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ORIGINAL ARTICLE

Clinical outcomes of TS-1 chemotherapy for advanced and recurrent gastric cancer

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Purpose: Titanium silicate (TS)-1 chemotherapy has been widely used against gastric cancer in Japan. The aim of the present study was to assess the efficacy and hematological safety of TS-1 as treatment for advanced and recurrent gastric cancer. **Methods:** From September 2006 to February 2011, 51 advanced or recurrent gastric cancers were treated with TS-1. One course of treatment consisted of 40, 50, or 60 mg/m^2 of TS-1 twice a day for 28 days, followed by withdrawal for two weeks. The primary end point was progression-free survival (PFS), and the secondary end point was overall survival (OS). **Results:** The disease control rate was 39.2% (complete response, 0/51; partial response, 6/51; stable disease, 14/51; progressive disease, 23/51; not evaluable, 8/51). The median PFS was 4.0 months (95% confidence interval [CI], 2.2 to 5.7); the median PFS of the advanced group was 6.0 months (95% CI, 2.8 to 9.1), and the median PFS of the recurrent group was 3.0 months (95% CI, 1.8 to 4.1). The median OS was 11.0 months (95% CI, 6.3 to 15.6); the median OS of the advanced group was 10.0 months (95% CI, 4.9 to 15.0), and the median OS of the recurrent group was 14.0 months (95% CI, 4.1 to 23.8). Grade 3 or 4 hematological toxicity occurred in three patients (5.9%), anemia occurred in two patients (3.9%), and thrombocytopenia occurred in one patient (2%). **Conclusion:** TS-1 chemotherapy was safe and effective, with relatively long PFS and OS in patients with advanced and recurrent gastric cancers.

Key Words: Gastric cancer, TS-1, Progression free survival, Overall survival

INTRODUCTION

In Korea, gastric cancer is the most common form of cancer (data from the Ministry of Health & Welfare, 2008). Early detection and curative surgery can improve survival of loco-regional gastric cancer [1], but the survival rates of far advanced and recurrent gastric cancers remain very low. Various approaches have been tried for far advanced and recurrent gastric cancers, including 5-fluorouracil (5-FU). Two pivotal phase II studies performed in Japan that evaluated the use of titanium silicate (TS)-1 in advanced gastric cancer showed response rates of 44% and 49%, times to progression of 135 and 158 days, and overall survivals (OS) of 207 and 250 days, respectively [2,3]. TS-1 is based on a biochemical modulation of 5-FU and contains tegafur, gimeracil and oteracil potassium in a molar ratio of 1:0.4:1 [4]. As a result of its structure, TS-1 has an increased anti-tumor effect and fewer adverse reactions

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compared to those of 5-FU. In the present study, we investigated the outcome, adverse reactions, and characteristics of long-term survivors of far advanced and recurrent gastric cancers who had received TS-1.

METHODS

The present study was based on a prospectively designed database of gastric cancer patients at the Department of Surgery, Kangbuk Samsung Hospital. The ethics committee at our institution approved the protocol. Between September 2006 and February 2011, 51 patients with either far advanced (locally advanced unresectable or metastatic disease) or recurrent (loco-regional, peritoneal, hematogenous metastasis after curative resection) gastric cancer were treated with TS-1. Analyses were performed according to the intention to treat principle. The initial dosage of TS-1 was calculated based on body surface area (BSA), and the patients received one of the following oral dosages twice daily after meals: 40 mg for patients with BSA $<1.25\ m^2$, 50 mg for BSA $\geq 1.25\ m^2$ and $<1.50\ m^2$, and 60 mg for BSA $\geq 1.50\ m^2$. One cycle of therapy involved the administration of TS-1 as a single agent for 28 consecutive days, followed by 14 days without treatment. This schedule was repeated every six weeks until the occurrence of disease progression, unacceptable toxicity, or patient refusal.

Measurement of efficacy was conducted every three months using abdominal pelvic computed tomography (CT) or positron emission tomography-CT. Laboratory tests were also conducted every three months. The responses of the lesions were evaluated using the Response Evaluation Criteria In Solid Tumors. Progression-free survival (PFS) was defined as the period from the date of the first course of chemotherapy to the date of disease progression or death. OS was defined as the period from the date of the first course of chemotherapy to the date of death from any cause. If neither event had occurred at the time of the last record, the patient was censored at that time.

During all of the treatment courses, toxicity was graded according to the National Cancer Institute Common Criteria. All of the data are presented as median values with ranges. The significances of the differences between the results were tested using the Chi-square test, Fisher's exact test, or Mann-Whitney test. P-values < 0.05 were considered statistically significant. PFS and OS were analyzed using the Kaplan-Meier method, and statistically significant differences in survival were identified using the log rank test. Statistical analysis was performed with a statistical analysis package SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient demographics and characteristics

The baseline characteristics of the 51 patients are listed in Table 1. Thirty-two male and 19 female patients were evaluated in this study, and the median age was 62 years (range, 51 to 71). Most patients had a pretreatment performance status (PS) of 0 to 1, and 30 patients (58.8%) had a history of gastrectomy (23 curative resection and 7 palliative resection) before chemotherapy was initiated. On his-

Table 1. Patient demographics and characteristics

Characteristic	No. of patients
Age (yr), median (range)	62 (51-71)
Sex	
Male	32
Female	19
Performance status (ECOG)	
0	3
1	31
2	17
3	0
Histologic type	
Intestinal type	19
Diffuse type	32
History of gastrectomy	
+	30
−	21
Metastatic site	
Peritoneum	29
Organ	
Liver	10
Bone	5
Others	7

ECOG, Eastern Clinical Oncology Group.

Table 2. Responses to treatment (n = 51)

Classification	CR	PR	SD	PD	NE	DCR, n (%)	P-value	TDCR, n (%)
Metastatic site							0.133	
Peritoneum	0	3	10	12	4	13/29 (44.8)		
Organ								
Liver	0	2	1	7	0			
Bone	0	0	0	2	3	7/22 (31.8)		
Others	0	1	3	2	1			20/51 (39.2%)
Disease status								
Far advanced	0	3	11	10	4	14/28 (50.0)	0.095	
Recurrent	0	3	3	13	4	6/23 (26.1)		

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated; DCR, disease control rate; TDCR, total disease control rate.

tology, 19 patients (37.2%) had intestinal-type and 32 patients (62.8%) had diffuse-type adenocarcinoma. Major sites of metastases were the peritoneum in 29 patients (56.8%), liver in ten (19.6%), bone in five (9.8%), and other locations in seven (13.8%).

Response and survival

Disease control rates (DCR) are listed in Table 2. Of the 51 patients, six (11.8%) achieved a partial response (PR) and 14 (27.4%) achieved stable disease (SD), with a DCR of 39.2% (20/51) on the intention to treat analysis. The DCR was 46.5% (20/43) in patients with evaluable lesions. The DCR according to the site of metastasis was somewhat higher for peritoneal metastasis (44.8%) than it was at other sites (31.8%), which included liver, bone, ovary, and other sites. However, the DCR was not statistically different according to metastasis site (P = 0.133). Evaluation of the DCR by disease status revealed a value of 50.0% for the far advanced group and 26.1% for the recurrent group. The far advanced group tended to have a higher incidence of disease control; however, there was not a statistically significant intergroup difference in DCR (P = 0.095). The median OS after the initiation of TS-1 administration in all 51 patients was 11 months (95% CI, 6.4 to 15.6). The one-, two-, and three-year survival rates were 49.0%, 24.8%, and 19.8%, respectively (Fig. 1). The median PFS was 4.0 months (95% CI, 2.3 to 5.7). Patients with intestinal-type (35.8%) tended to have a higher two-year survival rate than those with diffuse-type (18.0%). There were seven patients who survived for longer than two years, and their

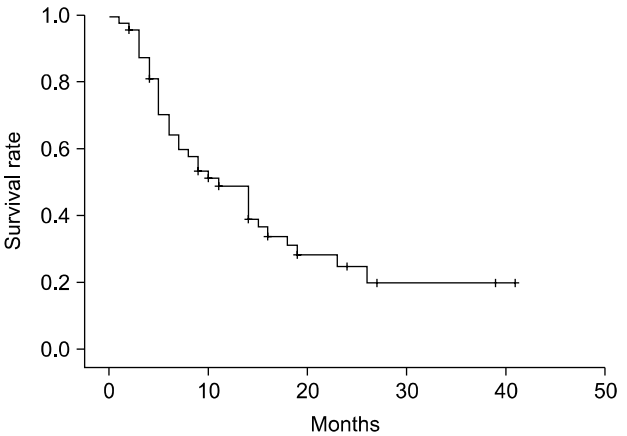

Fig. 1. Overall survival curve for all patients. The median survival time was 11.0 months with 1-, 2-, and 3-year survival rates of 49.0%, 24.8%, and 19.8%, respectively.

characteristics are listed in Table 3. Five of the seven patients surviving longer than two years had a good PS of 0 or 1. Of these seven patients, five (71.4%) had intestinal-type adenocarcinoma. Surgical resection performed in six (1 palliative total gastrectomy and splenectomy, 5 curative subtotal gastrectomy) of the seven patients before the start of TS-1 chemotherapy, and the remaining patient did not undergo gastrectomy. All of seven patients have not any postoperative complication. The metastasis sites in these seven patients included the peritoneum in two and a specific organ in five. Three of the seven patients were alive with no apparent tumor progression at two years after TS-1 chemotherapy.

Table 3. Two-year survivors treated with TS-1

Age (yr)	Sex	PS	HIS	Site of metastasis	Gastrectomy	Response	Cycle	Survival (mo)	Present status
64	M	2	I	Peritoneum	−	SD	12	26	Dead
60	M	2	I	Peritoneum	+	SD	6	39	Alive
78	M	0	I	Port-site	+	SD	6	39	Alive
70	F	1	I	Liver	+	SD	9	27	Dead
62	F	0	I	Liver	+	PR	6	41	Alive
62	M	1	D	Lung	+	SD	12	24	Alive
51	F	1	D	Ovary	+	SD	14	24	Alive

PS, performance status; HIS, histology; I, intestinal type; D, diffuse type; SD, stable disease; PR, partial response.

Table 4. Hematological adverse reactions

Toxicity	Grade (NCI-CTC)				
	1	2	3	4	Grade 3/4 (%)
Leukopenia	46	5	0	0	0.0
Neutropenia	46	5	0	0	0.0
Anemia	29	20	1	1	3.9
Thrombocytopenia	48	2	0	1	2.0

NCI-CTC, National Cancer Institute-Common Toxicity Criteria.

Adverse reactions

The adverse reactions that occurred throughout the treatment course are shown in Table 4. Adverse reactions were mostly mild; grade 3 or 4 hematological toxicities occurred in 5.9% of patients, and grade 3 or 4 adverse reactions with anemia were seen in two patients (3.9%). Of the 51 patients, only one (2%) had a grade 4 adverse reaction, which was thrombocytopenia. There were no chemotherapy-related deaths.

DISCUSSION

In gastric cancer, early detection and curative resection can improve survival in patients with loco-regional gastric cancer [1], but far advanced or recurrent gastric cancers are mostly treated with chemotherapy. Low dose 5-FU and cisplatin treatment (FP) were frequently used in Japan in the 1990s due to their low toxicities and high anti-tumor effects [5-7]. A randomized study conducted by the European Organization for Research and Treatment of Cancer reported a median PFS of 4.1 months and a median OS of 7.2 months with FP [8]. However, the disadvantage of FP was long-term hospitalization during treatment [8,9]. Furthermore, in a Japanese phase III study, 5-FU alone was shown to provide a survival benefit almost equivalent to that of FP, with less toxicity and an apparently better quality of life. 5-FU alone has a median PFS of 1.9 months and a median OS of 7.1 months, and the median PFS and median OS achieved with FP were 3.9 months and 7.3 months, respectively [9]. In the present study, the median PFS and OS of patients receiving TS-1 chemotherapy were 4.0 and 11.0 months, respectively, which were relatively longer than those of patients treated with 5-FU alone or FP in the Japanese phase III trial.

In the present study, the DCR was 39.2%, which consisted of a PR rate of 11.8% and an SD rate of 27.5%, and OS was 11 months. Up to now, no combination chemotherapy using conventional agents has contributed to a prolonged median OS longer than ten months. When compared with previous studies using combination chemotherapy, such as FAMTX (5-FU, doxorubicin, methotrexate), FAM (5-FU, doxorubicin, mitomycin C), and FP, our results demonstrated relatively low response rates and longer OS for the treatment of advanced gastric cancer [10-12]. A reason for the difference between the low response rate and relatively high OS is that peritoneal metastasis was the predominant metastatic pattern in far advanced and recurrent gastric cancers. It is usually difficult to measure the lesions in patients with peritoneal metastasis because small nodules cannot be precisely measured using CT [13,14]. Therefore, most patients with peritoneal metastasis are regarded as having SD.

Laparoscopy is very useful for evaluating the response

of peritoneal metastasis in gastric cancer to chemotherapy [15]. However, routine and repeated use of laparoscopy is impractical. If the response to chemotherapy for peritoneal disease were measured more precisely, the ratio of PR and SD would change because TS-1 has been reported to have the potential to prolong the survival of patients with peritoneal dissemination [16,17]. An experimental study to assess the effect of TS-1 on peritoneal dissemination of gastric cancer has confirmed that a high concentration of 5-FU is maintained in intra-peritoneal tumors after TS-1 administration, and that survival time is prolonged without any decrease in oral food intake or body weight [18].

The present study shows that all of the patients treated with TS-1 had an adverse hematological reaction. However, severe, grade 3 and 4 adverse reactions only occurred in 5.9% of the patients, and this frequency was consistent with frequencies of 4.0% and 5.9% of grade 3 or more adverse reactions reported in previous studies [19,20]. The other adverse reactions were generally mild and tolerable, and dose modifications or discontinuations were rarely necessary.

In the present study, seven patients survived longer than two years. Five of those seven patients had good PS, and all had a single organ metastasis, either in the peritoneum alone or in a specific organ, such as a port site, liver, ovary, or lung. They received a median of nine cycles of TS-1 treatment, and four of the patients received second-line chemotherapy (doxifluridine or tegafur + uracil) after disease progression. Long-term treatment with TS-1 and the second-line treatment may have prolonged their survival. Three patients had PFS for two years and had a single organ metastasis, such as in a port site, the liver, or the lungs. Those were detected during follow-up using imaging studies, and local treatment, such as radio frequency ablation or resection, was immediately performed. After local control of metastasis, they were treated with TS-1.

Our previous study reported that patients with metastasis from gastric cancer may not expect long-term survival with only local control of cancer in the liver due to intrahepatic recurrence from multiple metastatic foci that originated from the primary disease [21]. Several studies have suggested that combined therapy that includes aggressive local treatment and early postoperative adjuvant chemotherapy for advanced gastric cancer with liver metastasis may allow long-term survival in selected patients [21-23]. The present study suggests that combined therapy with local control and TS-1 could increase PFS if local control of metastasis can be achieved.

Several studies have surveyed prognostic factors of advanced gastric cancer. Poor PS, liver metastases, peritoneal metastases, an elevated alkaline phosphatase level, multiple metastatic sites, and a histological diffuse-type tumor have been shown to be associated with poor survival [24-27]. The present study also shows that patients with intestinal-type histology (median survival time, 14 months; 95% CI, 6.34 to 21.65) tended to have longer survival than did those with diffuse-type (median survival time, 9 months; 95% CI, 6.34 to 21.65), although the P-value was not statistically significant (P = 0.108). Therefore, a study focusing on more optimal inclusion criteria needs to be performed.

In conclusion, TS-1 chemotherapy was safe and effective with a relatively higher DCR and longer OS in patients with far advanced and recurrent gastric cancers and TS-1 had various advantages, such as its convenient oral form and mild adverse reactions. However, a prospective randomized controlled trial with a larger number of patients needs to be performed to confirm these results.

CONFLICTES OF INTEREST

No potential conflict of interest relevant to this article was reported.

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