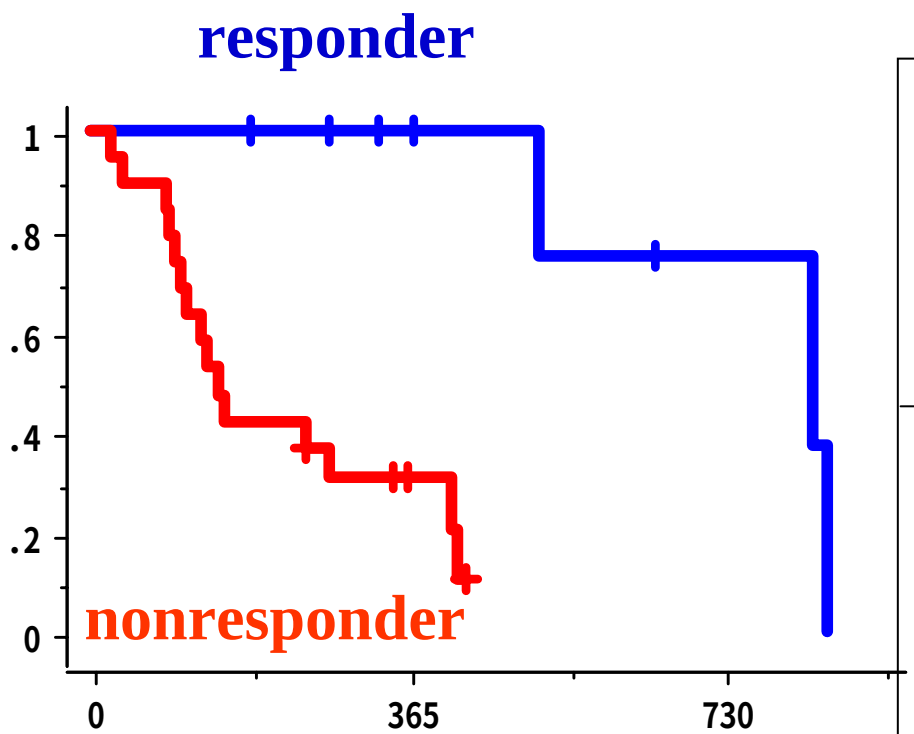
All 27 cases

1yr. surv.	51.1%
2yr.	27.4%
MST	417days

Kaplan-Meier method

Survival time : responder vs nonresponder

Follow up time : median 529days



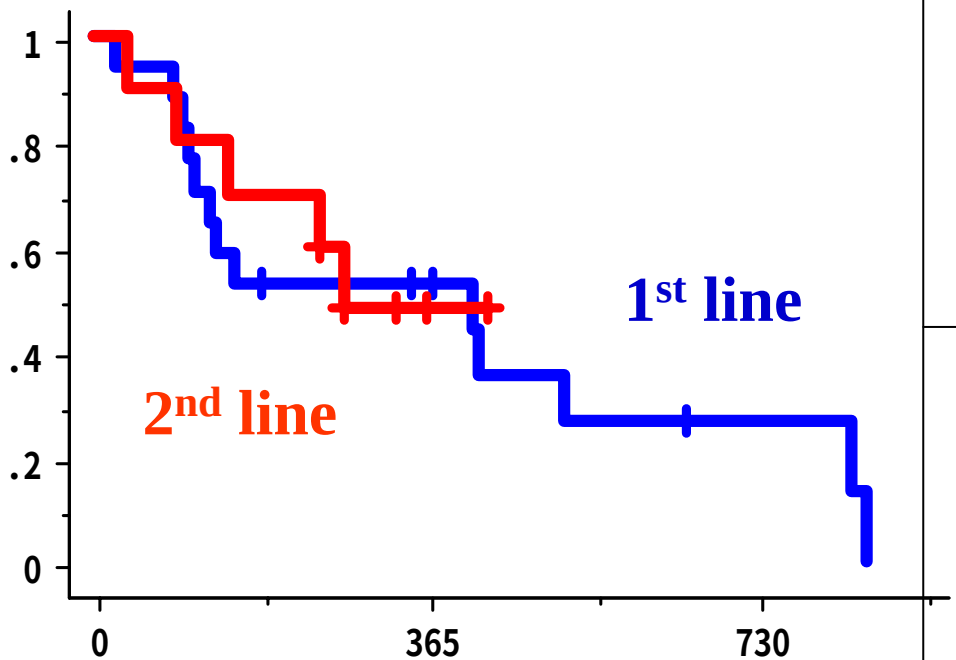
responder	**8 cases**
1yr. surv.	100%
2yr.	75%
MST	834days
nonresponder	**19 cases**
1yr. surv.	30.7%
2yr.	-
MST	149days

Kaplan-Meier method

Wilcoxon test: p=0.0007
Logrank test:p=0.0028

Survival time:
1st line vs 2nd line

Follow up time : median 529days



1st line 17 cases

response rate:	6/17=35.3%
1yr. surv.	52.9%
2yr.	26.5%
MST	417days

2nd line 10 cases

response rate:	2/10=20%
1yr. surv.	48%
2yr.	-
MST	276days

Kaplan-Meier method

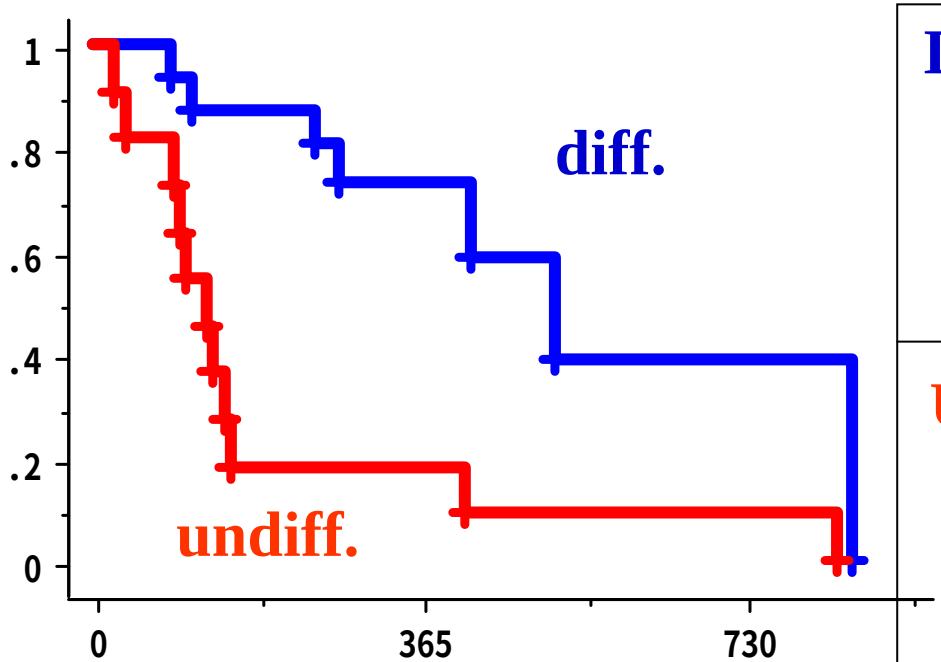
Wilcoxon test: p=0.81

Logrank test: p=0.76

Survival time: differentiated vs undiff.

(histological type)

Follow up time : median 529days



Diff. type 16 cases

1yr. surv.	73.4%
2yr.	39.2%
MST	517days

Undiff. type 11 cases

1yr. surv.	18.2%
2yr.	9.2%
MST	127days

Kaplan-Meier method

Wilcoxon test: p=0.0009

Logrank test: p=0.0008

Result / PhaseII

1) Chemotherapy with concomitant administration of CPT+TXL was performed in 27 patients with unresectable or recurrent gastric cancer and 25 of them were evaluable.

2) Neutropenia of grade 3 or 4 and anemia developed in 14.8% and 14.8% of the patients, respectively.

Three patients (11.1%) were rated grade 3 or 4, except for the patient with myelosuppression, and administration was safely performed in most patients.

3) The response rate was 29.6%, with 2 patients rated as CR, 6 patients as PR, 11 patients as SD, 6 patients as PD, and 2 patients as NE.

4) The MST of the 27 patients in the Phase II study was 417 days, while the 1-year and 2-year survival rate was 51.1% and 27.4%, respectively.

The 1-year and 2-year survival rates of the responding patients were 100% and 75%, respectively, whereas the 1-year survival rate of non-responding patients was only 30.7%.

conclusion

This new combination chemotherapy is considered useful for AGC/RGC because adverse reactions are mild , the response rate is 29.6% and MST is 417 days.

Moreover, it is helpful for improving QOL as one of the modalities for treatment of AGC/RGC because of the ease of its use on an outpatient basis for patients who cannot take oral antineoplastic agents and those who are refractory to other forms of chemotherapy.

This combination of second line is considered useful too, because the 1-year survival rate is 48% and MST is 276days.

With histological type it is more effective in differentiated type than undifferentiated type.