Eur J Cancer Clin Oncol, Vol. 22, No. 7, pp. 891–892, 1986.
Printed in Great Britain.

0277-5379/86$3.00+0.00
Pergamon Journals Ltd.

Letter to the Editor

Phase II Trial of a Combination of Low Dose Cisplatin (DDP) and Bolus 5-Fluorouracil (FU) in Recurrent and Metastatic Squamous Cell Carcinoma of the Head and Neck

F. COGNETTI,* M. CLERICO,† J. VERMORKEN,‡ M. VAN RYMENANT,§ A. ROSSI,‖ A. KIRKPATRICK,¶ O. DALESIC¶ and M. CLAVEL** For the EORTC Head and Neck Cooperative Group

**Istituto Regina Elena per lo Studio e la Cura dei Tumori, viale Regina Elena* 291, 00161 *Rome*; †*Ospedale San Giovanni, via Cavour* 35, 10123 *Turin, Italy*; ‡*Academish Ziekenhuis der Vrije Universiteit, De Boelelaan* 117, 1007 *MB Amsterdam, The Netherlands*; §*Institut Jules Bordet,* 1 *rue Héger Bordet,* 1000 *Brussels, Belgium*; ‖*Istituto Nazionale Tumori Milano, via Venezian* 1, 20133 *Milan Italy*; ¶*EORTC Data Center,* 1 *rue Héger Bordet,* 1000 *Brussels, Belgium*; ***Centre Léon Bèrard,* 28 *rue Laennec,* 69373 *Lyon Cedex* 08, *France*

ANIMAL models have shown a possible action synergism between DDP and FU [1], particularly with 5-FU prior to DDP administration [2].

Very impressive results have been obtained by the Wayne State University Group employing DDP plus continuous FU infusion both in previously untreated patients with locally advanced squamous cell carcinoma of the head and neck [3] and in patients with recurrent or metastatic disease [4]. The aim of the present study was to evaluate the antitumor activity and toxicity of a combination of low dose cisplatin and bolus FU, suitable for out-patient administration, particularly in patients with disease progression after first line combination chemotherapy (regimen ABO) consisting of methotrexate, bleomycin and vincristine [5]. Only patients with histologically or cytologically confirmed squamous cell carcinoma of the head and neck, were considered eligible for this trial. Measurable or evaluable lesions were required to enter into this study. Patients of more than 75 years of age or with a performance status of 3 or more on the ECOG scale or patients previously treated with FU or DDP were excluded. The patients could not have received prior radio- or chemotherapy during the last 4 weeks and all major toxic reactions of prior treatment had to have been resolved. All patients were required to have normal renal (serum creatinine $\leq$ 1.5 mg/dl), hepatic (bilirubin $\leq$ 1.5 mg/dl) and hematologic (WBC $\geq$ 4000/mm^3 and platelet count $\geq$ 100,000/mm^3) functions.

Treatment consisted of: FU 500 mg/m^2 i.v. push days 1,2 and 3; DDP 50 mg/m^2 i.v. day 4; 1 litre of 5% dextrose in 0.45% NaCl + 20 mEq KCl was given before and after DDP administration (2 hr each); furosemide 40 mg i.v. was given immediately prior to DDP. The courses were repeated every 3 weeks.

An adequate trial required completion of at least two courses of therapy except in the case of clear disease progression after one full course. Responses were defined according to the WHO criteria [6]. Treatment was continued until disease progression. Duration of response was calculated from the time of beginning the treatment to the time of relapse or death.

Forty-one eligible patients from seven different institutions were entered into this study. Of these, 35 patients were evaluable in terms of response and toxicity and two for treatment toxicity because of inadequate documentation and early death, respectively. Four of these patients could not be evaluated, having been lost to follow-up.

Accepted 2 January 1986.
Correspondence and reprint requests to: Francesco Cognetti, Istituto Regina Elena per lo Studio e la Cura dei Tumori, viale Regina Elena 291, 00161 Roma, Italy.

Table 1. *Characteristics of the* 35 *evaluable patients*

Sex: M/F = 31/4		Age: Median 57 (range 34–75)	
PS: Median 1 range 0–2		Extension: Locoregional = 24 Metastatic = 11	
Site of primary:		Prior treatment:	
larynx	= 11	no prior therapy	= 1
oral cavity	= 7	prior surgery	= 26
tongue	= 5	prior radiotherapy	= 28
oropharynx	= 4	prior chemotherapy	= 28
hypopharynx	4		
lip	= 2		
nasopharynx	= 1		
salivary glands	= 1		

Table 1 reports the characteristics of the 35 fully evaluable patients. A median number of three courses was administered (range 1–10). Eight patients achieved an objective response (three complete, five partial) with an overall response rate of 23%. Overall response rates decreased from 53% for primary tumor to 23% for regional lymph nodes and to 18% for lung metastases. Response rates were lower in patients with previously irradiated lesions (28%) than in those non-irradiated (56%) and in patients who had received prior chemotherapy (18%) as compared to those who had not. One previously untreated patient with locally advanced cancer of the oral cavity received four courses of this regimen, achieving a complete response before definitive radiotherapy.

The median duration of the responses observed was 12 weeks (range 6^{+}–31^{+}). The three patients who obtained a complete response are still disease-free 6, 10 and 31 weeks from beginning treatment.

Hematological toxicity was substantial in the 37 evaluable patients. Twenty-seven patients presented leukopenia ($< 4000/mm^3$), nine severe and two life threatening. Ten patients presented thrombocytopenia ($< 100{,}000/m^3$) which was always mild to moderate. One case of treatment-related infection was observed. Eighty-nine per cent of the patients had some degree of nausea and vomiting but only 8% presented grade III toxicity. Twenty-four per cent developed diarrhea, 19% fever, 16% mild neuropathy, 8% moderate stomatitis and 3% bilirubine increases or constipation.

The response rates obtained with this low dose cisplatin and bolus 5-fluorouracil regimen were low in this series of heavily pretreated patients, especially in those who had received prior chemotherapy and for whom the trial had been mainly designed.

The data reported confirm the lack of an active second-line chemotherapy regimen for patients affected with this disease. The activity of the regimen appears to be higher in patients who had never been submitted to chemotherapy. In this regard, however, a comparison cannot be made with the results obtained by the Wayne State University Group, that employ DDP plus a continuous infusion of FU.

Myelosuppression was found to be moderate to severe confirming the higher hematologic toxicity of schedules which include the administration in push of 5-FU as opposed to continuous infusion.

REFERENCES

1. Schabel FM Jr., Trader MW *et al. Cis*-diamminedichloroplatinum II: combination chemotherapy and cross-resistance studies with tumors of mice. *Cancer Treat Rep* 1979, **63**, 1459–1473.
2. Vietti T, Coulter D, Valeriote F. Interval and sequence dependent lethal combination with other agents. *Proc AACR and ASCO* 1979, **20**, 202.
3. Decker DA, Drelichman A, Jacobs S, Hoschner J, Kiuric S, Weaver A, Al-Sarraf M. Adjucant chemotherapy with cis-diamminedichloroplatinum II and 120-hour infusion 5-fluorouracil in Stage III and IV squamous cell carcinoma of the head and neck. *Cancer* 1984, **53**, 1819–1824.
4. Kish JA, Weaver A, Jacobs J, Cummings G, Al-Sarraf M. Cisplatin and 5-fluorouracil infusion in patients with recurrent and disseminated epidermoid cancer of the head and neck. *Cancer* 1983, **51**, 1553.
5. Clavel M, Wildiers J, Van Rijmenant M, Bruntsch U, Kirkpatrick A, Rozencweig M. Randomized trial of cisplatin (C), methotrexate (A), bleomycin (B) and vincristine (O) vs ABO in advanced squamous cell carcinoma of the head and neck. *Proc ASCO* 1983, **2**, 158.
6. WHO Handbook for Reporting Results in Cancer Treatment. Geneva, WHO, 1979.