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Cisplatin plus continuous infusion of 5-fluorouracil for 5 days effective for patients with advanced gastric cancer

Yasuyo Okada,[CA] Hideaki Anai, Takao Hattori, Yoshihiko Maehara, Junji Nishimura Keizo Sugimachi and Hajime Nawata

Y Okada and T Hattori are at Shakaihoken Nakabaru Hospital, Mitarai 6, Shime-machi, Kasuya-gun, Fukuoka-ken 811-22, Japan. Fax: 81 92 623 2247. H Anai, Y Maehara and K Sugimachi are at the Department of Surgery II; J Nishimura and H Nawata are at the Department of Internal Medicine III, Faculty of Medicine, Kyushu University, Fukuoka 812, Japan.

Seventeen consecutively treated patients with advanced gastric cancer were prescribed every 3 weeks intravenous cisplatin (20 mg/m²/day) and a continuous infusion of 5-fluorouracil (5-FU) (750 mg/m²/day) for 5 days. Twelve (71%) patients had been treated previously with other anticancer drugs. Seven (42%) patients showed a partial response and these responses persisted for over 4.4 months. Stabilization of the disease occurred in eight (47%) patients, and in two (12%) the disease progressed. At the time of analysis, mean survival of the responders was 8.2 months, while that of non-responders was 5.0 months. The toxicities were within acceptable limits and only a few had a grade III toxicity. This combined administration of cisplatin and 5-FU for 5 days is safe and effective for patients with advanced gastric cancer.

Key words: Chemotherapy, cisplatin, 5-fluorouracil, gastric cancer.

Introduction

For patients with an advanced gastric cancer, anticancer drugs such as 5-fluorouracil (5-FU), doxorubicin, mitomycin C and cisplatin have response rates of 15–25%.[1,2] Combination chemotherapy regimens of FAM,[3] FAMe,[2] FAP[4] and EAP,[5] when prescribed for patients with advanced gastric cancer, usually achieve 30–60% overall response rates, but are associated with grade IV severe toxicities. The continued search for a more appropriate combination chemotherapy regimen for advanced gastric cancer is therefore warranted. Because of its proven efficacy, we considered first a combination therapy based on 5-FU. We combined 5-FU with cisplatin because studies on mice showed that cisplatin is synergistic with 5-FU.[6] In addition, a number of studies showed that this combination is clinically effective against head and neck cancers[7,8] and colorectal cancers.[9,10] The continuous infusion of 5-FU for 5 days was found to be more effective than bolus 5-FU therapy.[11] The myelotoxicity rate of 5-FU is lower in those given a continuous infusion of the drug.[12,13] We report here our clinical evaluation of the efficacy of cisplatin in combination with a 5-day continuous infusion of 5-FU for patients with an advanced gastric cancer.

Materials and methods

Seventeen Japanese men and women with evaluable, pathologically confirmed advanced gastric cancer were admitted to hospital and enrolled in the study. Informed consent was obtained from each patient.

The following criteria were used: evaluable gastric cancer; age 20–75 years; no major cardiac or metabolic diseases; normal cardiac function; white blood cell (WBC) count $\geq 4000/mm^3$; platelet count $\geq 100{,}000/mm^3$; adequate renal function (blood urea nitrogen <20 ng/dl, serum creatinine <1.2 mg/dl, clearance of creatinine >60 ml/min); normal liver function tests.

The treatment plan involved cisplatin (Nihon Kayaku Co., Tokyo) at 20 mg/m² for 2 h i.v. with pre- and post-treatment hydration and the continuous infusion of 5-FU (Kyouwa Hakko Co.,

[CA] Corresponding Author

Tokyo) at 750 mg/m^2/day for five consecutive days. This cycle was repeated every 3 weeks. Efforts were made during this study to minimize the toxicities of this treatment, particularly nausea and vomiting, and metoclopramide and methylprednisolone sodium succinate were given, as required for each patient.

The characteristics of the patients are summarized in Table 1. The subject population included 5 men and 12 women, the age range being between 39 and 71 years with a mean age of 58. The mean performance status according to the criterion of the Eastern Cooperative Oncology Group (ECOG) was 2 (range 0–3). Eight of the 17 patients (47%) had undergone gastrectomy in our institution prior to this study; the remaining nine patients presented with advanced disease not amenable to surgical resection. Twelve patients had been prescribed chemotherapy.

Of 17 patients, seven (41%) had metastatic disease, two (12%) locally advanced inoperable disease and eight (47%) an inoperable cancer and metastases. After the administration of a minimum of two cycles, the response to the combined therapy was evaluated in each patient. A thorough physical examination, standard radiographs, sonograms, or computed tomography scans were obtained. WHO criteria were used to define the response, response duration and the degree of toxicity.[14] Response was evaluated as follows: complete response (CR) was defined as the complete disappearance of all tumor for at least 4 weeks; partial response (PR), $\geq 50\%$ reduction in tumor volume for at least 4 weeks; no change (NC), $\leq 50\%$ reduction or $< 25\%$ increase in tumor volume for 4 weeks; progressive disease (PD), $\geq 25\%$ increase in tumor volume or development of new sites of disease. To assess the toxicity, renal, liver, bone marrow and cardiac functions were tested before and after the treatment.

Table 1. Characteristics of patients

Factor	No. of patients (%)
Patients	17 (100)
Age (years)	
Mean	58
Range	39–71
Sex	
Male	5 (29)
Female	12 (71)
Performance status (ECOG scale)	
0	1 (6)
1	3 (18)
2	9 (53)
3	4 (23)
Previous treatment	
Surgery	8 (47)
Chemotherapy	12 (71)
Affected organs	
Stomach	9 (53)
Liver	5 (29)
Lung	1 (6)
Lymph nodes	3 (18)
Colon	3 (18)
Ovary	1 (6)
Peritoneum	9 (53)

Results

The patients were treated with 2–6 cycles (mean 3 cycles) of a combination of cisplatin and 5-FU. The clinical responses are summarized in Table 2. Of the 17 evaluable patients, seven (41%) achieved PR, NC was noted in eight (47%) and PD in two (12%). The mean duration of the response was 4.4 months (range 2.0–7.9). PR was obtained in five patients with an inoperable cancer plus metastases and in two with metastatic disease. Three patients who achieved PR had been treated previously with chemotherapy. At the time of analysis, the mean survival of responders was 8.2 months, while that of non-responders was 5.0 months.

The toxicities are summarized in Table 3. Grade III leukopenia and thrombocytopenia were observed in 18 and 12% of patients, respectively. These toxicities occurred between days 11 and 15 and bone marrow recovery was complete 3–10 days later. Gastrointestinal toxicities were mostly of grade I–II, and stomatitis of grade III was noted in one (6%) patient. Two (12%) patients had grade II renal toxicity, nine (53%) had some alopecia, one (6%) had ototoxicity (tinnitus) and four (24%) had mild neurotoxicity.

Discussion

Cisplatin[15] and 5-FU[16] each have superior antineoplastic activity against gastric cancer. In mice, cisplatin is synergistic with 5-FU.[6] A study done using the human ovarian carcinoma cell line A2780 revealed that cisplatin can increase the availability of the reduced folate necessary for 5-fluorodeoxyuridine 5'-monophosphate (FdUMP) to bind tightly to thymidylate (dTMP) synthase (EC 2.1.1.45) and thereby enhance the cytotoxicity of 5-FU.[17] The

Table 2. Response and survival time

Response	Frequency (%)	Mean response duration (months)	Mean survival (months)
PR	7 (41)	4.4+ (range 2.0–7.5+)	8.2+ (range 3.3–12.5+)
Stomach	4 (40)		
Liver	1 (20)		
Lung	1 (100)		
Lymph nodes	1 (33)		
Colon	1 (33)		
Ovary	0 (0)		
Peritoneum	4 (44)		
NC	8 (47)	3.5 (range 1.5–7.1+)	5.0+ (range 3.1–11.0+)
PD	2 (12)		4.8+ (range 3.5–6.5+)

PR, partial response; NC, no change; PD, progressive disease.

combination of cisplatin and 5-FU has also been used clinically in the treatment of head and neck cancers[7,8] and colorectal cancers.[9,10,18] It is important to determine the optimal therapeutic schedule for administration of drugs. As the activity of 5-FU occurs in the S phase of cells, only a small fraction of tumor cells will be susceptible when the drug is administered in a bolus form. It is also known that when 5-FU is given in the form of a continuous infusion rather than as a bolus, the response rate improves and myelosuppression is attenuated in cases of colorectal cancer.[11–13] Cisplatin has been given in Western countries by a bolus infusion, in combination with 5-FU.[7,8] To maintain the level of reduced folate necessary for the ternary complex of dTMP synthase,[17] the infusion of cisplatin at 20 mg/m^2/day for five consecutive days may be more effective than the infusion of a single high dose of cisplatin.

Table 3. Toxicity

Toxicity	Grade (%)				Total (%)
	I	II	III	IV	
Hematologic					
WBC	1 (6)	3 (18)	3 (18)	–	8 (41)
Platelet	1 (6)	–	–	–	1 (6)
Hemoglobin	1 (6)	2 (12)	2 (12)	–	5 (29)
Gastrointestinal					
Nausea/vomiting	2 (12)	1 (6)	–	–	3 (18)
Diarrhea	1 (6)	–	–	–	1 (6)
Appetite loss	1 (6)	–	–	–	1 (6)
Stomatitis	1 (6)	1 (6)	1 (6)	–	3 (18)
Renal	–	2 (12)	–	–	2 (12)
Alopecia	7 (41)	2 (12)	–	–	9 (53)
Ototoxicity	1 (6)	–	–	–	1 (6)
Neurotoxicity	2 (12)	2 (12)	–	–	4 (24)

For our patients, the combination treatment with cisplatin and continuous infusion of 5-FU for 5 days induced a response rate of 41% and the mean duration of response exceeded 4.4 months. The mean survival of the responders was 8.2 months, while that of the non-responders was 5.0 months. The clinical response achieved in our series was the same as that achieved in another study.[19] As complete response was not achieved with our regimen, this combined treatment shows a modest logarithmic cell kill and a limited effectiveness in completely eradicating large numbers of spreading cancer cells. The EAP (etoposide; doxorubicin; cisplatin) regimen for advanced gastric cancer led to a response rate of 64%; however, in 64% of the patients, there was a grade III–IV myelosuppression and in 12% severe infections occurred.[5]

The combination of cisplatin and 5-FU for 5 days was tolerated relatively well in most of our patients, only a few developed grade III toxicity and no patient developed grade IV toxicity. All these toxicities resolved within 1–2 weeks. The regimen of cisplatin together with a continuous 5-day infusion of 5-FU appears to be effective and can be given with lower toxicity for patients with advanced gastric cancer. This regimen is worthy to be used in an adjuvant setting in combination with surgical treatment.

Conclusion

Seventeen patients with advanced gastric cancer were treated with i.v. cisplatin and a continuous

infusion of 5-FU for 5 days. Seven (42%) patients showed a partial response. The toxicities were within acceptable limits and only a few had grade III toxicity. This combined treatment is safe and effective for patients with advanced gastric cancer.

References

1. O'Connell MJ. Current status of chemotherapy for advanced pancreatic and gastric cancer. *J Clin Oncol* 1985; **3**: 1032–9.
2. Haller DG. Chemotherapy in gastrointestinal malignancies. *Semin Oncol* 1988; **15**: 50–64.
3. MacDonald JS, Schein PS, Woolley PV, *et al.* 5-Fluorouracil, doxorubicin, mitomycin (FAM) combination chemotherapy for advanced gastric cancer. *Ann Intern Med* 1980; **93**: 533–6.
4. Moertel CG, Rubin J, O'Connell MJ, *et al.* A phase II study of combined 5-fluorouracil, doxorubicin and cisplatin in the treatment of advanced upper gastrointestinal adenocarcinomas. *J Clin Oncol* 1986; **4**: 1053–7.
5. Preusser P, Wilke H, Achterrath W, *et al.* Phase II study with the combination etoposide, doxorubicin, and cisplatin in advanced measurable gastric cancer. *J Clin Oncol* 1989; **7**: 1310–7.
6. Schabel FM Jr, Trader MW, Laster WR Jr, *et al.* Cis-dichlorodiammine-platinum(II): Combination chemotherapy and cross-resistance studies with tumors of mice. *Cancer Treat Rep* 1979; **63**: 1459–73.
7. Palmieri S, Gebbia V, Russo A, *et al.* Cis-diamminodichloroplatinum plus a 5-day continuous infusion of 5-fluorouracil in the treatment of locally recurrent and metastatic head and neck cancer patients. *J Cancer Res Clin Oncol* 1989; **115**: 579–82.
8. Kish JA, Weaver A, Jacobs J, *et al.* Cisplatin and 5-fluorouracil infusion on patients with recurrent and disseminated epidermoid cancer of the head and neck. *Cancer* 1984; **53**: 1819–24.
9. Loehrer PJ, Einhorn LH, Williams SD, *et al.* Cisplatin plus 5-FU for the treatment of adenocarcinoma of the colon. *Cancer Treat Rep* 1985; **69**: 1359–63.
10. Kemeny N, Niedzwiecki D, Reicham B, *et al.* The Community Clinical Oncology Program Physicians. Cisplatin and 5-fluorouracil infusion for metastatic colorectal carcinoma. *Cancer* 1989; **63**: 1065–9.
11. Lokich JJ, Ahlgren JD, Gullo JJ, *et al.* A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: A Mid-Atlantic Oncology Program, Study. *J Clin Oncol* 1989; **7**: 425–32.
12. Seifert P, Baker LH, Reed ML, Vaitkevicius VK. Comparison of continuously infused 5-fluorouracil with bolus injection in treatment of patients with colorectal adenocarcinoma. *Cancer* 1975; **36**: 123–8.
13. Fraile RJ, Baker LH, Buroker TR, *et al.* Pharmacokinetics of 5-fluorouracil administered orally, by rapid intravenous and slow infusion. *Cancer Res* 1980; **40**: 2223–8.
14. WHO Handbook for Reporting Results of Cancer Treatment. WHO Offset Publication No. 48. World Health Organization, Geneva, Switzerland, 1979.
15. LaCava AJ, Pereda MV, Izarzugaza I, *et al.* Phase II clinical trial of cis-dichlorodiamminoplatinum in gastric cancer. *Am J Clin Oncol* 1983; **6**: 35–8.
16. Moynihan T, Hansen R, Anderson T, *et al.* Continuous 5-fluorouracil infusion in advanced gastric carcinoma. *Am J Clin Oncol* 1988; **11**: 461–4.
17. Scanlon KJ, Nemman EM, Lu Y, Priest DG. Biochemical basis for cisplatin and 5-fluorouracil synergism in human ovarian carcinoma cells. *Proc Natl Acad Sci USA* 1986; **83**: 8923–5.
18. Posner MR, Belliveau JF, Weitberg AB, *et al.* Continuous-infusion cisplatin and bolus 5-fluorouracil in colorectal carcinoma. *Cancer Treat Rep* 1987; **71**: 975–7.
19. Lacave AJ, Antòn-Aparicio L, Gonzalez-Barón M, *et al.* Cisplatin (CDDP) and 5-fluorouracil (5FU) 120-hr infusion for advanced gastric cancer (GC): a phase II multicenter study. *Proc ASCO* 1987; **6**: 91.

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