Phase II study of bi-weekly CPT-11+CDDP for patients with gastric cancer refractory to S-1 (OGSG 0504 study)

Osaka Gastrointestinal Cancer Chemotherapy Study Group

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Abstract

Background: Chemotherapy has been widely used against advanced gastric cancer (AGC), however, the best treatment has not been confirmed. In 2007, S-1 showed the potential to be the standard treatment for AGC and stage II/III gastric cancer (Narahara et al. 2007 ASCO Abst.4514, Sasako et al. 2007 ASCO-GI Abst.8). CPT-11 has many reports showing the effectiveness as 2nd line treatment, and the combination therapy of CPT-11+CDDP available for outpatients is promising (Koizumi et al, Anticancer Res. 25:1257-62, 2005). Therefore, we performed a phase II study to evaluate CPT-11+CDDP as 2nd line after S-1 single agent failure.

Methods: Eligible patients(pts) with histologically confirmed AGC, which was unresectable or metastatic became ineffective in S-1 as previous, an oral possible, an ECOG PS of 0-2, an age of 20-75 years and adequate organ functions. The following treatment, CPT-11 60 mg/m2+ CDDP 30 mg/m2 iv on day 1, was repeated every 2 weeks until disease progression or appearance of unacceptable toxicity. Primary endpoint was response rate. Main secondary endpoints included toxicity, overall survival and time to progression. Based on planned sample size of 35 pts, the trial was designed to have 80% power to detect an improvement in response rate from 20 to 25% (2-sided log-rank test; significance level 0.05).

Results: A total of 35 pts were enrolled in this trial between August 2005 and August 2007. The male/female was 30/5. The median age was 59 years (range 28-75 years). PS 0/1/2 was 21/10/4. All pts were evaluated for effectiveness and safety. In the intention-to-treat analysis, the overall response rate was 28.6%, including 4CR, 6PR, 15SD, 4PD,and 6NE. The most common grade 3/4 toxicities were: neutropenia(22.4%), anemia(11.4%), anorexia(14.3%), fatigue(8.6%),and diarrhea(2.9%). The median overall survival was 416days at present.

Conclusions: The combination treatment of CPT-11 and CDDP is feasible and effective. Accordingly, this regimen can be regarded as one of 2nd line standard treatment for gastric cancer.

Back ground

- The potential of chemotherapy in the treatment of advanced gastric cancer became clear in the 1990's, and phase**III**studies were conducted worldwide to determine the standard application.
- In Japan, combination therapy with S-1 was investigated to determine which combination offered the best efforts for the patients. S-1+CDDP combination therapy produced the best therapeutic in earlier studies, so this study investigated its potential as a standard treatment.
- In addition, the effectiveness of S-1 alone has been established in adjuvant chemotherapy for stage II/III gastric cancer .
- CPT-11 and Taxans are the preferred options in S-1 resistant patients. Of these, CPT-11 is widely used either alone or with CDDP in pretreated gastric cancer, and has shown promising results in several studies.
- A bi-weekly CPT-11+CDDP regimen designed for outpatients in particular, showed high effectiveness and low side effects.
- Accordingly, we performed a phase II study to evaluate the efficacy and safety of CPT-11 ＋CDDP combination therapy as a 2nd line of treatment in patients preaviously treated with S-1 alone.

Accrual

Opened	August 2005
Closed	August 2007
Number of patients	35
Number of the institutions	12

Objective and Endpoints

■ **Objective**

To evaluate the efficacy and safety of bi-weekly CPT-11＋CDDP combined therapy for the patients of S-1 resistant gastric cancer.

■ **Endpoints**

Primary:

Response

Secondary:

1. **Safety and adverse events**
2. **Overall survival(OS)**
3. **Progression-free survival（PFS)**
4. **Time to treatment failure(TTF)**
5. **Relative dose intensity（RDI)**

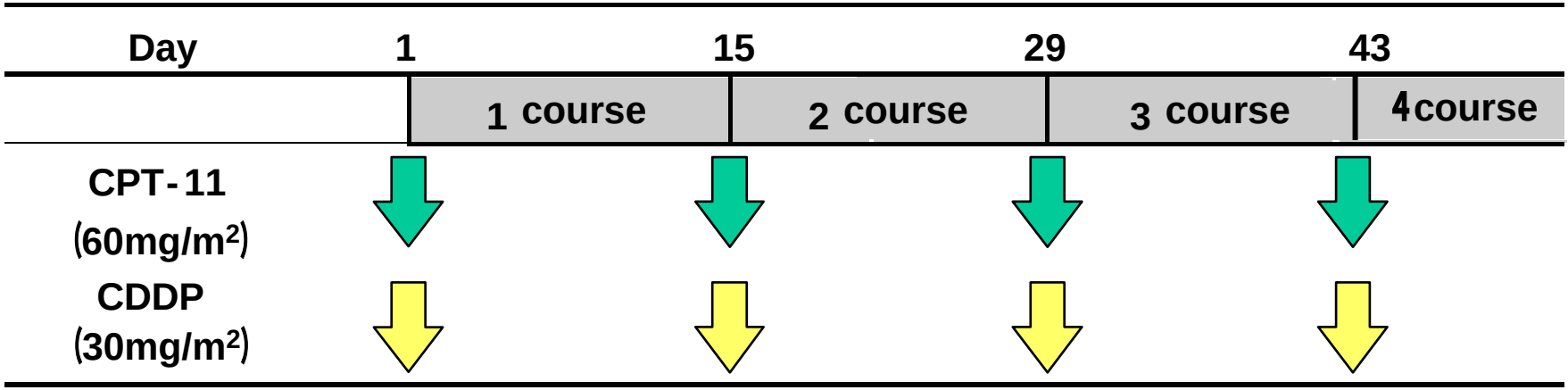
Eligibility criteria

1. Histologically or cytologically proven gastric cancer
2. S-1 resistant defined as:
   A. PD during course of after treatment with S-1 alone.
   B. Relapse within 26 weeks of treatment with S-1 alone as adjuvant chemotherapy.
3. Not treatment (chemotherapy, BRM, and radiotherapy) other than operation and S-1 alone.
4. Administered S-1 alone during 4 weeks or more in total and 4weeks or more after the S-1 alone administering ends.
5. Measurable lesions (RECIST).
6. Performance Status (ECOG scale): 0-2.
7. Age: 20- 75.
8. Life expectancy 3 months or more.
9. Adequate organ function (bone marrow, heart, lung, liver, kidney, etc.).

WBC	4,000 - 12,0000/mm3
Neu	2,500/mm3 or more
PLT	100,000/mm3 or more
Hb	8.0g/dl or more
T-Bil	1.5mg/dl or less
AST/ALT	2.5 UNL or less
Creatinine	1.5mg/dl or less
Ccr	60ml/min. or more

10. Written informed consent.

Treatment Schedule



The treatment above was repeated every 14 days.

CPT-11 was initially given over 90 min.

Safety was observed and, administration was continued for at least 4 courses or until PD.

Patient characteristics

Number of patients	35
Sex： Male/Female	29/6
Age：Median [Range]	59 [28 – 75]
PS(ECOG)： 0 / 1 / 2	21 / 10 / 4
Histology： tub / por / sig / others	16 / 14 / 3 / 2
Metastatic：Yes / No	31/4
Site ：Liver / Lymph / Peritoneum/others	11 / 18 / 8 / 3
Prior chemotherapy of S-1 alone	
PD /Adjuvant	32 / 3

Dosage situation

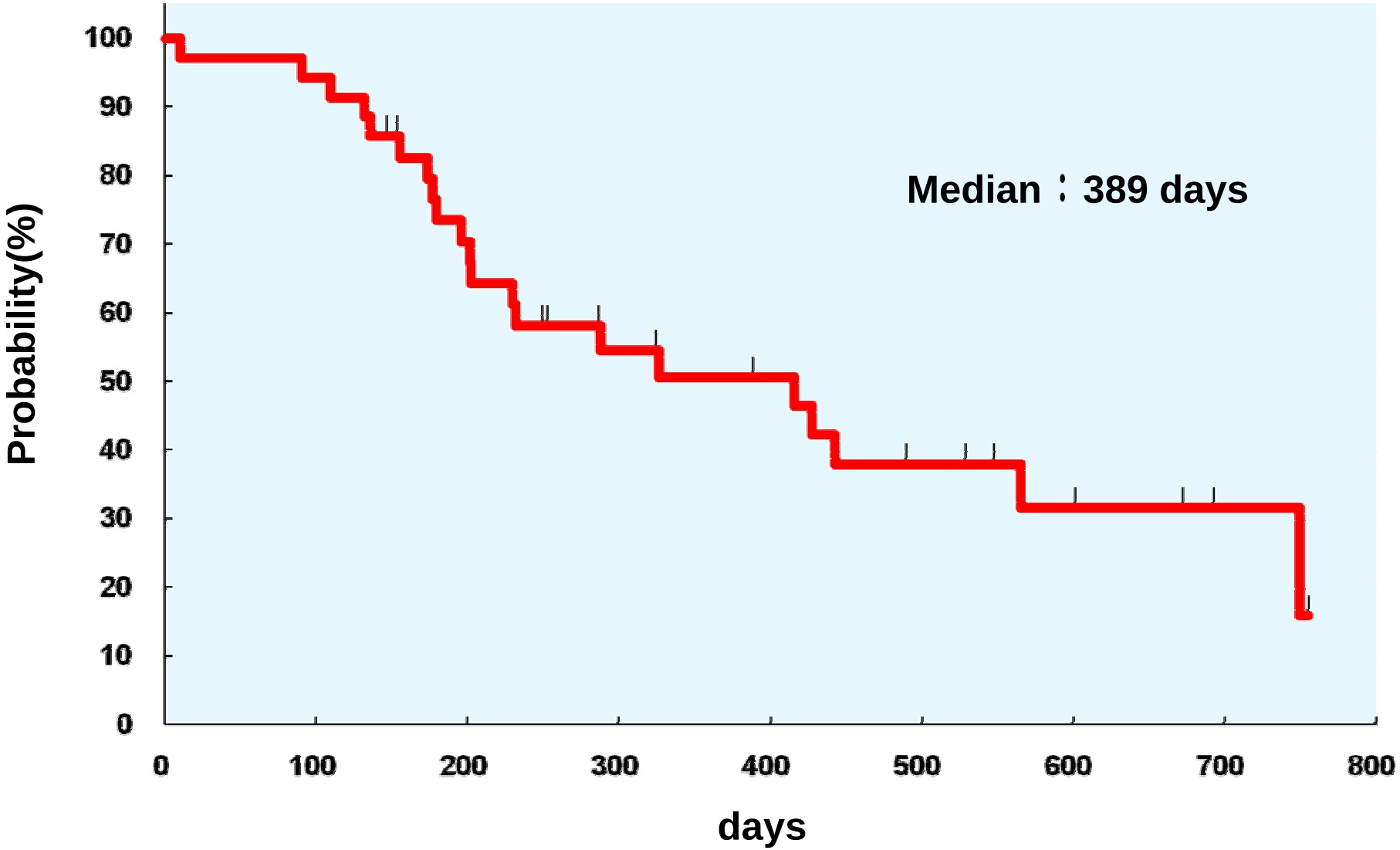
Number of Course	
—Overall	**305**
—Median [Range]	**8 [1～29]**
Dosage postponement	
—Course	**32.5% (99/305)**
Dosage reduction	
—Course	**5.9% (18/305)**
Relative Dose Intensity	**CPT-11 ： 74.0 %** **CDDP ： 75.3 %**

Response

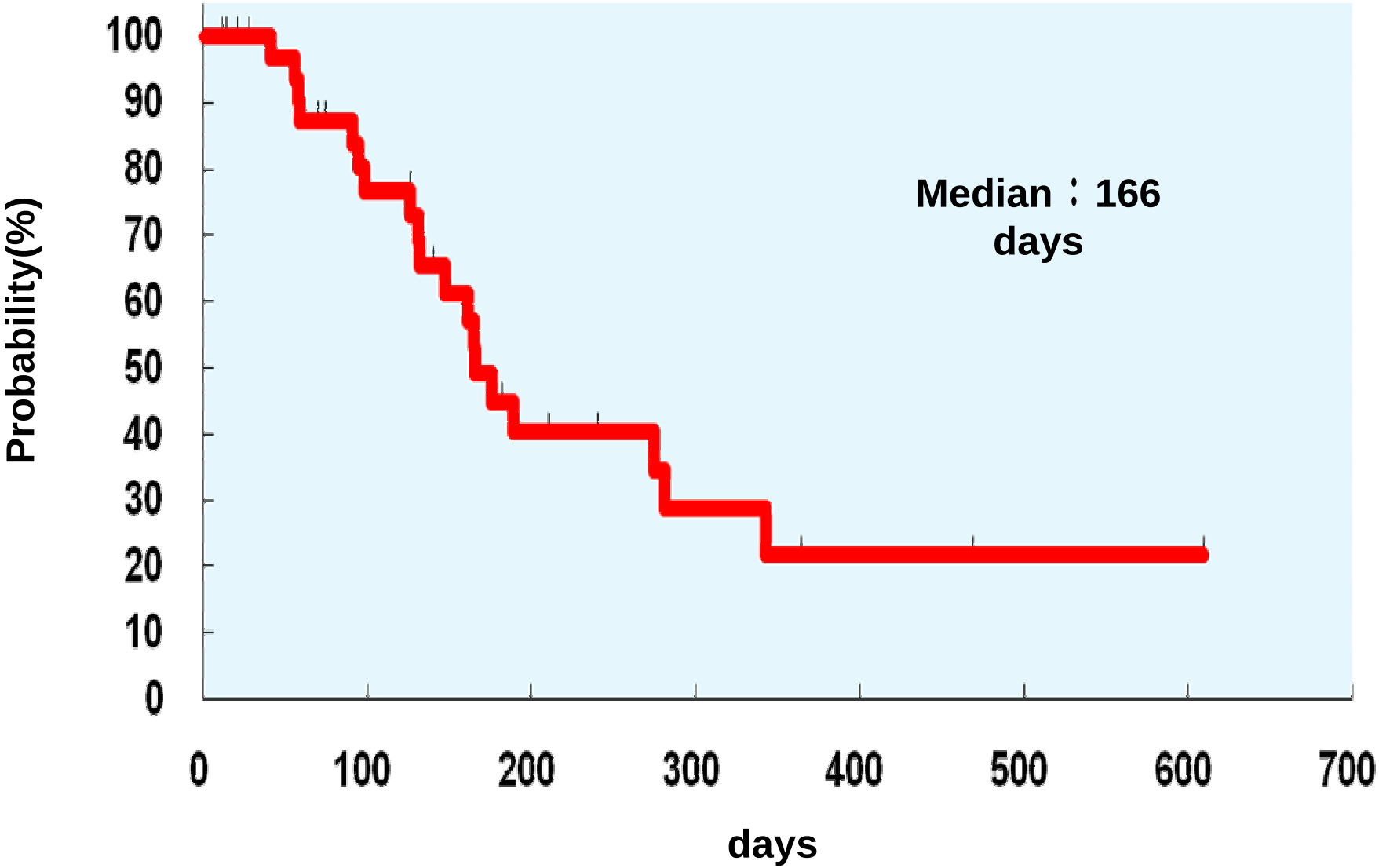
CR	PR	SD	PD	NE	Total	Response rate
4	6	15	4	6	35	28.6% (95%CI 14.65-46.30%)

Tumor control rate (SD or more) = 71.4% (25/35)

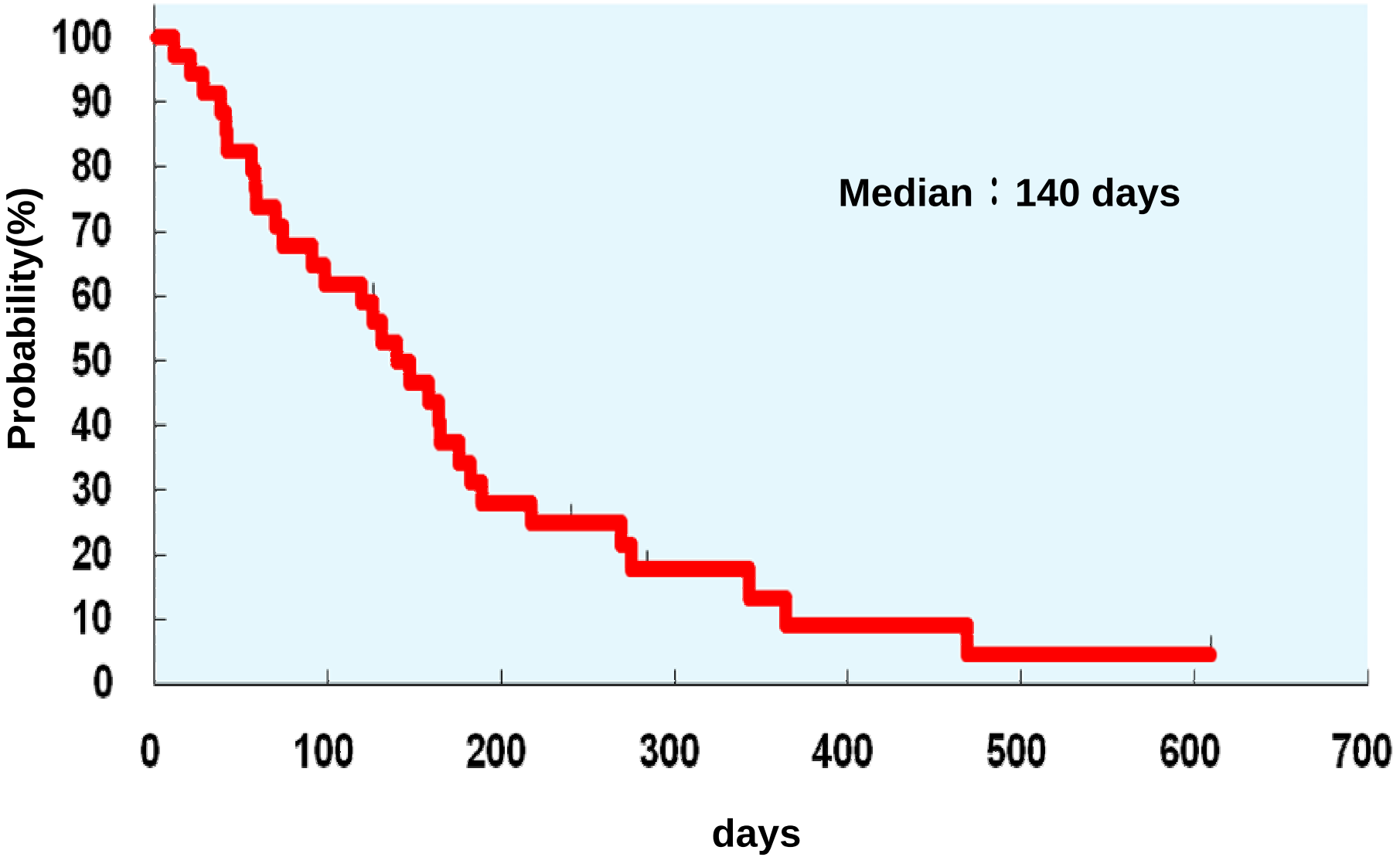
Overall Survival



Progression free survival



Time to treatment failure



Adverse events

N=35	Grade 1	2	3	4	≧G3
Hematorogic					
Anemia	22.9	40.0	11.4	0.0	11.4
Leukocytes	17.1	31.4	5.7	2.9	8.6
Neutrophils	17.1	20.0	22.9	0.0	22.9
Platelets	14.3	0.0	0.0	2.9	2.9
Non-Hematorogic					
Diarrhea	28.6	11.4	2.9	0.0	2.9
Stomachache	14.3	0.0	0.0	2.9	2.9
Anorexia	31.4	20.0	14.3	0.0	14.3
Nausea	37.1	8.6	8.6	0.0	8.6
Vomiting	17.1	8.6	5.7	0.0	5.7
Fatigue	28.6	22.9	8.6	0.0	8.6
Hair loss	14.3	8.6	-	-	-

Discussion

Comparison of effectiveness and side effects in phase III studies on S-1 for untreated gastric cancer

	CPT-11/ CDDP (OGSG)	CPT-11/ CDDP (JCOG)	S-1/ CDDP (SPIRITS)	S-1/ CPT-11 (GC 03)	S-1 (JCOG)	S-1 (SPIRITS)	S-1 (GC 03)
RR (%)	28.6	38	54	41.5	28	31	26.9
PFS(M)	5.5	4.8	6.0	-	4.2	4.0	-
TTF(M)	4.7	3.7	4.8	4.5	4.0	3.9	3.6
OS (M)	12.8	12.3	13	12.8	11.4	11	10.5
Toxicity							
(≧G3)	8.6	41.5	12	12	0.9	2	3
WBC↓	22.9	65.0	40	27	5.6	11	11
Neu↓	11.4	39.3	26	16	12.8	4	12
Hb↓	2.9	9.0	4	16	7.7	3	6
Diarrhea	8.6	20.5	12	7	5.6	1	6
Nausea	14.3	32.9	30	17	12.4	6	19
Anorexia							

Discussion

Comparison of this and other CPT-11+CDDP bi-weekly regimens for pretreated gastric cancer.

Prior- chemotherapy	RR	Course Median	TTF (days)	MST (days)	Toxicity (G3 or more)	Source
S-1 35pts.	28.6% (10/35)	8 (4)	140	389	WBC 8.6% Neu 22.9% Hb 11.4% Diarrhea 2.9% Anorexia 14.3%	OGSG 0504
None 15pts.	53.3% (7/15)	3.5	–	302	WBC 27.5% Neu 40.0% Hb 30.0% Diarrhea 2.5%	Koizumi Anticancer Res. 25:1257-62,2005
CDDP,5FU 25pts.	20% (5/25)		–	274		
S-1 9pts. S-1＋CDDP20pts.	20.7% (6/29)	–	110	229	–	Sasaki Annual Meeting of the Japan Society of Clinical Oncology OS67-5, 2005
S-1、TAL 26pts.	23.1% (6/26)	3	96	299	WBC 7.7% Neu 11.5% Hb 7.7% Anorexia 3.8%	Yoshida Anticancer Res. 261:1595-98, 2006

Summary

1. Response rate in gastric cancer to CPT-11+CDDP chemotherapy following failure of treatment with S-1 alone was 28.6%, and tumor control rate was 71.4%.
2. MST was 389 days. Median PFS was 166 days. Both were relatively longer than in other reports, showing promising results.
3. Median number of courses was 8. Median TTF was 140 days.
4. Treatment period was also longer than in other PIII studies.
5. Main toxicities included neutropenia, leukopenia, anorexia, nausea and fatigue. However, level and frequency were generally low.

Conclusions

1. The combination treatment of bi-weekly CPT-11+CDDP as 2nd line following S-1 alone failure is feasible and effective.

2. This regimen can be regarded as one of 2nd line standard treatment for gastric cancer due to long continuance and outpatient basis.

Participating institutions

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