Cancer Chemother. Pharmacol. 3, 57–59 (1979)

Cancer Chemotherapy and Pharmacology

Randomized Comparison of *cis*-Diamminedichloroplatinum Versus *cis*-Diamminedichloroplatinum, Methotrexate, and Bleomycin in Recurrent Squamous Cell Carcinoma of the Head and Neck

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Summary. *Fifty-seven patients with recurrent squamous-cell carcinoma of the head and neck area were randomized to two different chemotherapeutic regimens. Thirty patients received cis-platinum (DDP) alone and 27 patients received a combination of DDP, methotrexate, and bleomycin. All 57 patients had undergone previous radiation and/or ablative surgery. Of the 30 patients receiving DDP alone, one patient showed a complete response and three a partial response (13%). Amongst the 27 patients receiving DDP, methotrexate, and bleomycin, three showed a partial response (11%); there were no complete responders in this group. Major toxicity in the DDP alone group was renal. Renal toxicity and myelosuppression complicated the DDP, methotrexate, and bleomycin group. In summary, the combination of DDP, methotrexate, and bleomycin is no more effective than the use of DDP alone in recurrent squamous-cell carcinoma of the head and neck.*

Introduction

Chemotherapy for recurrent squamous-cell carcinoma of the head and neck has limited effectiveness. Although several agents such as methotrexate, bleomycin, cyclophosphamide, and adriamycin appear to be effective in untreated patients, their ability to induce a clinical response alone or in combination for recurrent disease is unusual. When a response is seen, it is incomplete and of short duration [2].

cis-Diamminedichloroplatinum (DDP) has been shown to be clinically active in carcinoma of the head and neck. Wittes et al. reported a 30% response rate in previously treated patients with head and neck carcinoma [4]. In a subsequent small uncontrolled study, Wittes and his group [3] reported no benefit from the addition of bleomycin to DDP in previously treated head and neck cancer cases. Recent trials using methotrexate in various schedules have given a response rate of 20%–25% in patients with no prior chemotherapy [1]. This paper will report on a randomized trial assessing the efficacy and toxicity of DDP alone and in combination with methotrexate and bleomycin in treating recurrent squamous cell carcinoma of the head and neck.

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Materials and Methods

A total of 57 male patients with histologically confirmed recurrent squamous-cell carcinoma of the head and neck were entered in the study. There was no selection and patients were accepted irrespective of their previous treatment, nutritional status, and tumor burden. All patients were required to have a Karnofsky status greater than 60. Patients had clinically detectable disease measurable either by physical examination of mass or by roentgenographic techniques. The group consisted entirely of men in the age range 42–73. All patients had undergone prior radiotherapy and/or ablative surgery. No patient entered the protocol who had received previous chemotherapy. Patient characteristics are shown in Table 1.

Table 1. Patient characteristics

	Group 1	Group 2
Mean age (years)	61	58
Range	42–73	46–71
Primary tumor site		
Tongue	5	7
Larynx	5	5
Palate	4	3
Nasopharynx	14	9
Tonsil	1	3
Pyriform fossa	1	0
Prior therapy		
Radiotherapy	30	27
Surgery (ablative)	26	25
Chemotherapy	0	0

0344-5704/79/0003/0057/$ 01.00

Pretreatment and evaluation consisted of history and physical examination, blood counts, liver function tests, BUN, creatinine clearance, urinalysis, and chest X-ray. A creatinine clearance of greater than 70 ml/min was required for entry into the study.

Response was evaluated weekly. A complete response was noted when biopsy of previous positive site(s) revealed no evidence of malignancy. A partial responder was categorized by a decrease of over 50% in all measurable disease, with no evidence of new malignant disease. Patients who had a subjective response, i.e., decrease in pain, but no associated decrease in measurable tumor burden were considered nonresponders. The duration of the response was noted as the time of onset of response to documented progression.

Patients were randomized to receive the following courses of chemotherapy: Group 1 received DDP 3 mg/kg IV over 4–6 h with mannitol diuresis, 75 g mannitol being administered IV over a 12-h period and saline diuresis continued for 24 h thereafter. Group 2 received DDP as described, plus methotrexate 50 mg/m^2 IV on days 1 and 15 and bleomycin 15 mg/m^2 given by IV push twice weekly. The cycle was repeated at 4-week intervals. Chemotherapy was continued until no further decrease in measurable disease occurred or obvious progression could be documented. Chemotherapy was discontinued after 8 weeks from the onset of therapy if no measurable response could be documented.

Results

Therapeutic Benefits

The results obtained in the 57 patients randomized to this protocol are shown in Table 2. The overall response rate was 13% in patients receiving DDP alone (Group 1). This included one patient who had a complete response and three patients who had partial responses. The patient in this group who showed a complete response had previously received only radiotherapy for his initial lesion (T_1, No, Mo; soft palate). The three partial responders had been treated with radiotherapy and ablative surgery for advanced disease (Stage III or IV). In the group receiving DDP, methotrexate, and bleomycin (Group 2) there were three partial responders. This group had also been treated for their initial disease with a combination of radiation and ablative surgery. All patients who responded showed evidence of response after one course of the drug. The duration of the response was identical in both chemotherapy groups evaluated. In Group 1 the mean duration response was 4.2 months, excluding the one patient with a complete response, and in Group 2 the mean duration response in partial responders was 5.2 months. The patient in Group 1 who achieved a complete response is still in complete remission at 9 months.

Toxic Effects

In Group 1 (DDP alone) toxicity consisted of mild azotemia and elevations in creatinine. Two responders developed creatinine elevations with levels of over 2 mg/dl; however, this was reversible following discontinuance of therapy. No patient developed renal failure. The azotemia associated with DDP has been extensively documented [3]. Three patients in Group 1 developed severe renal tubular dysfunction manifested in severe electrolyte disturbances (Table 3). These disturbances were seen in envolemia patients receiving adequate enteric alimentation. Renal tubular dysfunction was documented by renal clearance studies. This toxic effect of DDP has not been previously reported and will be documented in a separate paper (S. Davis et al., submitted for publication). Hematologic toxicity in Group 1 consisted in slight leukopenia and thrombocytopenia. No patient developed white cell counts less than 2,000 or platelet counts less than 50,000 (Table 2). Decreases in hemoglobin (by more than 2 g) were seen in all patients. There was no mortality in this group of patients.

Group 2 patients treated with DDP, methotrexate, and bleomycin experienced the same renal toxicities. Two patients in this group developed renal tubular dysfunction such as was seen in Group 1 (Table 3). This group was complicated by marked hematologic toxicity.

Table 2. Response rate of patients with recurrent squamous-cell carcinoma of the head and neck to DDP alone or DDP, methotrexate, and bleomycin

	Group 1[a]	Group 2[b]
Nonresponders	26	26
Partial responders	3	3
Complete responders	1	0
Total[c]	30 (13)	27 (11)

[a] DDP 3 mg/kg IV every 4 weeks

[b] Methotrexate 50 mg/m^2 every 2 weeks and bleomycin 15 mg/m^2 twice weekly

[c] Numbers in parentheses represent total percentage of partial + complete responders in each group

Table 3. Toxic manifestations

	DDP (Group 1)	DDP, methotrexate, bleomycin (Group 2)
Renal		
Elevated creatinine (2 mg/dl)	14	11
Renal tubular dysfunction[a]	3	2
Hematologic		
Leukopenia (2000/cm^3)	0	11
Thrombocytopenia (50,000/cm^3)	0	13
Nausea, vomiting, anorexia	30	27
Mucositis	0	9

[a] Manifested as one or more of the following: hypokalemia, hypophosphatemia, hypomagnesemia, hypocalcemia

Leukopenia of less than 2000/mm^3 occurred in 11 of 27 patients and thrombocytopenia of less than 50,000/mm^3 in 13 of 27 patients during the course of therapy. Bacteriologically proven infection was documented in seven patients of this latter group and hemorrhagic phenomena related to thrombocytopenia occurred in two patients. One death was related to hematologic toxicity.

Nausea, vomiting, and anorexia were universal in all patients. Mucositis was seen in Group 2 patients only (9 patients or 33%) was not dose-limiting. Ototoxicity was not evaluated.

Discussion

The results of this comparative randomized study show that DDP in combination with methotrexate and bleomycin has no greater efficacy in the treatment of recurrent squamous-cell carcinoma of the head and neck than DDP alone. Witte and his co-workers reported a response rate of 69% in previously treated cases of head and neck carcinoma with DDP; however, the major response rate (complete plus partial) was 30% [1, 4]. In our present study a major response was seen in 13% of DDP-treated patients. The difference in major response rates is not readily apparent [4].

It has been suggested by other investigators that the potential of DDP for combination chemotherapy is great, since its toxic effects are minimal [4]. We do not share this enthusiasm concerning toxicity. Firstly, although mannitol diuresis substantially reduces renal failure, it does not prevent the marked abnormalities in serum electrolytes (renal tubular dysfunction) or mild myelosuppression. Secondly, the introduction of DDP in sequence with methotrexate, as shown in this report, results in unacceptably high myelosuppression. Bleomycin, although not myelosuppressive, failed in our patients to add to the efficacy of DDP.

It appears obvious that DDP is an active agent in recurrent squamous-cell carcinoma of the head and neck. On the basis of our data there does not appear to be any benefit to its combined use with methotrexate and bleomycin; in addition, combined therapy appears to result in greater toxicity.

References

1. DeConti, R. C.: Phase III comparison of methotrexate with lencovorin vs. methotrexate alone vs. a combination of methotrexate plus leucovorin, cyclosphosphamide, and cytosine arabinoside in head and neck cancer. Proc. Am. Assoc. Cancer Res. **17**, 248 (1976)
2. Goldsmith, M. A., Carter, S. K.: The integration of chemotherapy into a combined modality approach on cancer therapy. Cancer Treat. Rev. **2**, 137–158 (1975)
3. Randolph, V. L., Vallejo, A., Spiro, R. H. et al.: Combination therapy of advanced head and neck cancer. Induction of remissions with diamminedichloroplatinum, bleomycin and radiation therapy. Cancer **41**, 460–467 (1978)
4. Wittes, R. E., Cvitkovic, E., Shah, J., Gerold, F. P., Strong, E. W.: *cis*-Dichlorodiammineplatinum (11) in the treatment of epidermoid carcinoma of the head and neck. Cancer Treat. Rep. **61**, 359–366 (1977)

Received January 31, 1979/Accepted March 23, 1979