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A Phase II Study of Cisplatin in Advanced Gastric Cancer

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Abstract—*Twenty patients with recurrent or metastatic gastric adenocarcinoma and prior chemotherapy were treated with cisplatin, 60–120 mg/m² as a 6-hr infusion repeated every 3 weeks. There were 4 partial responses in 18 evaluable patients. Seven patients had stable disease. Time to progression ranged from 6 to 28 weeks. Median WBC nadir was 3.2×10^3/mm³ (range, 1.5–7.1) and platelet nadir 120×10^3/mm³ (range, 13–220). A transient increase in serum creatinine was observed in 6 cases, and nausea and vomiting in all. We conclude that this drug is active in stomach cancer and that it warrants further trials in combination chemotherapy.*

INTRODUCTION

AMONG all gastrointestinal tumors, adenocarcinoma of the stomach has shown the greatest sensitivity to chemotherapy [1–3]. Effective drugs in this disease include fluorouracil, doxorubicin, mitomycin, carmustine and semustine [1–8]. Over the last few years various combination chemotherapy regimens have yielded encouraging results suggesting, in some trials, superior antitumor activity as compared to single agent treatments [1–11].

Cisplatin has become a major drug in the therapy of a wide variety of malignancies [12, 13]. Reports on its single agent activity in gastric cancer have been promising and have prompted its incorporation into combination chemotherapy regimens [14–16]. However, data to properly evaluate its role in this disease are still scanty [17–20]. Moreover, cisplatin may produce significant toxic effects, especially major gastrointestinal distress and nephrotoxicity, requiring careful methods of drug administration. We initiated this disease-oriented phase II trial to further document the single agent activity of cisplatin in gastric cancer and substantiate the rationale for its use in combination.

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MATERIALS AND METHODS

Patients

All patients had histologically proven recurrent or metastatic gastric adenocarcinoma not amenable to chemotherapy. At least one month had elapsed between the last course of chemotherapy and the first cisplatin treatment. None of the patients had received radiotherapy. Indicator lesions were bidimensionally measurable, except in the case of liver metastases, which were considered evaluable in the presence of hepatomegaly palpable at least 5 cm below the costal margin on the midclavicular line and below the xyphoid process on the median line, and if lesions of at least 3 cm in diameter had been detected on pretreatment sonographical examination. Serum creatinine ≤ 1.3 mg/100 ml, WBC $\geq 4 \times 10^3$/mm³, platelets $\geq 100 \times 10^3$/mm³ and absence of congestive heart failure were required upon entry in the trial.

Cisplatin was diluted in 2000 ml of a solution of dextrose in saline and infused over 6 hr, preceded and followed by i.v. hydration with 2000 ml of fluids in 12 hr. Furosemide was given when necessary to maintain a diuresis rate of 100 ml/hr. Metoclopramide, 10 mg i.v., was administered when needed to control vomiting.

The initial dose of cisplatin received by 14 patients was 120 mg/m², 4 patients were given 90 mg/m² and 2 received 75 mg/m². Courses were repeated every 3 weeks in the absence of disease progression and postponed for 1–1.5 weeks in the case of persisting leukopenia, thrombopenia or

rise in serum creatinine. In 4 cases dosage was reduced by 25–50% in subsequent courses for a worsening of the patients' performance status.

Blood counts and serum creatinine were determined weekly. Lesions were re-assessed every 3 weeks.

Tumor response was evaluated as follows: partial response: regression by >50% of the product of the two largest perpendicular diameters of all measurable lesions for 4 weeks or more; minor response: tumor shrinkage of 25–50% and an improvement in performance status during more than 4 weeks; no change: stable disease for 6 weeks at least. Partial response in liver metastases was defined as a reduction in the sum of liver measurements below the costal margin on the midclavicular and median lines by at least 30% in the presence of clear-cut sonographical regression of metastases.

Twenty patients were entered into the study. Their pretreatment characteristics are shown in Table 1. Two patients had received fluorouracil only and the others had been treated with one or more combination regimens. Partial responses to previous chemotherapy had been observed in 3 cases, with doxorubicin and mitomycin in 2 and fluorouracil in 1.

RESULTS

Eighteen patients were evaluable for response to treatment. Two were not assessable because of sudden death before the third week of treatment with no evidence of toxicity. Responses are shown in Table 2. There were no complete responses but four patients achieved partial response, the best responses being observed at 3 weeks in 3 cases and after 12 weeks in the fourth. Three of these patients had already received the FAM combination and one had responded; one had progressive disease under a combination of carmustine, doxorubicin, fluorouracil and mitomycin. A shrinkage of skin metastases by more than 50% for only 2 weeks was observed in one patient whose disease was considered to have failed to respond to treatment.

Survival in patients achieving a partial remission was 16, 16 and 30 weeks from initiation of the study respectively, the fourth being alive at 36 weeks. Patients with a minor remission or stable disease survived 14–26 weeks, with a median of 24. Those with progressive disease survived 4–68 weeks (median 6). Median survival for all patients was 16 weeks.

The average cisplatin dose per course received by the responding patients was 90 mg/m^2 in 2

Table 1. Characteristics of patients

		No. of patients
Age (yr)	38–75, median 60	
Sex	18 men, 2 women	
Performance status*	0–3, median 2	
Primary tumor	Inoperable	3
	Metastases present at diagnosis	7
	Radical surgery	10
Disease-free interval (months, radical surgery)	2–24, median 11	
Lesions	Locoregional only	3
	Skin and lymph nodes	3
	Local and skin	1
	Local and bone	1
	Lung	2
	Liver	2
	Liver and other sites	8
Previous chemotherapy	Adjuvant	3
	Adjuvant + palliative	2
	Palliative	15
	Regimens† F	2
	FB	2
	FMe	2
	FA	1
	AM	2
	FAM	9
	BAFM	4

*WHO score.

†F: fluorouracil; B: carmustine; Me: semustine; A: doxorubicin; M: mitomycin.

Table 2. Tumor response

Response*	No. of patients	Time to progression (weeks)	Median
PR	4	6, 10, 14, 28	12
MR	3	13–24	22
NC	4	8–25	11
PD	7	—	—
NE	2	—	—

*PR: partial remission; MR: minor remission; NC: no change; PD: progressive disease; NE: not evaluable.

cases, 75 mg/m^2 in one and 60 mg/m^2 in another. Those with stable or progressive disease had received an average dose per course of 75–120 mg/m^2.

A total of 53 courses were administered. Six evaluable patients had evidence of progressive disease after only one course. Four patients had 2 courses, 3 patients 3, 2 patients 4, 1 patient 6 and the 2 others 7 courses. Nausea and vomiting occurred in all courses and were severe in 15. Leukopenia ($<4 \times 10^3$) was observed in 8 patients; median WBC nadir was 3.2×10^3/mm^3 with a range of 1.5–7.1. Thrombocytopenia ($<100 \times 10^3$) occurred in 7 patients; median platelet nadir was 120×10^3 (range 13–220). In 14 patients a fall in hemoglobin levels by 1–4 g/100 ml was observed, with a median value for all patients of 1.7. Serum creatinine increased to 1.5 mg/100 ml or more in 8 patients (range 1.5–3.8), recovering after 7–21 days in all but one, who had a bilateral ureteral obstruction. Hypoacousia was observed in 2 patients.

DISCUSSION

Four of 18 evaluable patients from a total of 20 achieved short partial remissions with cisplatin; stable disease was seen in 7 patients. On the whole, the performance status of the patients was relatively poor, and all but one had bulky disease. The toxicity encountered was the usual expected toxicity of cisplatin [12]. It should be observed that 8 of 15 patients with previous mitomycin treatment had an increase in serum creatinine. Nausea and vomiting were frequent and severe. The patients received no anti-emetics other than low-dose metoclopramide.

Phase II results with cisplatin, including ours, are rather consistent [17–20] and comparable to those achieved with other active agents. Table 3 reports overall response rates from some reviews of single agent trials; figures for fluorouracil and mitomycin include a majority of previously untreated patients.

Table 3. Overall response rates for some active agents

Drug	No. of patients	Responses	References
Fluorouracil	392	21%	[2]
Mitomycin	116	25%	[2, 3]
Doxorubicin	119	18%	[7, 8]
Cisplatin	82	19%	[17–20, present trial]

We might assume that cisplatin is active in the treatment of gastric cancer and that it should be included in new combination chemotherapy trials.

REFERENCES

1. MOERTEL CG. Clinical management of advanced gastrointestinal cancer. *Cancer* 1975, **36**, 675–682.
2. COMIS RL, CARTER SK. A review of chemotherapy in gastric cancer. *Cancer* 1974, **34**, 1576–1586.
3. COMIS RL. Mitomycin C in gastric cancer. In: CARTER SK, CROOKE ST, eds. *Mitomycin C. Current Status and New Developments*. New York, Academic Press, 1979, 129–132.
4. OGAWA M. An overview of chemotherapy for advanced gastric cancer. In: FRIEDMAN M, OGAWA M, KISNER D, eds. *Diagnosis and Treatment of Upper Gastrointestinal Tumors*. Amsterdam, Excerpta Medica, 1981, 357–368.
5. BUROKER TR, KIM PN, BAKER LH, RATANATHARATHORN V, WAJTASZAK B, VAITKEVICIUS VK. Mitomycin-C alone and in combination with infused 5-fluorouracil in the treatment of disseminated gastrointestinal carcinomas. *Med Pediatr Oncol* 1978, **4**, 35–42.
6. KOVACH JS, MOERTEL CG, SCHUTT AJ, HAHN RG, REITEMEIER RJ. A controlled study of combined 1,3-bis(2-chloroethyl)-1-nitrosourea and 5-fluorouracil therapy for advanced gastric and pancreatic cancer. *Cancer* 1974, **33**, 563–567.
7. MOERTEL CG, LAVIN PT. Phase II–III chemotherapy studies in advanced gastric cancer. *Cancer Treat Rep* 1979, **63**, 1863–1869.
8. THE GASTROINTESTINAL TUMOR STUDY GROUP. Phase II–III chemotherapy studies in advanced gastric cancer. *Cancer Treat Rep* 1979, **63**, 1871–1876.
9. MOERTEL CG, MITTELMAN JA, BAKEMEIER RF, ENSTROM P, HANLEY J. Sequential and combination chemotherapy of advanced gastric cancer. *Cancer* 1976, **38**, 678–682.

10. MOERTEL CG, O'CONNEL MF, LAVIN PT. Chemotherapy of gastric carcinoma. *Proc Am Assoc Cancer Res* 1979, **20**, 288.
11. MACDONALD JS, SCHEIN PS, WOOLLEY PV *et al.* 5-Flourouracil, doxorubicin, and mitomycin (FAM) combination chemotherapy for advanced gastric cancer. *Ann Intern Med* 1980, **93**, 533–536.
12. ROZENCWEIG M, ABELE R, VON HOFF DD, MUGGIA FM. Cisplatin: impact of a new anticancer agent on current therapeutic strategies. *Anticancer Res* 1981, **1**, 199–204.
13. ROZENCWEIG M, VON HOFF DD, ABELE R, MUGGIA FM. Cisplatin. In: PINEDO HM, ed. *Cancer Chemotherapy* 1981. Amsterdam, Excerpta Medica, 1981, 120–132.
14. SCHAUER P, MAGILL GB, HOWARD J, GOLBEY RB, BURCHENAL JH. Combination chemotherapy of gastric cancer with MIFA II or with AAFC-CPDD. *Proc Am Assoc Cancer Res* 1979, **20**, 335.
15. WOOLLEY P, SMITH F, ESTEVEZ R *et al.* A phase II trial of 5-FU, adriamycin and cisplatin (FAP) in advanced gastric cancer. *Proc Am Assoc Cancer Res* 1981, **22**, 455.
16. CAVALLI F. New drugs in the treatment of gastric cancer: methodological problems and some data. In: FRIEDMAN M, OGAWA M, KISNER D, eds. *Diagnosis and Treatment of Upper Gastrointestinal Tumors.* Amsterdam, Excerpta Medica, 1981, 412–417.
17. IZARZUGAZA I. Phase II clinical study of CDDP in gastric cancer resistant to chemotherapy. Paper presented at The Second NCI–EORTC Symposium on New Drugs in Cancer Therapy, 1979, Brussels, Belgium.
18. KARLIN DA, STROEHLEIN JR, BENNETTS RW, HEIFETZ LJ. *Cis*-platinum chemotherapy for advanced gastrointestinal cancer. *Proc Am Assoc Cancer Res* 1981, **22**, 451.
19. LEICHMAN L, MACDONALD B, DINDOGRU A, SAMSON M. Platinum: a clinically active drug in advanced adenocarcinoma of the stomach. *Proc Am Assoc Cancer Res* 1982, **23**, 110.
20. LACAVE AJ, WILS J, DIAZ-RUBIO E *et al.* Chemotherapy studies in advanced gastric cancer. Paper presented at The 8th Congress of the European Society for Medical Oncology and Plenary Session of the EORTC, 1982, Nice, France.