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96-Hour Continuous Infusion of *Cis*-platinum, 5-Fluorouracil and Bleomycin in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma, Unexpected Anemia

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Abstract—Cis-*platinum, 5-fluorouracil and bleomycin are active agents in head and neck SCC. When given by continuous infusion (C.I.) lower toxicity and increased activity have been reported. A 4-day trial of triple C.I. including these reagents was conducted for recurrent and/or metastatic head and neck SCC.* Cis-*platinum* 25 mg/m^2/*day*, 5-*FU* 650 mg/m^2/*day and bleomycin* 10 mg/m^2/*day were given for 4 days every 4 weeks. Twenty-nine patients were entered, 27 were evaluable for toxicity and 3 for response. The response rate was* 30% (*one CR and seven PR*). *Patient compliance was poor (one central and one peripheral i.v. line) and toxicity was acceptable except for the unexpected anemia;* 48% *of patients required red cell transfusion. One patient died of bleomycin-induced lung toxicity and minor renal toxicity related to parenteral hydration was observed in the first* 16 *patients.*

In conclusion, this combination is moderately active in recurrent and/or metastatic head and neck SCC. Patient compliance was poor and cumulative anemia was an unexpected toxic event. Further trials with this triple C.I. chemotherapy are not recommended for the alcoholic, undernourished, very advanced cancer patient population.

INTRODUCTION

Patients with recurrent and/or metastatic head and neck squamous cell carcinoma have a bad prognosis with a median survival between 6 and 10 months despite systemic chemotherapy [1]. Reported objective response rates vary from 13 to 70% [1, 2]. The variation in reported results is probably attributable to heterogeneous patient populations [3, 4].

Cis-platinum [5], 5-fluorouracil [6, 7] and bleomycin [6] are active drugs in head and neck cancer. Fluorouracil [8, 9] and bleomycin [10, 11] have been reported to be less toxic and more active when given by continuous infusion. The combination of *cis*-platinum with continuous infusion bleomycin [12, 13] and with continuous infusion 5-fluorouracil [14] have become references for other treatment programs in head and neck cancer. In our experience *cis*-platinum and continuous infusion 5-fluouracil and bleomycin in combination have been very active in previously untreated patients with undifferentiated nasopharyngeal carcinoma [15] and squamous cell carcinoma [16].

Cis-platinum administered by continuous infusion was first reported by Salem *et al.* [17]. Definitive phase I sudies recommended doses of 25–30 mg/m^2/day for 5 days [18, 19]. The reduced incidence of gastrointestinal toxicity and the increase in free platinum levels [20] obtained by continuous infusion suggested a possible improvement in the therapeutic index of the drug.

We were prompted with these considerations in mind to administer *cis*-platinum, 5-FU and bleomycin concomitantly by continuous infusion in patients with recurrent and/or metastatic head and neck cancer. The object of this study was to test the feasibility and the activity of the triple continuous infusion.

MATERIAL AND METHODS

From July 1986 to January 1987, 29 patients with recurrent and/or metastatic head and neck SCC were included in this program. Eligibility requirements included: (1) recurrent and/or metastatic squamous cell carcinoma of head and neck origin proven by histology or cytology; (2) WHO

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performance status 0–3; (3) adequate renal function (creatinine below 100 mol/l or creatinine clearance above 60 ml/min); (4) adequate bone marrow function (WBC >4000/mm^3, platelets >100,000/mm^3 and Hb ≥ 10.5 g/dl). As this was a feasibility study, two patients with proven but not measurable or evaluable disease were included. Four patients had previously received neoadjuvant chemotherapy with *cis*-platinum containing regimens. Clinical characteristics are listed in Table 1.

The chemotherapy regimen (Table 2) was given every 4 weeks and consisted of *cis*-platinum 25 mg/m^2/day for 4 days by continuous infusion in 1 l of normal saline; 5-fluorouracil 650 mg/m^2/day for 4 days by continuous infusion in 500 ml of 5% dextrose; and bleomycin 10 mg/m^2/day for 4 days by continuous infusion in 500 ml of normal saline.

Cis-platinum and bleomycin were administered through one central line and 5-fluorouracil through a peripheral line because a risk of degradation exists when *cis*-platinum and 5-fluorouracil in 5% dextrose are administered concomitantly [21]. A 21/day hydration and 40 mg/day of Metoclopramide were given during the 4 days of continuous infusion. We increased hydration to 3 l/day in the middle of the study owing to possible cumulative renal toxicity as has been suggested by Posner [4].

Treatment was suspended for a week if WBC or platelets did not return to normal values. *Cis*-platinum was reduced to 20 mg/m^2/day if the creatinine clearance was between 40 and 60 ml/min. Bleomycin was discontinued if clinical and/or radiological suspicion of interstitial pulmonary disease transpired.

Response and toxicity were evaluated after at least two cycles according to WHO criteria [22].

Table 1. *Patient characteristics*

Patients entered	29
Evaluable for toxicity	27
Evaluable for response	23
Sex	
male	28
female	1
Age (36–72 years)	54 y
Performance status (WHO)	
0	4
1	20
2	3
3	1
4	1
Histology	
well differentiated	23
poorly differentiated	6
Primary sites	
oral cavity	3
oropharynx	10
larynx	7
hypopharynx	7
unknown	2
Previous treatment	
surgery and radiotherapy	14
radiotherapy	10
surgery and chemotherapy	1
chemotherapy	4
previously untreated	4
Sites of disease	
locoregional (previous RT)	11
locoregional and metastasis (4 previously untreated)	15
metastasis only	3

Table 2

CDDP	25 mg/m^2/day—96-h C.I.
5-Fluorouracil	650 mg/m^2/day—96-h C.I.
Bleomycin	10 mg/m^2/day—96-h C.I.

RESULTS

Twenty-nine patients were entered. Their detailed characteristics are listed in Table 1. Two patients died of disease within a month of the initiation of therapy and were not evaluable for response or toxicity. Two patients had disease which was not evaluable for response (pleural effusion treated by drainage and talcum powder intrapleurally) and two refused a second cycle while still with stable disease. Therefore 27 patients were evaluable for toxicity and 23 patients evaluable for response.

The average number of cycles/patient was 2.6 (1–4 cycles). One CR and six PR were observed with a response rate of 30% (7/23). Three out of four previously untreated patients had an objective response. They all had a substantial volume of locoregional disease with simultaneous lung metastasis at presentation (Table 1). Only 4/19 previously treated patients responded (two with lung metastasis and two patients with locoregional disease relapsing more than 2 years after surgery and radiotherapy). One patient with previous chemotherapy responded. The duration of response was 7 months for the CR and 5 months (3–7 months) for partial responses.

Overall median survival was 7 months and 9 months for responders. Only two patients were alive 12 months after the first cycle and no patients were alive at 15 months.

TOXICITY

The regimen was poorly tolerated from the point of view of comfort since all patients had two i.v. lines. There was mild to moderate nausea and vomiting which were satisfactorily controlled by standard metoclopramide doses. Only 3/27 patients had Grade III vomiting. Mucositis was seen on only one patient (Grade II).

Renal toxicity was cumulative, reversible and hydration dependent. Eight Grade I and 3 Grade III renal toxicity were observed after two or more

cycles in the first 16 patients. This toxicity decreased when the total daily parenteral hydration was increased to 3 l/day and only 1/11 patients had Grade I renal toxicity. In 70 cycles there were four episodes of Grade III leucopenia and three episodes of Grade III thrombopenia.

Of particular interest is the anemia; chemotherapy related and greater than expected (Table 3). This anemia was cumulative and severe. Eighteen of 23 patients who received two or more cycles had a Hb decrease of ≥3.5 g/dl. Thirteen patients required packed red cell transfusion. We compared retrospectively the red cell toxicity of these patients with the anemia observed in a group of patients treated at our institution with the same drugs and schedule with the exception that 100 mg/m^2/day of *cis*-platinum was given in a 1 h infusion. All patients had recurrent and/or metastatic head and neck squamous cell carcinoma. Of the 33 patients entered in this particular control trial, 31 were evaluable for toxicity and 29 for response. Median age was 55 years and median PS 1 (0–3). Twenty-seven patients had previously been treated by surgery and/or radiotherapy. Grade II and III anemia (Table 4) was observed in 2/23 patients after two cycles (vs. 8/23; *P*: 0.03) and in 3/16 patients (vs. 7/15; *P*: 0.05) after three cycles. Five out of 31 patients required red cell transfusion vs. 13/23 patients (*P*: 0.003) in the triple perfusion group. Decrease in Hb ≥ 3.5 g/dl after two cycles was also significantly increased in the continuous infusion *cis*-platinum-treated patients (18/23 patients vs. 5/23; *P*: 0.0001). Four patients had an objective response (13%) which was not statistically different from the 30% response rate observed in this study (*P*: 0.3).

Table 3. *Red cell toxicity (WHO criteria)*

	No.	Grade 0	I	II	III	IV
1 cycle	27	14	9	3	1	0
2 cycles	23	9	6	7	1	0
3 cycles	15	1	7	3	4	0

WHO toxicity criteria for anemia
Grade 0: 11 g/dl
Grade I: 9.5–10.9 g/dl
Grade II: 8–9.4 g/dl
Grade III: 6.5–7.9 g/dl
Grade IV: 6.5 g/dl.

Table 4

	No.	Grade 0	1	2	3	4
1 cycle	31	18	8	5	0	0
2 cycles	23	11	10	1	1	0
3 cycles	16	7	6	2	1	0

Red cell toxicity of 31 patients treated with *cis*-platinum 1 h infusion and continuous infusion bleomycin and fluorouracil (control group).

Other toxicities were observed: four patients developed orthostatic hypotension, two patients symptomatic hyponatremia and one patient presented paresthesias after one cycle of therapy.

One patient died 1 month after the 3rd cycle of chemotherapy due to respiratory failure and interstitial pulmonary disease. The cumulative dose of bleomycin in this case was 180 mg (110 mg/m^2). The autopsy confirmed interstitial fibrosis. Another patient developed a radiological pattern of interstitial fibrosis without symptoms. This patient had Grade III renal toxicity.

DISCUSSION

The protocol was conducted to test the feasibility and the potentially reduced toxicity of continuous infusion *cis*-platinum, 5-fluorouracil and bleomycin which has been reported for each drug [8–11, 18] separately.

In this group of patients 30% response rates were achieved (confidence limits 11–49%) and therefore comparable with other active combinations in this kind of patient population [23, 24]. The median duration of response was 5 months and survival in responding patients was short (9 months).

In previously untreated patients (with metastatic disease at presentation) objective responses were seen in three out of four patients which further points to the chemosensitivity of previously untreated disease [4].

Protocol acceptance was poor, due to the two lines necessary for continuous infusion. Cumulative toxicities appeared after two or three cycles. Two patients developed interstitial pulmonary disease and three patients Grade III reversible renal toxicity which may have influenced the bleomycin toxicity seen in one patient. Most important and yet unexpected was the anemia, which was cumulative (see Table 3) and probably *cis*-platinum schedule dependent. No patients had macroscopic bleeding nor an increase in reticulocyte counts or bilirubin. Forty-eight per cent of patients required red blood cell transfusion. Most patients had a long history of alcohol ingestion and were malnourished (14/27 patients had a MCV above 90[3]).

Anemia was reported as *cis*-platinum toxicity in patients treated with conventional doses [25], high doses [26] or by continuous infusion [18–27].

Despite isolated cases of positive antiglobulin tests and hemolytic anemia [29, 30] reported with *cis*-platinum, this mechanism did not explain the progressive decrease in Hb values in our patients. Ferrokinetic studies in patients with ovarian carcinoma treated with *cis*-platinum have shown that

Fe-59 incorporation was below detectable levels 2 weeks after *cis*-platinum therapy suggesting the existence of a central mechanism for *cis*-platinum induced anemia [31]. A decrease in erythropoietin levels (independent of renal toxicity) has been reported in patients with head and neck cancer treated with *cis*-platinum [32]. This deficit was not confirmed by others, who have suggested that a defective iron delivery to erythroid precursors may explain the phenomenon [31].

Three factors may have played a contributory role in the red cell toxicity in this study: (1) the defective marrow function in our population (chronic alcohol ingestion), (2) the increased free platinum exposure (AUC) obtained with *cis*-platinum given by continous infusion [33] and (3) the decrease in renal function in some patients.

In conclusion, the triple 96 h continuous infusion of *cis*-platinum, 5-fluorouracil and bleomycin is a moderately effective association in recurrent or metastatic head and neck SCC. Interesting results were obtained with previously untreated patients.

Nevertheless this regimen administered by continuous infusion cannot be recommended for patients with advanced, previously treated head and neck squamous cell carcinoma due to its cumulative toxicity, in particular the *cis*-platinum schedule-related anemia.

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