Clinical Trials Summaries

A Phase II Study of Carboplatin in Advanced or Metastatic Stomach Cancer*

MEIR BEER,[†] FRANCO CAVALLI,^{†‡} STANLEY B. KAYE,[§] LOUISE M. LEV,^{||} MICHEL CLAVEL,[¶]
JOHN SMYTH,^{**} MARTINE VAN GLABBEKE,^{††} JOSETTE RENARD^{††} and HERBERT M. PINEDO^{‡‡}
for the Early Clinical Trials Group of the European Organization for Research on Treatment of Cancer (EORTC)

[†]*Servizio Oncologico, Ospedale S. Giovanni, Bellinzona, Switzerland*, [§]*Department of Oncology, University of Glasgow, Glasgow, U.K.*, ^{||}*Rambam Medical Center, Haifa, Israel*, [¶]*Centre Léon-Bérard, Lyon, France*, ^{**}*University of Edinburgh, Department of Clinical Oncology, Western General Hospital, Edinburgh, U.K.*, ^{††}*EORTC Data Center, Brussels, Belgium* and ^{‡‡}*Akademisch Ziekenhuis der Vrije Universiteit, Amsterdam, the Netherlands*

CISPLATIN was shown to have some activity in gastric cancer [1-6]. This drug has also been used in a few combination chemotherapy trials [7-9].

The different toxicity pattern of carboplatin prompted the study group to evaluate the anti-tumor activity of this cisplatin analog in gastric cancer [10, 11].

PATIENTS AND METHODS

Fifty-three patients with histologically confirmed, advanced or inoperable adenocarcinoma of gastric origin participated in the trial between January 1984 and March 1986. Measurable or evaluable disease, age ≤ 75 , a performance status of 1-3 (WHO), life expectancy of 8 weeks, serum creatinine $120 \mu\text{mol/l}$, WBC $4 \times 10^9/\text{l}$, platelet counts $100 \times 10^9/\text{l}$ were required. Treatment had to be started after a period of 4 weeks after the last course of prior chemotherapy. Blood counts were assessed weekly, blood chemistry before every course and tumor size every two courses. Tumor response and toxicity were rated according to World Health Organization recommendations. Two full courses of treatment were required prior to response assessment, except in case of early, rapid progression; patients with progressive dis-

ease were taken off the study.

Protocol treatment consisted of carboplatin, 400 mg/m^2 infused i.v. in 150-250 ml dextrose 5%, once every 5 weeks. The dose per course was reduced to 350 mg/m^2 for the last 8 patients with prior treatment, after cases of toxic death were reported.

RESULTS AND DISCUSSION

The characteristics of the patients are shown in Table 1. Three patients had received a second chemotherapy which in one, contained cisplatin.

Exposure to carboplatin and toxicity are shown in Table 2. A drop in hemoglobin levels by 1-5 g/dl was seen in 16 patients. Six of the patients with an elevated serum creatinine ($120-160 \mu\text{mol/l}$) recovered to normal during treatment, while one patient died of bleeding with a creatinine of $250 \mu\text{mol/l}$. The following on-treatment conditions were also recorded: facial dysesthesia, pulmonary thromboembolism, fever, cerebral ischemic accident and diarrhea. Three deaths were attributable to toxicity, of sepsis in one patient previously treated with FAM, and of bleeding in two others pretreated with fluorouracil, doxorubicin and cisplatin.

Tumor response is reported in Table 3. The term 'early progression' refers to documented disease progression before the end of the first course. Of the three previously untreated patients who received less than the protocol dose, two had 'no

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†To whom reprint requests should be addressed.

Table 1. Characteristics of the patients

Entered	53		
No evaluable tumor	4		
Concomitant radiation	1		
Performance status 4	1		
Eligible	47		
27 male, 20 female			
Age			
31–69, median	56		
Performance status (WHO)			
0: 7, 1 (median): 18, 2: 17, 3: 5			
Previous treatment			
Radical surgery:	17		
(Time from surgery 2–55 months, median 21)			
		Previous response	n evaluable
Combination chemotherapy:*	27		
FAM	21	3	12
AF	3	0	3
FAP	2	2	2
Disease localization			
Primary/abdominal wall recurrence	22		
Liver	21		
Nodes	13		
Bone	3		
Lung	4		
Soft tissue/skin	3		
Ascites/pleural fluid	9		

*F: fluorouracil, A: doxorubicin, M: mitomycin, P: cisplatin.

Table 2. Carboplatin treatment

1–9 courses, median 2.	Dose per course	193–460 mg/m ² (median 400)
Total courses 47	Total dose	240–3300 mg/m ² (median 800)
(1 course only: 21 patients)		
Toxicity	(Fully documented: 33 patients)	
Hematologic	Pretreated (21)	Non-pretreated (12)
Platelets ($\times 10^9/l$)		
Nadir range 10–310, day 15–35 (median 22)		
100	5	7
50–100	8	3
25–50	3	2
25	5	0
WBC ($\times 10^9/l$)		
Nadir range 0.7–10.8, day 11–42 (median 27)		
4.0	6	7
2–4	9	4
1–2	2	1
1	3	0
Non-hematologic	(43 patients assessed)	
	WHO grade	Number
Nausea/vomiting	1	11
	2	18
	3	3
Renal	1	7
Hair loss	2	6
Stomatitis	1	1
	2	1
Paresthesia	1	1

Table 3. Response evaluation

<i>Previously treated patients</i>		
Eligible		27
Response not evaluable:		7
Treatment stopped too early	2	
Follow-up stopped too early	1	
Combination treatment	1	
Toxic death	3	
Response evaluable:		20
Partial response	2	(2, 4+ months)
No change	1	(3 months)
Progression	17	
(Early progression: 6)		
<i>Previously untreated patients</i>		
Eligible		20
Response not evaluable		5
Early death, tumoral	4	
Early death, PTE	1	
Response evaluable		15
Partial response	1	(12 months)
No change	6	(3-12 months, median 5.5)
Progression	8	
(Early progression: 3)		

change'. Indicator lesions in the responding patients were primary tumor, abdominal wall recurrence, lung and lymph node metastases.

The 95% confidence intervals for the response rate are 0-32% in the non-pretreated group and 0.1-24% in the other. This minimal response rate is compatible with recently published data [12]. The pattern of toxicity is also similar to published results; in particular, the three cases of toxic death stress the necessity of a dose reduction for previously treated patients.

These data confirm also that the inclusion of patients with a poor performance status is likely to impair the evaluability of phase II studies.

REFERENCES

- Greenwald E, Vogl SE, Camacho F *et al.* Cis-platinum in refractory gastric cancer. *Proc Am Assoc Cancer Res* 1983, **24**, 147.
- Beer M, Cocconi G, Ceci G, Varini M, Cavalli F. A phase II study of cisplatin in advanced gastric cancer. *Eur J Cancer Clin Oncol* 1983, **19**, 717-720.
- Lacave AJ, Izarzugaza I, Anton Aparicio LM *et al.* Phase II clinical trial of cis-dichlorodiammineplatinum in gastric cancer. *Am J Clin Oncol* 1983, **6**, 35-38.
- Leichman L, McDonald B, Dindogru A *et al.* Cisplatin. An active drug in the treatment of disseminated gastric cancer. *Cancer* 1984, **53**, 18-22.
- Ajani J, Kantarjian H, Kanojia M, Karlin D. Phase II trial of cis-platinum in advanced upper gastrointestinal cancer. *Proc Am Soc Clin Oncol* 1984, **3**, 147.
- Aabo K, Pedersen H, Rørth M. Cisplatin in the treatment of advanced gastric carcinoma: a phase II study. *Cancer Treat Rep* 1985, **69**, 449-450.
- Wadler S, Green M, Muggia F. The role of anthracyclines in the treatment of gastric cancer. *Cancer Treat Rep* 1985, **12**, 105-132.
- Rougier P, Droz JP, Piot G, Theodore C, Ruffie P, Kac J. Phase II trials of combined 5FU + adriamycin + cisplatin (FAP) in gastric carcinoma. *Cancer Chemother Pharmacol* 1986, **18**, Suppl. A, 62.
- Wilke H, Preusser P, Achterrath W *et al.* Neoadjuvant chemotherapy with etoposide/adriamycin/cisplatin (EAP) in patients with inoperable locally advanced gastric carcinoma and intraabdominal lymph node metastasis (N2-N3). *Cancer Chemother Pharmacol* 1986, **18**, Suppl. A, 77.
- Rose WC, Schurig JE. Preclinical antitumor and toxicologic profile of carboplatin. *Cancer Treat Rev* 1985, **12**, Suppl. A, 1-20.
- Canetta R, Rozencweig M, Carter SK. Carboplatin: the clinical spectrum to date. *Cancer Treat Rev* 1985, **12**, Suppl. A, 125-136.
- Einzig A, Kelsen DP, Cheng E *et al.* Phase II trial of carboplatin in patients with adenocarcinomas of the upper gastrointestinal tract. *Cancer Treat Rep* 1985, **69**, 1453-1454.