Weekly Paclitaxel as Second-line Chemotherapy in Japanese Patients with Advanced Gastric Cancer

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Abstract. *Aim: The use of weekly paclitaxel (wPTX) has become a common practice as second-line chemotherapy in Japanese patients with advanced gastric cancer. The aim of the present study was to assess the efficacy of wPTX. Patients and Methods: We retrospectively analyzed data from 229 patients with advanced gastric cancer who received wPTX as second-line chemotherapy between March 2001 and January 2011 at our hospital. Patients received PTX at a dose of 80 mg/m^2 on days 1, 8, 15 of a 28-day cycle. Response and survival were evaluated. Results: The overall response rate was 12.5% in 96 patients who had measurable lesions that were assessable for response. In 107 patients who had malignant ascites, the response rate for therapy of ascites was 38.3%. The median progression-free survival was 3.6 months, and the median overall survival was 6.3 months. Multivariate analysis revealed that the number of metastatic sites [hazard ratio (HR)=1.56, p=0.009], bone metastasis (HR=2.11, p=0.006), ascites (HR 1.75, p<0.001), and the presence of the primary lesion (HR=1.77, p<0.001) were independent prognostic factors of poor survival. Conclusion: wPTX is an effective regimen for advanced gastric cancer refractory to first-line chemotherapy.*

Despite a continuous decline in incidence, gastric cancer remains the second leading cause of cancer-related deaths worldwide, with an estimated 700,349 deaths annually (1). In Japan, gastric cancer is also the second leading cause of cancer-related deaths with 50,160 new cases in 2008, accounting for 15.3% of all cancer deaths. Although surgical resection is the only curative treatment, two-thirds of patients are usually diagnosed in the advanced or metastatic stage. Furthermore, 50% of patients experience a relapse after curative resection. Systemic chemotherapy aims to improve the survival time of patients with metastatic disease.

Combination therapy with fluoropyrimidine and cisplatin is considered the standard-of-care for the greater part of the world (2-5). In Japan, S-1, an oral fluoropyrimidine pro-drug, and cisplatin are considered the standard first-line chemotherapy (6, 7). Several phase II trials have been conducted on patients with gastric cancer in the second-line therapy setting (8-12). Recent phase III trials showed that addition of second-line chemotherapy to best supportive care (BSC) achieved significant and clinically meaningful improvement in overall survival (OS) for pre-treated patients with advanced gastric cancer (13, 14). The regimen used in those phase III trials was irinotecan or docetaxel. Weekly paclitaxel at a dose of 80 mg/m^2 has also been recognized as a second-line chemotherapy for gastric cancer and used as a control arm in phase III trials, leading to a response rate (RR) of 13-20% and an OS of 5-9 months, with modest toxicity (8, 15-17). In addition, paclitaxel has shown efficacy for gastric malignant ascites due to peritoneal carcinomatosis (10). In Japan, weekly paclitaxel has become common as second-line chemotherapy for patients with advanced gastric cancer.

We retrospectively assessed the efficacy of weekly paclitaxel as second-line chemotherapy in Japanese patients with advanced gastric cancer.

Patients and Methods

Patient eligibility. We retrospectively analyzed 229 patients with advanced gastric cancer who received weekly paclitaxel as second-line chemotherapy between March 2001 and January 2011 at the National Cancer Center Hospital, Tokyo. They all fulfilled the following criteria: confirmed advanced gastric cancer failing the first-line chemotherapy; prior treatments should not have included taxanes; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2; adequate baseline bone marrow, hepatic (serum bilirubin ≤2.0 mg/dl, serum alanine aminotransferase or aspartate aminotransferase twice the upper limit of normal or three times the

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Key Words: Gastric cancer, paclitaxel, second-line therapy.

upper limit of normal in the case of known liver metastasis) and renal (serum creatinine ≤2.0 mg/dl) functions.

Treatment dose and schedule. Paclitaxel at a dose of 80 mg/m^2 was administered as 90 min intravenous infusion on days 1, 8, and 15 of a 28-day cycle. This treatment was repeated until disease progression or unacceptable toxicity occurred.

Treatment evaluation. At baseline, medical history and physical examinations were reviewed from medical records. Tumor assessment was performed by computed tomographic (CT) scan according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 (18). Malignant ascites was also evaluated. We defined the amount of ascites by CT scan as none, low (ascites only on surface of the liver or pelvis), moderate (intermediate between low and massive) and massive (entire abdominal cavity involved). The ascites response was evaluated as follows: Complete response (CR) was defined as disappearance of ascites; partial response (PR) was defined as a decrease of ascites by one or more levels; incomplete response/stable disease (IR/SD) was defined as response other than CR, PR, or progressive disease (PD); and PD was defined as an increase of ascites by one or more levels, or need for more frequent drainage.

Statistical analysis. The median follow-up time was calculated by using the reverse Kaplan–Meier method. Survival curves were estimated according to the Kaplan–Meier method, and differences were evaluated with the log-rank test. The confidence intervals for median survival time were calculated by the Greenwood formula (19). Variables that achieved statistical significance ($p<0.05$) in univariate analysis were entered into multivariate Cox regression analysis to identify significant independent factors predicting survival. We also calculated the hazards ratio (HR) and 95% confidence intervals. All p-values of <0.05 by the two-tailed test were considered significant. All statistical analyses were performed with the use of IBM SPSS Statistics version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients' characteristics. Out of 229 patients, 21 patients were excluded for the following reasons: PS ≥3 in nine patients; liver dysfunction in nine patients; and renal dysfunction in three patients. A total of 208 patients were analyzed in this study.

Patients' characteristics are shown in Table I. In the majority (76.4%), the tumor histological type was diffuse. First-line chemotherapy was 5-fluorouracil (5-FU) alone (5-FU continuous infusion or S-1) in 95 patients, S-1 and cisplatin in 71, 5-FU and methotrexate in 27, and irinotecan-based chemotherapy in 15. A total of 112 patients (54%) had only non-measurable lesions such as bone metastases and peritoneal carcinomatosis.

Response and survival. We analyzed 96 patients who had measurable lesions (Table II). None achieved CR. An overall response rate of 12.5% was observed in 12 of these patients, and SD was documented in 37, so the disease control rate was 51%. A total of 107 patients who had malignant ascites at the start of weekly paclitaxel therapy were analyzed for ascites response (Table III). Ascites disappeared in 18 patients and decreased in 23, so that the response rate for therapy of ascites was 38.3%.

The median follow-up time was 26.9 (range=0.4-50.6) months. The median progression-free survival (PFS) was 3.6 months (Figure 1A) and the median OS was 6.3 months (Figure 1B). Including first-line chemotherapy, the total OS was 15.6 months.

Reasons for treatment discontinuation and subsequent treatment. Weekly paclitaxel was discontinued in a total of 200 patients: 182 patients had disease progression, 11 had

Table I. *Patients' characteristics (n=208).*

Category	No. of patients (%)
Gender	
Male	130 (62.5)
Female	78 (37.5)
Age (years)	
Mean	62.2
Median (range)	64 (31-82)
ECOG PS	
0-1	169 (81.3)
2	39 (18.8)
Histology	
Intestinal type	43 (20.7)
Diffuse type	159 (76.4)
Unknown	6 (2.9)
Disease status	
Recurrent	84 (40.4)
Advanced	124 (59.6)
Number of metastatic sites	
1	145 (69.7)
2	52 (25)
≥3	11 (5.3)
Peritoneum	144 (69.2)
Liver	37 (17.8)
Bone	18 (8.7)
Lung	13 (6.3)
First-line chemotherapy	
S-1 alone	95 (45.7)
S-1 + cisplatin	71 (34.1)
5-FU + methotrexate	27 (13.0)
Irinotecan + cisplatin	13 (6.3)
Irinotecan alone	2 (1.0)
Response to first-line chemotherapy	
CR	0
PR	38 (18.3)
SD	110 (52.9)
PD	60 (28.8)

ECOG: Eastern Cooperative Oncology Group; PS: performance status; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; 5-FU: 5-fluorouracil.

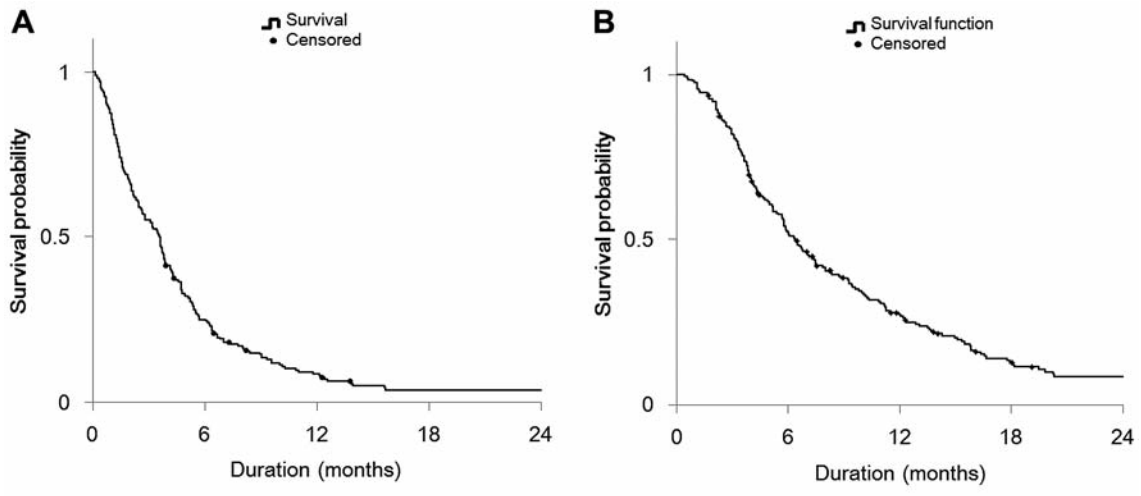

Figure 1. *Kaplan-Meier estimates for overall (A) and progression-free (B) survival.*

Table II. *Response rate and disease control rate.*

Best response	No. of patients (%)
Complete response	0
Partial response	12
Stable disease	37
Progressive disease	43
Not evaluated	4
Response rate	12.5% (95% CI=6.6 to 20.8%)
Disease control rate	51.0% (95% CI=40.1 to 61.4%)

Table III. *Efficacy for therapy of ascites.*

	Baseline amount of ascites			
Ascites	None (n=101)	Mild (n=52)	Moderate (n=17)	Massive (n=38)
Disappearance		9	9	7
Decrease		5	5	12
No change	97	21	21	11
Increase/appearance	4	17	17	8
Response rate	38.3% (41/107) (95% CI=29-48%)			
Disease control rate	71.0% (76/107) (95% CI=61-79%)			

unacceptable toxicity, five stopped therapy due to other disease, and two refused further treatment. The remaining eight patients are still being treated with weekly paclitaxel. Out of the 200 patients discontinuing weekly paclitaxel, 73 (36.5%) received third-line chemotherapy which was irinotecan-based in 43, S-1 alone in seven, S-1 and cisplatin in seven, 5-FU and methotrexate in six, docetaxel in seven, and other regimens in the remaining three.

Multivariate analysis for independent prognostic factors. We explored prognostic factors (Table IV). ECOG PS 2 (p=0.001), advanced disease (p=0.01), presence of the primary lesion (p<0.001), more than two metastatic lesions (p=0.001), bone metastasis (p=0.01), malignant ascites (p<0.001), and PFS of first-line chemotherapy of less than six months (p=0.02) were revealed to significantly reduce survival on univariate analysis.

Multivariate analysis was undertaken to identify pre-treatment variables that correlated with the prognosis. The multivariate analysis revealed that presence of the primary lesion (HR 1.77, p<0.001), more than two metastatic sites (HR=1.56, p=0.009), bone metastasis (HR=2.11, p=0.006), and malignant ascites (HR=1.75, p<0.001) were independent prognostic factors of poorer survival.

Discussion

This retrospective analysis demonstrates that weekly paclitaxel as second-line chemotherapy provided similar RR (12.5%) and OS (6.3 months) as did previous studies (8, 10, 15, 16).

To date, there is no evidence that second-line chemotherapy for advanced gastric cancer results in substantial prolongation of survival when compared with BSC. Empirically, a regimen that includes drugs that were not used in the first-line chemotherapy is selected as a

Table IV. *Analyses to detect independent prognostic factors*.

Variable	n	Survival (months)	Univariate *p*-value	Multivariate	
				HR (95% CI)	*p*-Value
Gender					
Male	130	6.3	0.35		
Female	78	6.5			
Age					
<65 years	108	7.1	0.36		
≥65 years	100	5.8			
ECOG PS					
0-1	169	7.1	0.001	1	0.29
2	39	3.8		1.24 (0.83-1.86)	
Disease status					
Advanced	124	5.8	0.01	1.24 (0.69-2.23)	0.44
Recurrent	84	8.7		1	
Histology					
Intestinal type	43	8.7	0.41		
Diffuse type	159	5.8			
Unknown	6	5.5			
Primary tumor					
Absent	102	9.4	<0.001	1	<0.001
Present	106	5.2		1.77 (1.29-2.42)	
Number of metastatic sites					
1	145	7.5	0.001	1	0.009
≥2	63	4.1		1.56 (1.12-2.18)	
Bone metastasis					
Absent	191	6.7	0.015	1	0.006
Present	17	3.6		2.11 (1.24-3.60)	
Ascites					
Absent	101	9.3	<0.001	1	<0.001
Present	107	5.2		1.75 (1.29-2.36)	
First-line chemotherapy					
5-FU (S-1) + cisplatin	69	5.7	0.56		
Irinotecan + cisplatin	13	12.0			
5-FU (S-1) alone	124	6.3			
Irinotecan alone	2	12.2			
PFS of first-line chemotherapy					
<6.0 months	108	4.7	0.02	1.15 (0.85-1.57)	0.383
≥6.0 months	100	9.2		1	
Measurable lesions					
Absent	112	6.7	0.21		
Present	96	6.3			

ECOG: Eastern Cooperative Oncology Group; PS: performance status; PFS: progression-free survival; 5-FU: 5-fluorouracil.

second-line for patients with good general status. A recent phase III trial comparing second-line chemotherapy plus BSC with BSC alone for advanced gastric cancer showed that second-line chemotherapy was tolerated and significantly improved OS when added to BSC (14). On the basis of this study, docetaxel or irinotecan were established as standard second-line chemotherapy in advanced gastric cancer.

Paclitaxel is recognized as a key therapeutic agent for gastric cancer. In particular, weekly paclitaxel is generally less toxic and well-tolerated compared with irinotecan in standard second-line chemotherapy (17, 20). In addition, irinotecan is often unusable because of the accumulation of malignant ascites and intestinal hypomotility caused by peritoneal dissemination that increases the toxicity of irinotecan. In this study, the most frequent histological type was the diffuse type (76.4%) and the most frequent metastatic site was the peritoneum (69.2%). In Japanese clinical practice, weekly paclitaxel is being used more frequently, owing to the equivalent therapeutic efficacy and reduced hematological toxicity compared with tri-weekly paclitaxel at a dose of 210 mg/m^2, which was the approved original

administration of paclitaxel for advanced gastric cancer (21, 22). Moreover, a recent phase III trial showed that irinotecan did not improve OS compared with weekly paclitaxel of the control arm (17). Therefore, weekly paclitaxel is recognized as a second-line chemotherapy and has been selected as the control arm of several phase III trials (23, 24).

There are several limitations in this study. Firstly, this study population included many patients with peritoneal carcinomatosis, which is a well-known factor of poor prognosis. Moreover, physicians will tend to choose weekly paclitaxel instead of irinotecan if patients have peritoneal carcinomatosis. Secondly, prior chemotherapy regimens were different from those of other facilities or countries where S-1 is not used as standard chemotherapy for advanced gastric cancer. Thirdly, this study was a retrospective design, not a prospective design.

Although the utility of this second-line chemotherapy was shown, the identification of prognostic factors is an important challenge. Previous studies showed that potential factors influencing OS were PS, baseline hemoglobin level, number of metastatic sites, PFS of first-line chemotherapy and level of carcinoembryonic antigen (25, 26). In the current study, the presence of the primary lesion, malignant ascites, bone metastasis and more than two metastatic sites were identified as independent factors conferring poorer prognosis. Interestingly, the response to first-line chemotherapy did not affect the OS. The PFS of first-line chemotherapy was also not an independent prognostic factor although it showed a tendency to be so (Table IV). This paradox might be due to the different second-line chemotherapies used, the majority of which (85%) in the above report were 5-FU based (26).

In conclusion, weekly paclitaxel is an effective regimen in Japanese patients with advanced gastric cancer refractory to first-line chemotherapy.

Funding

None.

Conflicts of Interest

The Authors have no potential conflicts of interest to declare.

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Received July 19, 2013
Revised September 13, 2013
Accepted September 16, 2013