Effects of Intermittent 5-Fluorouracil and Low-dose Cisplatin Therapy on Advanced and Recurrent Gastric Cancer

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Abstract. *Background: Although combination therapy consisting of 5-fluorouracil (5-FU) and cisplatin for the treatment of gastric cancer has been reported, no consistent regimen has been established. Our aim was to determine the optimal treatment schedule of this therapy, for patients with advanced or recurrent gastric cancer. Patients and Methods: We conducted a phase II study to evaluate the efficacy and safety of combination therapy consisting of intermittent 5-FU and low-dose cisplatin in 26 patients with advanced or recurrent gastric cancer. The treatment cycle consisted of intravenous cisplatin at 3.3 mg/m^2/day for 5 consecutive days. 5-FU was administered as a continuous intravenous infusion at 300-500 mg/body every other day (days 1, 3, 5) for 4 weeks. Results: The partial response rate was 34.6%. The median survival duration was 12.8 months and the one-year survival was 53.1%. There were a few adverse effects. Conclusion: Our results suggest that this mode of combination therapy led to a fairly favorable outcome for patients with advanced or recurrent gastric cancer.*

The efficacy of combination chemotherapy consisting of 5-fluorouracil (5-FU) and cisplatin (FP therapy) utilizing biochemical modulation for advanced gastric cancer has been recently reported. However, the doses and the administration methods used differ among institutions (1, 2), while there was also a negative report on the efficacy of this combined therapy (3). It is thus important to determine the optimal dose and method of administration for the FP therapy. The efficacy of a combination of low-dose cisplatin and continuous intravenous infusion of 5-FU has been reported, and this therapy is widely used in clinical practice in Japan (4).

In this mode of therapy, cisplatin is not expected to induce anticancer effects by itself, but to modulate the action of 5-FU, and also to minimize adverse reactions (5). However, bone marrow suppression, stomatitis, and diarrhea are still sometimes observed after repeated cycles of continuous intravenous injection of 5-FU (6). An intermittent 5-FU schedule has been developed based on the biological differences between the generation times of tumor cells and normal cells, and it has been proposed to allow for a further reduction of these adverse reactions (7).

In the present study, we examined the efficacy and safety of intermittent 5-FU plus low-dose cisplatin combination therapy to determine the optimal administration for the FP therapy.

Patients and Methods

Twenty-six Japanese patients who were registered in the Nagasaki Study Group for Digestive Organ Cancer Chemotherapy from 2000 through 2004 were included in this study. The eligibility requirements for study entry were as follows: (i) histologically proven gastric cancer, which was judged not to be indicated for curative resection at the time of diagnosis, such as cancer at a far advanced stage or recurrence after gastric resection, (ii) a performance status of 0-2 on admission, (iii) lesions which could be evaluated by imaging studies, endoscopic examination and/or serum levels of tumor markers. All

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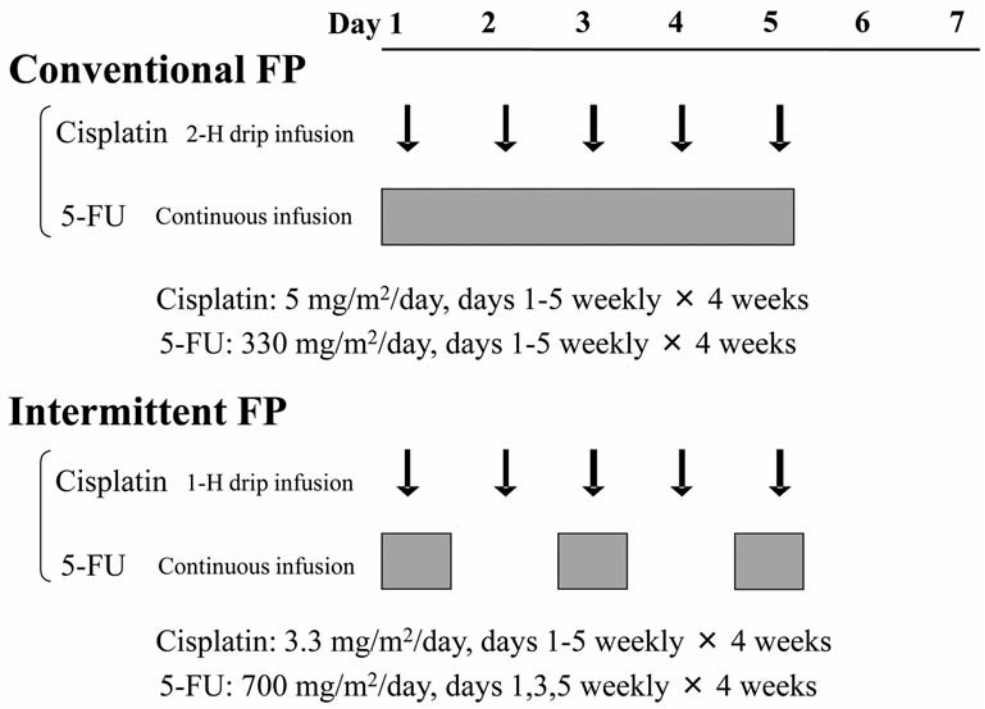

Figure 1. *The treatment schedule for the conventional 5-FU plus low-dose cisplatin (FP) and intermittent FP therapy.*

patients were treated with intermittent 5-FU plus low-dose cisplatin combination therapy (intermittent FP therapy).

To evaluate the efficacy of intermittent FP therapy, we compared the results between the current study and a previous study which included 37 patients with advanced gastric cancer treated with conventional FP therapy, performed in the 1990 by the Nagasaki Study Group for Digestive Organ Cancer Chemotherapy (8). The patients in the intermittent FP group were treated with one or more cycles of combined 5-FU and low-dose cisplatin therapy, repeated at 4-week intervals. Each cycle consisted of a continuous intravenous infusion of 5-FU (700 mg/m^2/day) every other day, and the intravenous infusion of cisplatin for 5 consecutive days (3.3 mg/m^2/day, for 1 h, in 100 ml saline) on days 1 to 5. In the conventional FP group, the schedule consisted of 4-week courses of continuous intravenous infusion of 5-FU (300-500 mg/body for 5-7 days), UFT (400-600 mg/body for 7 days), or 5'DFUR, (800 mg/bay for 7 days) as 5-FU, and intravenous infusion of cisplatin for 5 days (5-20 mg) (Figure 1).

For measurable lesions, the response rate to chemotherapy was evaluated according to the World Health Organization criteria (9). The evaluation of the anticancer effects on the measurable tumors was carried out using computed tomography and ultrasonography. We adopted the roentgenographic and endoscopic evaluation criteria proposed by the Japanese Research Society of Gastric Cancer to evaluate the primary lesions (10). The assessment method used to determine the objective response was unified with that used in the previous study to enable a comparison of the results between the previous and the current study. Therefore, the Response Evaluation Criteria in Solid Tumors were not adopted for the current study. Adverse effects were graded according to the Eastern Cooperative Oncology Group (ECOG) common toxicity criteria grade (11). The overall survival was estimated using the Kaplan Meier method. *p*-values less than 0.05 were considered statistically significant.

Results

The patients' characteristics are summarized in Table I. The mean age of the patients was 60.5±9.1 years in the conventional FP group and 63.7±9.7 years in the intermittent FP group. Ten patients in the conventional FP group and 16 patients in the intermittent FP group had a good performance status (PS0) at the initiation of chemotherapy (p=0.002). In the conventional FP group, 15 patients had recurrent and 22 patients had unresectable gastric cancer. On the other hand, 11 had recurrent and 15 had unresectable cancer in the intermittent FP group.

The objective responses in the intermittent FP group were as follows: partial response in 9 patients (34.6%), no change in 10 patients (38.5%), and progressive disease in 5 patients (19.2%), with a response rate (complete plus partial response) of 34.6% (95% confidence interval=16.3-52.9%) (Table II). These results showed that use of the regimen achieved results not inferior to these of the conventional FP group. The response rate to the intermittent FP therapy was 40% for primary lesions, for liver metastases, and for celiac lymph nodes, 50% for differentiated histological type and 23% for the undifferentiated type. There were no significant

Table I. *Patients' characteristics*.

	Conventional FP therapy (n=37)	Intermittent FP therapy (n=26)	*p*-Value
Age (years)			0.160
Mean±SD	60.5±9.1	63.7±9.7	
Gender			0.932
Male/female	29/8	21/5	
Performance status			0.002
0/1/2/3/4/	10/13/7/6/1	16/7/3/0/0	
Disease status			0.888
Advanced	22	15	
Recurrent	15	11	
Histology			0.248
Differentiated	8	12	
Undifferentiated	17	13	
Not determined	12	1	
Sites of metastasis			0.046
Stomach	10	15	
Lymph nodes	13	15	
Liver	12	5	
Lung	5	0	
Others	5	8	

Table II. *Clinical response*.

	Conventinal FP therapy (n=37)	Intermittent FP therapy (n=26)	*p*-Value
Efficacy*			0.769
CR/PR/NC/PD	1/12/13/10	0/9/10/5	
Response rate (%)	35.1	34.6	

CR: Complete response; PR: partial response; NC: no change; PD: progressive disease. *Efficacy was not examined for one patient in the conventional group and two patients in the intermittent group respectively.

Table III. *Response rate according to lesions*.

	CR	PR	NC	PD	Response rate (%)
Sites of metastasis					
Stomach	0	6	8	1	40.0
Lymph nodes	0	6	8	1	40.0
Liver	0	2	1	2	40.0
Other	0	3	3	1	42.9
Histology					
Differentiated	0	6	4	1	50.0
Undifferentiated	0	3	5	4	23.1
Not determined	0	0	1	0	0

CR: Complete response; PR: partial response; NC: no change; PD: progressive disease. Response rate=complete plus partial response.

differences between the response rates for the different histological types (Table III).

We achieved down-staging in six patients after intermittent FP therapy, and these patients then underwent gastrectomy. Three out of these six patients attained long-term survival without recurrence (data not shown). The median survival duration for the intermittent FP group was 12.8 months, and the one-year survival was 53.1% (Figure 2). The median overall survival was significantly longer for patients in the intermittent than in the conventional group (12.8 months *vs*. 7.1 months, p=0.006). This difference was lost when the data from the patients who underwent surgery were excluded (Figure 3). There were no treatment-related deaths. Table IV shows the adverse effect profile of the regimen. The major adverse effect observed in the current study was bone marrow suppression. The incidence of grade 2-3 leukopenia was lower than that observed following the conventional treatment, with marginal significance (p=0.06). The only grade 3-4 adverse reaction was a decrease in the neutrophil count in 12.5% of the patients. The occurrence of symptoms related to the gastrointestinal tract, including anorexia, nausea, vomiting, stomatitis, diarrhea and liver dysfunction was not noted in any of the patients.

Discussion

A variety of regimens that utilize biochemical modulation theories have been developed in order to enhance the efficacy for 5-FU treatment. Combination of low-dose cisplatin and 5-FU therapy is such a regimen (4). Although FP therapy has been reported to be highly efficient and to have reduced adverse reactions, such as bone marrow suppression, stomatitis, and diarrhea, these are still considered to be dose-limiting toxicities after repeated cycles of continuous intravenous infusion of 5-FU. To minimize the toxicity of 5-FU while preserving its anticancer activity, an intermittent schedule for 5-FU was recently introduced. An intermittent 5-FU schedule, which is theoretically based on the differences between the generation times of tumor cells and normal cells, has been proposed to achieve a further reduction of adverse reactions (7). The generation time of tumor cells is generally 5 to 7 days, while those of normal bone marrow cells and intestinal epithelial cells is as short as 0.52 days. During chemotherapy, the recovery of the normal cells is therefore expected to occur within 24 h of drug suspension, and administering 5-FU every other day has been implemented to reduce the adverse reactions by taking this. Under this condition, a similar total 5-FU dose is achieved during the generation times of the tumor cells to maintain the anticancer effect. Terashima *et al*. have already reported the efficacy of intermittent 5-FU therapy and indicated that adverse reactions are indeed reduced, although they indicated the necessity for performing randomized comparative studies (12).

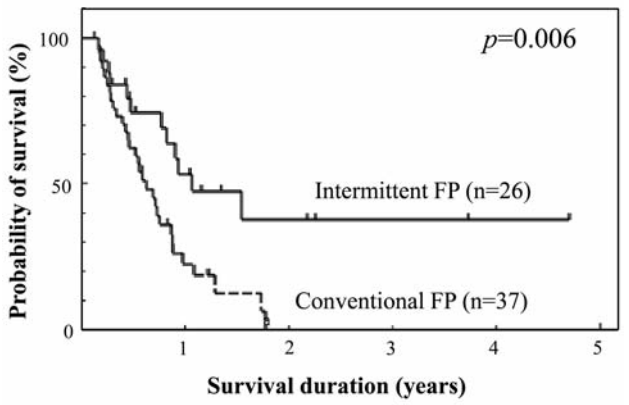

Figure 2. *The overall survival rates of patients treated with conventional 5-FU plus low-dose cisplatin (FP) and intermittent FP therapy.*

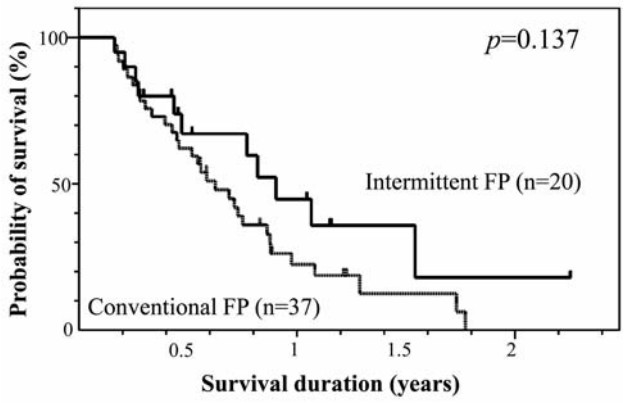

Figure 3. *The overall survival rates of patients treated with conventional 5-FU plus low-dose cisplatin (FP) and intermittent FP therapy, excluding the data from the six patients who were able to undergo gastrectomy after chemotherapy.*

The present study is not a randomized comparative study, however, intermittent 5-FU plus low-dose cisplatin combination therapy was compared with the conventional method we have previously reported, in which 5-FU was administered at 350 mg/m^2/day by continuous infusion. The present results show that there was a response rate of 35.1%, which is similar to that obtained using the conventional method (8). We did not find any significant differences in the response rate based on the affected site. In addition, the only major grade 3-4 adverse reaction was a decrease in the granulocyte count in 12.5% of the patients. The incidence of reduction in the leukocyte count of grade 2-3 was significantly lower than that occurring when the conventional method was used, but no difference from the conventional method was observed for the other adverse reactions. The incidence of diarrhea, stomatitis, and liver dysfunction was 0%, and those of anorexia, nausea and vomiting were very low, thus supporting the safety of this regimen.

Another type of drug based on the biochemical modulation of 5-FU is S-1, which is a novel oral prodrug of fluorouracil. This drug contains gimeracil and oteracil; the former reversibly inhibits dihydropyrimidine dehyrogenase (DPD), and the latter suppresses FdUMP in the digestive tract. These two modulators can both increase fluorouracil concentration and reduce gastrointestinal toxicity compared with conventional oral drugs such as Tegafur-Uracil (UFT) and 5'-deoxy-5-fluorouridine (5'DFUR). Phase II trials of S-1 showed a response rate of 45% and a two-year survival of 17% (13, 14). In a phase III study, Boku *et al*. reported that S-1 was non-inferior to continuous infusion of fluorouracil with respect to the median overall survival of 11.4 months for those assigned to S-1, whereas the median survival for those allocated to the continuous infusion was 10.8 months. They concluded that S-1 could replace continuous infusion of fluorouracil for first-line chemotherapy for metastatic gastric cancer (15). In addition, Koizumi and co-workers designed a randomized study to assess whether combination therapy using S-1 and cisplatin was superior to S-1 alone in patients with unresectable or recurrent gastric cancer (16). Their results showed that the median overall survival was significantly longer in the S-1 plus cisplatin group (13.0 months) than those assigned to S-1 alone (11.0 months). More recently, a large randomized controlled trial (the FLAGS trial) demonstrated the non-inferiority of S-1 plus cisplatin compared to infusional 5-FU plus cisplatin regarding first line treatment for advanced gastric or

Table IV. *Hematological and non-hematological toxicities.*

	ECOG grade					
	0	1	2	3	4	3+4 (%)
Hematological toxicities						
Leukopenia	15	2	2	1	0	0
Neutropenia	16	1	0	2	0	12.5
Lymphopenia	20	0	0	0	0	0
Thrombocytopenia	19	2	0	0	0	0
Anemia	20	2	1	0	0	0
Renal dysfunction	20	0	0	0	0	0
Liver dysfunction	20	0	0	0	0	0
Non-hematological toxicities						
Anorexia	17	2	1	0	0	0
Nausea/vomiting	17	1	1	0	0	0
Diarrhea	18	2	0	0	0	0
Stomatitis	20	0	0	0	0	0
Others	18	2	0	0	0	0

ECOG: Eastern Cooperative Oncology Group.

gastroesophageal cancer (17). Combined therapy using the oral administration of S-1 and infusional cisplatin is now considered a standard treatment in Japan.

On the other hand, we often encounter patients with advanced gastric cancer presenting with outlet obstruction. Therefore, these patients cannot undergo promising chemotherapy using S-1 plus CDDP because of the inability to ingest the S-1. In the present study, a partial response was attained, that was sufficient to achieve down-staging and enable surgery in six patients through intermittent 5-FU plus low-dose cisplatin combination therapy. We suggest that this intermittent FP combination therapy is useful as pre-surgical chemotherapy for inducing down-staging because of its reduced adverse reactions; moreover, this treatment can be used for selected patients with advanced gastric cancer presenting with outlet obstruction.

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