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Phase II Study of Protracted Infusional 5-fluorouracil Combined with Cisplatinum for Advanced Gastric Cancer: Report from the Japan Clinical Oncology Group (JCOG)

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A phase II study of protracted infusional 5-fluorouracil (5FU) combined with cisplatin (CDDP) was conducted in patients with advanced gastric carcinoma. 55 previously untreated patients, including 40 patients with measurable disease, were treated with 5FU (800 mg/m², days 1–5, protracted infusion) and CDDP (20 mg/m², days 1–5, drip infusion). Objective tumour responses were observed in 17/40 (43%) patients with measurable disease. Median survival was 7 months. WHO grade 3 or 4 leucopenia occurred in 10/55 patients (18%) and grade 3/4 thrombocytopenia was observed in 4 patients (7%). A randomised trial including this regimen is now underway in a JCOG study.

Key words: gastric cancer, chemotherapy, 5-fluorouracil, cisplatinum
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INTRODUCTION

THERE IS intense interest in the chemotherapy of gastric cancer because this disease is believed to be more sensitive to chemotherapeutic agents than other gastrointestinal adenocarcinomas. Several agents have been shown to be effective against gastric cancer, including 5-fluorouracil (5FU), mitomycin C (MMC), doxorubicin (ADM) and cisplatin (CDDP), which, individually, achieve a response rate of less than 25% [1–3]. In recent years, a combination of 5FU, ADM and CDDP (FAP) has been reported with favourable outcomes [4].

Some experimental data have revealed synergistic effects between 5FU and CDDP both *in vitro* and *in vivo* [5, 6]. Based on these findings, we performed an early phase II trial using a combination of 5FU and CDDP, which had not yet been reported when this trial was initiated, in patients with previously treated advanced gastric cancer and observed a response rate of 45% (9/20) [7]. These encouraging results led us to conduct the present phase II trial in patients with untreated advanced gastric cancer.

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PATIENTS AND METHODS

Eligibility criteria

Between December 1990 and October 1991, 57 patients, 75 years old or less, with histologically proven gastric adenocarcinoma which was not potentially curable by surgery, were entered into this study. Performance status of 3 or less on the ECOG scale and life expectancy of at least 8 weeks were required. No prior chemotherapy or radiation therapy was permitted. Patients were required to have adequate bone marrow (WBC count $\geq$4000/μl, platelet count $\geq$100 000/μl), hepatic (total serum bilirubin level $\leq$2 mg/dl) and renal functions (BUN level $\leq$25 mg/dl, serum creatinine level $\leq$1.5 mg/dl, creatinine clearance $\geq$50 ml/min). All of the patients gave their signed informed consent.

Treatment schedule

5FU was administered by continuous infusion at a dose of 800 mg/m² day for 5 consecutive days, with CDDP administered at 20 mg/m²/day in a 30-min infusion over the same 5 days. The regimen was repeated every 4 weeks until disease progression, refusal of treatment by the patient or a total of six courses of treatment. Response to therapy was assessed every 4 weeks.

Assessment of response to therapy

Objective responses to therapy in measurable lesions and toxicities were determined by standard WHO criteria. The responses of primary lesions were evaluated by the roentogenographic and endoscopic evaluation criteria proposed by the Japanese Research Society for Gastric Cancer [3, 7].

Table 1. Patients' characteristics

	No. of patients
Total no. of patients	55
Median age, years (range)	59 (35–74)
Male/female	38/17
Performance status (ECOG scale)	
0, 1	40 (73%)
2, 3	15 (27%)
Macroscopic type of primary lesions	
Diffuse	13 (29%)
Non-diffuse	32 (71%)
Histological type	
Intestinal	19 (35%)
Diffuse	36 (65%)

Table 3. Toxicity

	WHO grade				Incidence of grade 3 or 4	
	1	2	3	4	*n*	(%)
Leucopenia	13	17	8	2	10/55	(18)
Thrombocytopenia	3	4	2	2	4/55	(7)
Anaemia	11	25	4	1	5/55	(9)
Nausea/vomiting	17	14	14	0	14/55	(26)
Stomatitis	12	5	2	0	2/55	(4)
Diarrhoea	8	6	0	0	0/55	(0)
Hepatotoxicity	12	2	4	0	4/55	(7)
Nephrotoxicity	9	1	0	0	0/55	(0)

RESULTS

Of the 57 patients entered into this phase II trial, 2 patients were excluded from analysis because they refused treatment after registration. One patient was not evaluated for response due to protocol violation. Patients' characteristics are shown in Table 1. 15 patients had locally advanced diseases which were considered incurable by laparotomies. 10 patients had histories of gastrectomy, 5 for palliation and 5 with curative intent (Table 2). A median number of three cycles was administered (range 1–6).

Objective responses were observed in 17/40 (43%) patients with measurable disease, with a 95% confidence interval of 27–59%. A complete response was not observed. Other organ-specific response rates were 36% (8/22) for liver, 38% (9/24) for abdominal lymph nodes and 43% (3/7) for cervical lymph nodes. Evaluation of primary lesions for 45 patients showed that 9/45 patients (20%) responded (Table 2). In 15 with locally advanced diseases, 2 cases were operated with palliative intent after chemotherapy. The median survival time for all of the cases was 7 months and 8 months for the measurable cases.

The major toxicities were nausea/vomiting and leucopenia (Table 3). Leucopenia was observed in 40 patients (73%), including 8 with grade 3 and 2 with grade 4. Thrombocytopenia was observed in only 11 patients (20%), including 2 with grades 3 and 4, respectively. Non-haematological toxicities were mild except nausea/vomiting; grade 3 mucositis was seen in only 2 patients (4%). Grade 3 hepatotoxicities were observed in 4 patients (7%), which were recovered without treatment.

DISCUSSION

In the present study, the response rate of 43% (17/40) in patients with measurable diseases was obtained. Two reports, using infusional 5FU and CDDP, have recently been published. Lacave and colleagues reported a phase II trial of 5FU and CDDP and achieved a response rate of 41% (22/55) [8]. The other, a Korean phase III study, compared 5FU and CDDP with 5FU alone and a combination of 5FU, ADM and MMC [9]. Although no survival advantage was observed, the response rate with 5FU and CDDP was 51% (28/55). This better response rate than our study and that by Lacave and associates may be due to the fact that the evaluation criteria in the Korean study included hepatomegaly as measured by palpation. Based on these results, including those from our study, the true response rate to 5FU and CDDP chemotherapy of advanced gastric cancer is probably approximately 40%.

Several combination chemotherapies with high response rates have recently been reported in advanced gastric cancer. Klein and associates reported a favourable outcome, with a response of 63% using 5FU, ADM and methotrexate [10]. However, the follow-up study showed response rates between 33 and 45% [11–13]. Preusser and colleagues, using a combination of etoposide, ADM and CDDP, also reported a high, overall response rate of 64% [14]. This was followed by disappointing results, with response rates of 20–33% and a high incidence of treatment-related death [13,15]. When these results are compared to those with 5FU and CDDP, the regimens appear to have similar efficacies. However, the 5FU and CDDP regimen is less toxic than the others, particularly with regard to myelotoxicities.

Although median survival time for all patients was 7 months, is no better than survival from others studied, survival benefit should be studied in the subsequent randomised study. The JCOG has initiated a randomised phase III study in patients with gastric cancer to compare types of treatment, including 5FU alone, a combination of uracil and tegafur plus MMC, and 5FU and CDDP to evaluate survival advantages.

Table 2. Patient response

Extent of disease	No. of responses
Locally advanced (n = 15)	2
Primary excised, metastatic (n = 10)	5
Primary not excised, metastatic (n = 30)	12
Total (n = 55)	19 (35%)

* Response was assessed by the criteria proposed by the Japanese Research Society for Gastric Cancer.

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A Phase II Study of the Sequential Administration of Dacarbazine and Fotemustine in the Treatment of Cerebral Metastases From Malignant Melanoma

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34 patients with cerebral metastases from malignant melanoma received sequential dacarbazine at 250 mg/m^2 followed 2 h later by fotemustine at 100 mg/m^2; this was repeated on day 8. Maintenance therapy was given every 4 weeks to patients with radiological evidence of response or stable disease until a maximum response was achieved plus two more cycles. A 12% response rate was obtained for cerebral metastases, with 2 complete responses lasting 12 and 36+ months, and 2 partial responses lasting 2.5 and 3.75 months. Toxicity was mainly haematological with grade 3–4 leucopenia and thrombocytopenia in 23.5% of patients. No pulmonary toxicity was seen. This schedule of sequential dacarbazine and fotemustine has low activity against metastatic melanoma, and the response rate for cerebral metastases is not superior to that shown in other studies with single agent fotemustine, but the treatment was well tolerated and can be delivered on an outpatient basis.
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INTRODUCTION

CEREBRAL METASTASES from malignant melanoma are associated with poor prognosis; without treatment the median survival of patients is between 3 and 4 weeks, and in most treatment series, this is prolonged to 2–3 months. Dacarbazine is the most effective drug in metastatic melanoma with response rates of 15–20% [1, 2], while nitrosureas, cisplatin and vindesine have response rates of approximately 15%. Combination chemotherapy occasionally produces higher response rates but the duration of response is not prolonged over single agents [3, 4]. The effectiveness of chemotherapy is site dependent, with only cerebral or hepatic metastases responding in approximately 8% of cases [5].

Fotemustine is a chloronitrosurea and its chemical formula includes a bioiostere of alanine which facilitates cellular penetration and passage across the blood brain barrier. It is reported to have particular activity against cerebral metastases with response rates of approximately 28% [6]. Adducts formed at the O^6 guanine position are cytotoxic, and this is the initial site of fotemustine attachment. The normal guanine structure is