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Randomized Phase II Study Comparing Mitomycin, Cisplatin Plus Doxifluridine with Cisplatin Plus Doxifluridine in Advanced Unresectable Gastric Cancer

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Abstract. *Various chemotherapies have been used to treat inoperable gastric cancer. Most combination therapies include cisplatin (CDDP) and fluoropyrimidine (5-FUs), which are thought of as key drugs. In the present study, we randomly compared mitomycin (MMC) and CDDP plus doxifluridine (5'-DFUR), which is an oral 5-FU and an intermediate metabolite of capecitabine (Xeloda), with CDDP plus 5'-DFUR in advanced unresectable gastric cancer. Regimen A was CDDP (70 mg/m^2, by 2-hour intravenous drip infusion on day 1), MMC (7 mg/m^2, injected intravenously on day 2), and oral 5'-DFUR (1200 mg/m^2, on days 4 to 7, 11 to 14, 18 to 21 and 25 to 28; 3 days rest and 4 days administration). Regimen B was identical to regimen A without MMC. Results: The response rate was 25.0% (8/32 patients) in Regimen A, 17.2% (5/29) in Regimen B (p=0.541). The median survival time was 241 days in Regimen A and 179 days in Regimen B (p=0.498). In Regimen A, although no significant difference was observed, end points such as response rate and survival improved. Thus, we concluded that a randomized controlled phase III study with more subjects should be conducted.*

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Japan has the world's highest mortality from gastric cancer (39.8 deaths per hundred thousand people, 1997) (1). Therefore, it has become an urgent task to develop effective chemotherapy for gastric cancer. In particular, for highly advanced gastric cancer deemed to be inoperable, various chemotherapies have been tried. At present, some chemotherapeutics are useful, for example, a combination of tegafur, 5-choloro-2, 4,-dihydroxyprimidine, and potassium oxonate (S-1) (2), camptothecin (CPT-11) (3), and taxanes (4). Combination therapy with these drugs is effective in some cases, resulting in longer than expected survival and eventual resection. Most of these combination therapies include cisplatin (CDDP) and fluoropyrimidine (5-FUs), thought of as key drugs.

In the present study, we conducted a randomized phase II study assessing the clinical significance of combining CDDP + FUs with mitomycin (MMC). The rationale for this drug regimen includes: 1) A basic study showed that MMC demonstrates synergistic efficacy when combined with CDDP (5); 2) basic and clinical studies revealed that combination treatments with MMC and 5-FUs show favorable results (6,7); and 3) a phase II study with combined therapy of 5-FUs + CDDP + MMC was highly effective, 56.3 % (9/16) (8).

In the present study, we employed an oral doxifluridine (5'-DFUR) as the 5-FU. The reasons for this were: 1) 5'-DFUR had been used in the phase II study we previously conducted, meaning that the results of both studies can be

compared easily; 2) favorable findings had been shown in studies using either 5'-DFUR + CDDP + MMC (8) or 5'-DFUR + CDDP (9). Further, 5'-DFUR is an intermediate metabolite of oral capecitabine (Xeloda) which has been favorably evaluated worldwide for treating breast and colorectal cancers; and 3) in 1987 5'-DFUR was approved in Japan as a drug to treat gastric cancer (10).

Patients and Methods

Patients diagnosed as having advanced unresectable gastric cancer at participating centers between July 1991 and December 1996 were eligible for the study if: 1) the diagnosis was confirmed by histological examination of specimens obtained by biopsy and/or surgery; 2) the tumor was unresectable because of advanced stage; 3) lesions were measurable or evaluable; 4) no other cancers were identified; 5) the patient was not more than 80 years of age at entry; 6) performance status was 0-3 according to World Health Organization (WHO) criteria; 7) on laboratory examination, renal function tests revealed a serum creatinine of ≤1.5 mg/dl, a blood urea nitrogen of ≤25 mg/dl and a creatinine clearance of ≤60 ml/min; 8) in the bone marrow, the neutrophils were ≥4,000 /mm^3 and the thrombocytes ≥100,000 /mm^3, the hemoglobin was ≥10g/dl, and in liver function tests, total bilirubin was ≤3.0 mg/dl; 9) there were no serious concurrent conditions; 10) there was no history of anticancer therapy (excluding surgery); and 11) the patient gave written informed consent to participate in the trial.

Patient registration and assignment to treatment. On identifying a candidate, the investigator contacted the study office and confirmed with the administrator that the patient met all eligibility criteria before registration. The patients were stratified according to the extent of their cancers and according to the study center. They were randomly assigned to receive Regimen A or B. The four classifications according to tumor extent were: cancer limited to abdomen, cancer present in ascites, metastasis to liver and metastasis to other sites.

Treatment methods. In Regimen A (CDDP+5'-DFUR+MMC), the following regimens were additionally given: 1) CDDP (70 mg/m^2) by 2-hour intravenous drip infusion on day 1; 2) MMC (7 mg/m^2) injected intravenously on days 2 and 3) oral 5'-DFUR (1200 mg/m^2) on days 4 to 7, 11 to 14, 18 to 21 and 25 to 28 (3 days rest and 4 days administration). Each 28-day regimen comprised one treatment cycle. Regimen B (CDDP+5'-DFUR) was identical to Regimen A, but without MMC. Therapy was continued for as long as possible based on disease progression and/or development of serious adverse events.

Criteria for reducing the dose or terminating treatment. The doses of all drugs were reduced by 20% in patients who were over 70 years of age at entry. After study initiation, treatment was terminated immediately for the following events: 1) myelosuppression of ≥grade 3 of WHO criteria; and 2) nephrotoxicity of ≥grade 2 of WHO criteria. After recovery, the treatment was resumed with dosages of all drugs reduced by 20%.

Table I. *Patient characteristics.*

Regimen		A	B	Test
Sex				
Male		17	19	$p=0.436$[a]
Female		15	10	
Age				
Median		58 yrs	58 yrs	$p=0.840$[b]
Min. – Max.		37 – 79 yrs	36 – 79 yrs	
Performance Status				
Grade	0	5	3	
	1	20	13	$p=0.065$[c]
	2	6	9	
	3	1	4	
Histology				
Differentiated		10	11	$p=0.602$[a]
Undifferentiated		22	18	
Primary Lesion				
No		3	2	$p=1.000$[a]
Yes		29	27	
Target Lesion				
Primary		29	27	
Local lymph node		7	6	
Distant lymph node		3	4	
Liver		9	10	
Lung		1	1	
Bone		0	1	
Others		5*	3**	
Carcinomatous fluid				
Ascites		8	5	
Pleural effusion		0	1	

[a]Fisher; [b]Wilcoxon; [c]U test
*Kidney, Ovary, Brain, Large intestine, Spleen
**Adrenal glands, Douglas's pouch, Large intestine

Response criteria and treatment evaluation. The response to treatment was evaluated according to the General Rules for Gastric Cancer Study (11), compiled by the Japanese Research Society for Gastric Cancer. These criteria classify the primary foci into two subtypes based on radiographic or endoscopic findings: 1) measurable lesions; and 2) non-measurable but evaluable lesions (including diffusedly infiltrated lesions). The criteria for metastastic lesions were the same as the WHO criteria.

Complete response (CR) was disappearance of all the lesions, determined by 2 observations not less than 4 weeks apart and, in addition, there could be no new lesions. Partial response (PR) required a 50% or greater reduction in total tumor size based on 2 observations within 4 weeks and no new lesions or tumor progression. No change (NC) was a 50% reduction of the total tumor size or a 25% increase in the size of one or more tumor lesions. Progressive disease (PD) was a 25% or greater increase in a tumor or other measurable lesion, or development of a new lesion. All of the above lesions were assessed by radiographic, endoscopic, ultrasound examination and/or computed tomography (CT) scan. These findings were recorded on film, which facilitated objective measurement of lesion size.

Table II. *Response.*

	Regimen A						Regimen B					
	CR	PR	NC	PD	NE	Response rate	CR	PR	NC	PD	NE	Response rate
Overall	0	8	13	9	2	25.0% (8/32)	0	5	7	15	2	17.2% (5/29)
Primary												
Overall	1	7	13	6	2	27.6% (8/29)	0	3	15	5	4	11.1% (3/27)
a-lesion	1	1	3	2	0	28.6% (2/7)	0	3	2	0	0	60.0% (3/5)
b-lesion	0	4	5	2	2	30.8% (4/13)	0	0	4	3	2	0% (0/9)
c-lesion	0	2	5	2	0	22.2% (2/9)	0	0	9	2	2	0% (0/13)
Lymph nodes												
Local	0	2	3	1	1	28.6% (2/7)	1	0	3	0	2	16.7% (1/6)
Distant	2	0	1	0	0	66.7% (2/3)	2	0	0	2	0	50.0% (2/4)
Liver	1	2	3	3	0	33.3% (3/9)	1	2	2	3	2	30.0% (3/10)
Lung	1	0	0	0	0	100% (1/1)	0	0	0	1	0	0% (0/1)
Bone	0	0	0	0	0	0% (0/0)	0	0	0	1	0	0% (0/1)
Others	0	1*	3	0	1	20.0% (1/5)	0	0	2	0	1	0% (0/3)
*Spleen												
Performance Status												
Grade 0/1	0	6	10	8	1	24.0% (6/25)	0	4	3	9	0	25.0% (4/16)
2/3	0	2	3	1	1	28.6% (2/7)	0	1	4	6	2	7.7% (1/13)
Histology												
Differentiated	0	2	6	2	0	20.0% (2/10)	0	0	1	9	1	0% (0/11)
Undifferentiated	0	6	7	7	2	27.3% (6/22)	0	5	6	6	1	33.3% (5/18)
Primary Lesion												
With	0	8	11	8	2	27.6% (8/29))	0	5	6	14	2	18.5% (5/27)
Without	0	0	2	1	0	0% (0/3)	0	0	1	1	0	0% (0/2)

CR: complete response; PR: partial response; NC: no change; PD: progressive disease; NE: not evaluable

Adverse events were graded according to WHO criteria. Survival curves were calculated by the Kaplan-Meier method. All evaluations, including eligibility and response to the treatment, were performed by an independent evaluation committee, who also reviewed all case report forms and imaging data. All data were compiled and analyzed with Statistical Analysis System Software (SAS version 8.2; SAS Institute, Cary, NC, USA).

End point. The primary end point was tumor response; secondary end points were survival, toxicity and drug compliance.

Results

Case analysis and background factors. A total of 67 patients were registered, of whom 6 (Regimen A, 2; Regimen B, 4) were judged ineligible and excluded from the study. Reasons for exclusion were: 1) the 2 cases in Regimen A had had previous treatments; and 2) in Regimen B, 2 cases had had previous treatments and the other 2 cases had no target lesions. Table I shows the characteristics of eligible patients; there were no significant differences among the patients as to age, gender, performance status, histological type, primary as well as target lesions.

Treatment cycle. The treatment cycles were: 1) Regimen A included 0.25 cycles minimum, and 8 cycles maximum, median, 3 cycles; Regimen B included 0.25 cycles minimum and 5 cycles maximum, median, 2 cycles (Wilcoxon test, $p=0.149$). The main reason to terminate treatments was disease progression [Regimen A, 17 patients (53.1%) and 21 patients (72.4%) in Regimen B]. Treatments were terminated due to adverse events for 5 patients in each group.

Response to chemotherapy. Table II shows response rates to the chemotherapies. Although no significant differences were seen among the rates, the overall responses were: 25.0% (8/32) in Regimen A (95% CI, 11.5-43.4%); and 17.2% (5/29) in Regimen B (95% CI, 5.9-35.8%). Thus the response rate was better with Regimen A (Fisher exact test, $p=0.541$). As for effects according to target lesion, both groups showed higher effects on lymph node metastasis and liver metastasis. Effects on the primary lesion were higher with Regimen A than with Regimen B, although there was no significant difference between groups ($p=0.185$). There were no large differences in effects by patient characteristics, although no response was confirmed in

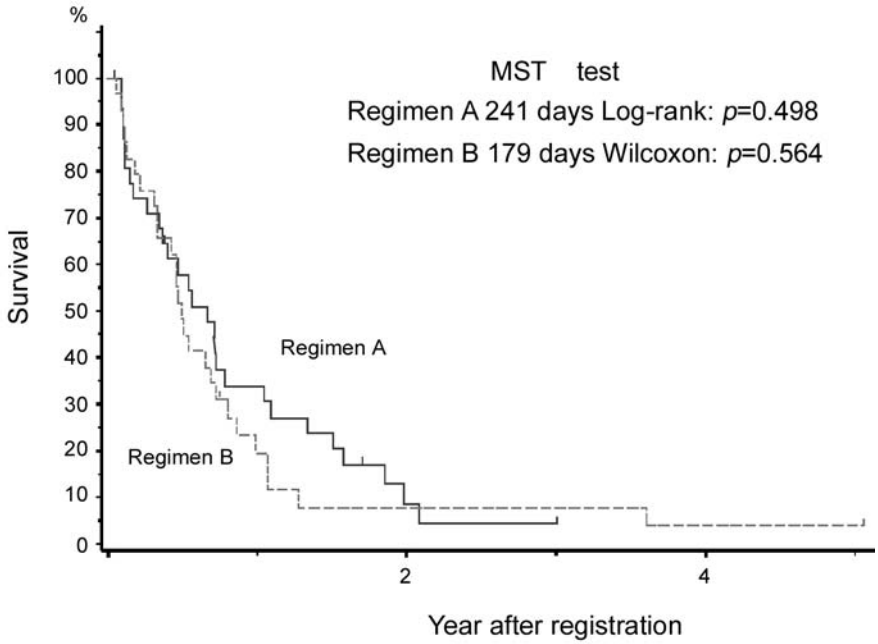

Figure 1. *Median survival time was better in Regimen A than that in Regimen B, but there was no significant difference between groups.*

patients of Regimen B with histologically differentiated type tumor. No response was seen in patients of both the regimens without having the primary lesion.

Durations of response were: 71-475 days (median, 167 days) with Regimen A; and 84-484 days (median, 89 days) with Regimen B.

Survival. Overall survival is shown in Figure I. Median survival time was 241 days with Regimen A and 179 days with Regimen B, resulting in a longer survival time with Regimen A but without a significant difference between groups (log-rank test, $p=0.498$).

Toxicity. Patients developing side-effects included: 24 patients (75.0%) on Regimen A and 24 patients on Regimen B (Fisher exact test, $p=0.541$). The main side-effects were gastrointestinal symptoms and bone marrow suppression. Table III shows the side-effects according to grade. Although no significant differences were observed between groups, Regimen A showed higher rates of leukocytopenia and thrombocytopenia, including those over grade 3. Other side-effects showed no large differences between groups.

Discussion

Although the present study showed better results of such end points as response rate and survival by using a treatment regimen combined with MMC, there were no significant differences between groups. However, based on finding that treatment combined with MMC may yield favorable results, we believe another randomized phase III study with many more subjects is necessary.

The response rate with Regimen A in the present study was 25.0%, which was lower than the results of two other studies, *i.e.*, 50.0% with 5'-DFUR + CDDP and 56.3% with 5'-DFUR + CDDP + MMC (8, 9). The reasons for the differences in these results are, we suppose, as follows. First, the dosing schedules and doses differed among the 3 studies. In the 2 studies that we previously conducted, 5'-DFUR was administered on days 1-4 followed by CDDP administration on day 5. In the present study, on the other hand, CDDP was administered on day 1 followed by 5'-DFUR administration on days 4-7. In particular, 5'-DFUR and CDDP were administered in reverse order. As for the dosing order of 5-FUs and CDDP, there are conflicting reports (12, 13). Neither a conclusive nor a clinical report has been presented. The present study suggests that the response rate may be higher if 5-FUs are administered first. In the present study, 5'-DFUR was administered on the final 25-28 days in one cycle, while CDDP was administered on the first day 29 in 2 cycles. Thus, 5'-DFUR was initially dosed and then followed by CDDP administration from 1 to 2 cycles. The dosing schedule for the present study was decided on considering the administration schedule of 5'-DFUR followed by CDDP. Thus, response rates in patients given 2 or more cycles

Table III. *Side-effects.*

	Regimen A (n=32)					Regimen B (n=29)				
Grade	1	2	3	4	Over G3 Frequency	1	2	3	4	Over G3 Frequency
Signs and symptoms										
Nausea/vomiting	8	4	4	0	12.5%	4	7	6	0	20.7%
Diarrhea	1	0	1	1	6.3%	0	1	2	0	6.9%
Anorexia	0	1	1	0	3.1%	1	1	0	0	0%
Others	2*	3**	0	0	0%	2***	0	0	0	0%
*Alopecia, **Taste disorder, Dermatitis, Fever, ***Deafness, Rash										
Abnormal laboratory test findings										
WBC	3	7	7	0	21.9%	5	2	1	1	6.9%
PLT	4	3	2	4	18.8%	2	0	1	0	3.4%
Hb	1	3	1	0	3.1%	2	1	3	0	10.3%
AST	1	2	0	0	0%	4	0	0	0	0%
ALT	1	2	0	0	0%	5	0	0	0	0%
Bilirubin	0	1	0	0	0%	1	1	0	0	0%
BUN	1	1	0	0	0%	2	1	0	0	0%
Cr	0	0	0		0%	2	2	0	0	0%
Others	0	0	0	0	0%	1*	1**	0	0	0%
*TP, **Urinary protein										

showed rates of 34.8% (8/23 patients) with Regimen A and 25% (5/20) with Regimen B.

Second, the CDDP dose in the present study was 70 mg/m^2, which was lower than in the other 2 studies, *i.e.*, 80 mg/m^2. In one of the other 2 comparison studies, 5'-DFUR + MMC together with CDDP of either 80 mg/m^2 or 60 mg/m^2, the 60 mg/m^2 group resulted in a response rate of 18.8%. This suggested that CDDP of 80 mg/m^2 was needed to increase the response rate. In contrast, the present study administered 1.7 times the 5'-DFUR dose intensity in a cycle compared to the other 2 studies, but did not increase the response rate.

As described above, the response rate in the present study was, unfortunately, lower than that in the other 2 studies, although the mean survival time (MST) of the present study was 241 days, similar to or better than that in the other 2 studies (268 days with 5'-DFUR + CDDP, and 223 days with 5'-DFUR + CDDP + MMC). This made it difficult to interpret the results of the present study.

Regarding the safety of the regimens employed in the present study, leukocytopenia and thrombocytopenia developed in approximately 20% of the patients with Regimen A, probably due to bone marrow suppression from concomitant use of MMC. Nevertheless, regimen A was used for many more administration courses. This suggested there are fewer problems with this regimen.

The present study was conducted from 1991 to 1996. Since then many anticancer drugs have been introduced for combination therapies for gastric cancer. Of these new drugs, S-1 is expected to be specific for gastric cancer treatment and showed a response rate of 44.6% (45/101 patients) in phase II study (2, 14). In Japan, at present, S-1 has been assessed extensively under a large-scale phase III study as to whether this drug can be a standard treatment for gastric cancer. A phase II study of S-1 + CDDP demonstrated a response rate as high as 73.7% (14/19 patients) (15). A new drug with a higher tumor selectivity, capecitabine, is under development for treating gastric cancer (16) and, in Korea, it has already been approved for this purpose. Capecitabine + CDDP showed a favorable response rate of 54.8% (23/42 patients) together with MST of 10.1 months (17). Other reports show capecitabine + epirubicin + CDDP had a response rate of 64.9% (24/37 patients) with MST of 13 months (18); capecitabine + docetaxel resulted in a response rate of 67% (20/30 patients) with MST of 17.1 months (19). In the United Kingdom, a large-scale (600 patients) phase III study for gastric cancer patients is being conducted with a combination regimen of oxaliplatin (a CDDP class drug, originally introduced for treating colorectal cancer) and capecitabine (20).

As described above, various promising drugs have been introduced since the present study. Thus, the next phase III study should be conducted considering new drugs and new combination chemotherapies.

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