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Phase-II study of *cis*-diammine-dichloro platinum (*cis*-platinum), bleomycin and methotrexate for advanced squamous cell carcinoma of head and neck

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Summary. *Twenty-one patients with head and neck carcinomas relapsing after radiotherapy were treated with a combination of cis-platinum, bleomycin, and methotrexate. Four patients (19%) achieved a partial response. Toxicity was significant in selected cases; three patients developed WBC counts less than 1,000/mm^3 and one of these patients died with sepsis. Severe mucositis was present in three of the twenty-one patients. Considering the toxicity of this combination and the limited therapeutic activity with the dose and schedule used in this study, this regimen is not recommended for the treatment of squamous head and neck carcinomas relapsing after radiotherapy.*

Introduction

Epidermoid carcinomas of head and neck are in general treated initially with surgery and radiotherapy; the lifespan of patients relapsing after previous surgery or radiotherapy is poor, with a median survival of 6 months [2]. Consequently it was hoped that chemotherapy would become an important component in the management of patients with this group of tumors, and encouraging results have been reported when chemotherapy was combined with radiotherapy and/or surgery [1, 4, 5, 8, 11, 12].

Methotrexate is the most active single agent for the treatment of head and neck carcinomas, producing response rates of 30%–50%. The median duration of response is short, however, lasting only 3–4 months [1]. Bleomycin has been widely used in squamous cancer of head and neck, with an overall reported response rate of 37%, but as with methotrexate, remissions are quite finite in duration [2]. Platinum has shown important antitumor activity in many tumors, and a 26% response rate has been recorded in head and neck cancers treated with this drug [13]. Combinations of *cis*-platinum and bleomycin have been shown to be effective when used prior to radiotherapy [4, 5], and a regimen incorporating all three drugs has been reported to produce a 61% response [17]. Whereas in four randomized trials comparing methotrexate with combination chemotherapy no significant advantage of the combinations has been established, no studies have compared methotrexate against *cis*-platinum, bleomycin, and methotrexate in combination [15].

At the Vincent T. Lombardi Cancer Research Center we examined the efficacy and toxicity of a combination of these drugs, methotrexate, bleomycin, and *cis*-platinum, in patients with advanced or recurrent epidermoid carcinoma of head and neck that had previously been treated with radiotherapy.

Materials and methods

Twenty-one patients with advanced, histologically confirmed epidermoid carcinoma of head and neck were entered in this protocol. All had relapsed following previous treatment with radiotherapy. Only one patient had received prior chemotherapy with weekly methotrexate. There were 12 females and nine males. The median age was 56 years (4–70 years). The Eastern Cooperative Oncology Group (ECOG) performance scale was used. Performance status (PS) at the time of chemotherapy was PS 0 in seven patients, PS 1 in four patients, and PS 2, 3, and 4 in one patient each. The median interval from original diagnosis was 17 months (4–124), and that from radiotherapy was 10 months (1–60). All patients had to have a creatinine clearance greater than 60 cm^3/min and BUN less than 20 mg/100 ml prior to entry on study and before each new cycle of chemotherapy was administered.

Complete remission (CR) was defined as the disappearance of all clinical evidence of disease. Partial remission (PR) was defined as a decrease of 50% or greater in the products of the two largest perpendicular diameters of measurable lesions, without evidence of worsening at any site and without deterioration in the general health of the patient; this result must be observed at least a month after the onset of therapy. Stabilization meant reduction by less than 50% of the initially measurable lesions, without increase or appearance of any other lesions. Progression was defined as any increase in tumor size or appearance of one or more lesions. Duration of remission was defined from the first day of treatment to the first day of documented progression. Patients were evaluable for toxicity and response if they completed one cycle of treatment.

Drug administration. The chemotherapy program employed in this study is shown schematically in Table 1. Mannitol, 20 g

Table 1. Combination drug schedule

Methotrexate	40 mg/m^2	IV	Day 3 and 10
cis-Platinum	50 mg/m^2	Push, 15 min	Day 1
Bleomycin	10 mg/m^2	IV	Day 1 and
	5 mg/m^2	IV	Day 10

Repeat every 4 weeks

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with 600 ml 5% dextrose, was administered during the initial 2-h period. Platinum was then given in 50 ml 5% dextrose as a push over a 15-min period, followed by 4 h of mannitol infusion at 100 cm^3/h. Bleomycin 10 mg/m^2 was administered IV on day 1 and 5 mg/m^2 on day 10. Methotrexate 40 mg/m^2 IV was aministered on days 3 and 10.

Methotrexate was reduced to 50% of the original dosage if at the beginning of the cycle the WBC count was less than 3,000/mm^3 or the platelet count less than 100,000/mm^3. If at day 10 the WBC count was less than 2,000/mm^3 or the platelet count less than 75,000/mm^3, methotrexate was withheld for that treatment cycle.

Results

Responses

Four of the 21 evaluable patients achieved PR. No CRs were observed. Two patients evidenced stable disease, and the other 11 patients all had progressive tumor growth. The duration of PR was 3, 6, 7, and 7 months. Two patients had stable disease for 3 and 6 months. The overall median survival was 7 months. Responding patients survived longer than nonresponders; the median survival for responders was 12.5 months (3–15 months), against 5 months for nonresponders (3–24+). These results, however, are not statistically significant. Three patients are still alive; all were nonresponders under this protocol but two of them responded to subsequent chemotherapy using cyclophosphamide and 5-fluorouracil.

Toxicities

All patients were evaluable for toxicity. Nausea and vomiting was observed in all but two patients; in two it was considered severe, but no patient refused chemotherapy because of this toxicity. Mucositis was seen in five patients and considered severe in three, with one patient requiring hospitalization. Four patients experienced diarrhea. Three patients had treatment delayed because of low blood counts (Table 2). There was one episode of sepsis with a WBC of 300/mm^3, which resulted in death of the patient after a single course of treament. Two patients received platelet transfusions because of thrombocytopenia less than 20,000/mm^3, but no episodes of bleeding were documented.

Twelve patients evidenced some decrease of their creatinine clearance. Three patients had creatinine clearance reduced to less than 50 cm^3/min; in two cases the renal function improved and creatinine returned to 56 and 73 cm^3/min. The third patient, who died of sepsis, had at the time of his death a serum creatinine of 3.2 mg/100 ml, with a uric acid level of 12 mg/100 ml and BUN of 77 mg/100 ml. There was no clinical evidence of ototoxicity or neurotoxicity. Hypomagnesemia was not evaluated methodically; no decreased magnesium levels were encountered.

Bleomycin was discontinued in one patient after two cycles of treatment because of severe mucositis and skin toxicity. Two patients had fever and chills during administration of this drug.

Table 2. Lowest blood counts in patients treated

WBC nadir	Patients	Platelets nadir	Patients	HT nadir	Patients
3,000	12	150,000	9	35	4
2,999–2,000	3	150,000–100,000	6	34–30	4
1,999–1,000	1	100,000– 50,000	1	29–35	11
1,000	3[a]	50,000	3	–	–

[a] WBC of these patients: 200, 300, and 500/mm^3

Discussion

The PR rate of 19% with no CRs with our program of *cis*-platinum, bleomycin and methotrexate, is lower than has been previously reported by other authors using the same chemotherapeutic agents in a variety of regimens [3, 7, 11, 16, 17]. The overall median survival in our patients was 7 months and it does not differ significantly from that of untreated patients [2]. The median survival of 12.5 months for responding patents is encouraging, but the number of patients is too small to consider a definite prolongation of survival in these patients.

The potential explanation for the low response rate observed in our patients could be related to the dose and schedule employed in this regimen. Bleomycin has been administered as a 24-h infusion in several recent protocols, and there is rationale to support an improved therapeutic index when the drug is administered by this route [6, 9, 14]. The dose used in our protocol was low, and the 4-week interval between cycles is longer than that in most other studies of these drugs in combination. Nonetheless, this combination of drugs produced significant hematologic toxicity and demonstrable biologic activity, and one patient died from sepsis secondary to treatment-related neutropenia. Two patients required platelet and red cell transfusions during their treatment. Kidney toxicity was moderate and but one patient sustained severe renal function impairment. The contribution of durg sequencing, i.e., methotrexate following *cis*-platinum, to overall toxicity cannot be determined.

The results of this study show that with the dose and schedule employed, combination chemotherapy with *cis*-platinum, bleomycin, and methotrexate produced considerable toxicity with no significant therapeutic activity in patients with head and neck cancer relapsing after radiotherapy. The results obtained with this regimen are no better than those seen in published series in which single-agent methotrexate was used, and it does not warrant further study.

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