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Cis-platinum as Second-line Chemotherapy in Advanced Gastric Adenocarcinoma. A Phase II Study of the EORTC Gastrointestinal Tract Cancer Cooperative Group*

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Abstract—*Thirty-four patients with measurable metastatic gastric adenocarcinoma refractory to prior chemotherapy were treated with* cis-*platinum* 100 mg/m² *in a 6-hr infusion at 3-week intervals. Thirty-one patients were evaluable for response. There were three complete and three partial responses. Median duration of response was* 4 months. *Toxicity consisted mainly of nausea and vomiting and was severe in* 12 *patients. One patient had a severe but reversible renal failure. These results confirm other data reported in the literature. Cis-platinum has activity in gastric adenocarcinoma and should now be further investigated in first-line chemotherapy.*

INTRODUCTION

ACTIVE drugs in the treatment of advanced gastric cancer include 5-fluorouracil (5-FU), mitomycin-C, adriamycin and nitrosoureas [1]. Encouraging results were obtained with combinations of these drugs [2-5], but could not be reproduced in all series [6-9]. Complete response remains a rare event and median survival of all treated patients does not exceed 6 months. Therefore other agents and drug combinations must be further explored.

Cis-platinum (CDDP) has a well-defined activity in a wide variety of malignant tumors [10]. The effectiveness of CDDP in gastric cancer was first reported in 1979 [11]. A 22% response rate was observed in 18 patients previously treated [12]. Based on this experience the EORTC Gastrointestinal Tract Cancer Cooperative Group decided to conduct a multicenter phase II clinical trial in order to assess the activity of this drug in advanced gastric cancer.

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MATERIALS AND METHODS

Criteria of eligibility included measurable progressive disease defined as: abdominal masses if there were clear limits in the two largest perpendicular diameters; palpable lymph nodes; subcutaneous or skin lesions; lung metastases surrounded by aerated lung and hepatomegaly or more than 5 cm below the costal margin if the liver metastases were documented also by CT-scan, ultrasound, radionuclide scan or laparotomy. Other criteria for the entry of patients into the study included age less than 70 yr, Karnofsky performance status ⩾ 50%, adequate bone marrow function and serum creatinine less than 1.3 mg/100 ml. Patients with other primary tumors, severe malnutrition, CNS disease or active infection were not included in the study.

Cis-platinum was given in a dose of 100 mg/m² i.v. at 3-week intervals. The drug was administered in a slow 6-hr infusion with adequate pre- and posthydration. Furosemide was given when

necessary to maintain a diuresis rate of 100 ml/hr. Doses were reduced or chemotherapy delayed as appropriate for patients with day 1 or nadir myelosuppression. Treatment was continued until progression of disease.

Baseline data included history, physical examination, complete blood counts, serum electrolytes, hepatic and renal function and chest radiograph. Other appropriate investigations were performed in individual cases. All the laboratory parameters and tumor measurements were repeated before each treatment.

Definition of response and grades of toxicities used were those defined by the WHO [13]. Cases of early death due to tumor progression were considered evaluable for response even though they had only received one course of chemotherapy.

RESULTS

Between January 1980 and February 1984, 34 patients with advanced gastric cancer were entered in the study by five European institutions. Of these 34 patients 31 were evaluable for response. One patient was not eligible because he had no measurable disease (bone metastases) and two patients were inevaluable, in one the treatment dose being insufficient and the second dying from cerebral thrombosis a few days after starting the treatment. All patients had biopsy-proven adenocarcinoma of the stomach and were previously treated by chemotherapy. None had received radiotherapy. The histologic specimens were centrally reviewed. The characteristics of the 31 evaluable patients are summarized in Table 1. All patients received CDDP in second-line chemotherapy: two patients were previously treated with 5-FU only, and the others had different drug combinations containing 5-FU, adriamycin, methyl-CCNU or methotrexate. A median number of three cycles of CDDP (range 1-8) was administered. Twenty-six patients (84%) had visceral metastases and five (15%) had soft tissue metastases as the only evidence of the disease. The measurable disease sites of the 31 patients are listed in Table 1.

There were three complete responses lasting 16, 17 and 39 weeks and three partial responses lasting 11, 11 and 22 weeks respectively, giving an overall response rate of 19% (6/31). The patients who achieved a complete response received 5, 6 and 7 courses respectively. Nine patients had stable disease, with a median time to progression of 15 weeks (range 10-21 weeks), and the remaining 16 patients had progressive disease.

Median survival time for all patients was 15 weeks (range 3-47 weeks). Median survival time for patients with objective response was 24 weeks (range 17-31 weeks), and 7 weeks (range 3-18 weeks) for those who did not respond (Table 2). Responses were seen in either well-differentiated or undifferentiated ('diffuse' type) tumors. The characteristics of those patients who achieved response are listed in Table 3.

Table 1. Evaluable patient characteristics

Clinical features	No. of patients
Evaluable patients	31
Age (yr)	
Median	58
Range	26-67
Sex	
Male	25
Female	6
Performance status	
50	4
60-70	18
≥80	9
Previous chemotherapy	
F	2
FA	12
MeFA	15
FAMTX	2
Sites of measurable disease	
Liver	14
Abdomen	10
Lymph nodes	8
Subcutaneous	3
Skin	2

F = fluorouracil; A = adriamycin; M = mitomycin C; MTX = methotrexate.

The maximum toxicity per patient is presented in Table 4. Nausea and vomiting were observed in all patients and were severe (WHO grade 3 and 4) in 12. One patient had severe reversible renal toxicity. There were no toxic deaths.

DISCUSSION

The results of this phase II study, with an overall response rate of 19% (95% confidence interval: 5-33%), confirms the activity of CDDP in gastric cancer. Our experience reproduces the results reported by others [14-16]. In one study it was suggested that the histologic characteristics of gastric cancer might influence the potential response to CDDP because all the patients who responded to CDDP had gastric cancer of the 'intestinal' type [15]. Our study does not support this idea because we obtained remissions not only in well-differentiated but also in poorly differentiated ('diffuse' type) tumors as well.

This level of activity obtained with CDDP in patients with gastric cancer previously exposed to

Table 2. Therapeutic results

Response	No. of patients	Median time to progression (weeks)	Median survival time (weeks)
CR	3	17	26
PR	3	11	21
NC	9	15	17
PD	16	—	7
Overall	6/31 (19%)		

CR = complete response; PR = partial response; NC = no change; PD = progressive disease.

Table 3. Characteristics of patients with objective response

Case	Age	Sex	KI	Histology	Previous chemotherapy	Tumor site	Response by site	Type of response	Duration (weeks)	Survival (weeks)
No. 1	62	M	70	MD	FA	epigas. mass Douglas mass	CR CR	CR	39	47
No. 2	67	M	60	U	FA	abd. mass	CR	CR	16	17
No. 3	39	M	70	U	MeFA	liver	CR	CR	17	26
No. 4	58	F	70	U	MeFA	skin ascites	PR improvement	PR	11	15
No. 5	59	F	90	WD	MeFA	l. node	PR	PR	22	30
No. 6	49	M	70	—	FA	l. node skin lymphangitis	PR CR improvement	PR	11	21

WD = Well differentiated; U = undifferentiated; MD = moderately differentiated.

Table 4. Toxic side-effects by WHO grading system

	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	38	16	9	0
WBC	16	6	9	0
Platelets	9	6	3	3
Nausea and vomiting	12	48	35	3
Renal	16	0	3	0
Stomatitis and diarrhea	16	9	3	0

chemotherapy might be considered of importance in selecting the drug for further clinical evaluation [17]. A higher response rate may be expected in patients who did not receive previous chemotherapy [15], but its use as palliative treatment in combination chemotherapy could be hampered by its gastrointestinal toxicity. Some reports have been published using CDDP in first-line combination chemotherapy. In these trials CDDP was combined with 5-FU and adriamycin. In one study ten partial responses out of 35 patients were reported with a median duration of response of 7 months [18]. In another trial eight partial responses were noted out of 16 patients [19] and in the last one there were three complete and six partial responses out of 17 patients [20]. Median survival for all treated patients in the last two series was 10 months. Further investigations are justified in order to discover the best schedule of CDDP administration as well as the dose-response relationship when CDDP is used in first-line combination chemotherapy.

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