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Dibromodulcitol plus Bleomycin Compared with Bleomycin Alone in Head and Neck Cancer

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Summary. *Advanced recurrent squamous cell head and neck cancer patients were prospectively randomized to receive or not receive dibromodulcitol 10 mg/kg PO weekly for 8 consecutive weeks in addition to bleomycin chemotherapy. Patients initially entered in the study received bleomycin 15 μ/m² three times weekly for 8 weeks. This was later changed to 15 μ/m² twice weekly for 8 weeks because of unacceptable stomatitis. Most patients had relapsed following surgery and/or radiotherapy, but none had received prior chemotherapy. A 2 : 1 randomization in favor of the dibromodulcitol-containing therapy was used. There were 12 partial responses in the 44 evaluable patients receiving the combination (27%), and 4 partial responses in the 18 patients receiving single-agent bleomycin chemotherapy (22%). This difference was not statistically significant. Response durations were also relatively short for both therapies. Within the limitations of this study, we were unable to demonstrate that patient benefit resulted from the addition of dibromulcitol to bleomycin chemotherapy for this patient population.*

Introduction

Bleomycin (BLM) has established activity as a single agent in advanced squamous cell head and neck cancer [2]. Dibromodulcitol (DBD), as a single agent, showed evidence of some activity in three of 12 patients responding in a broad phase II study [1]. A phase III prospective randomized study was therefore initiated to compare DBD plus BLM with BLM alone in this disease. The combination of DBD with BLM was attractive because of the different dose-limiting toxicities of each compound.

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Patients and Methods

Patients seen at the National Institute of Oncology, Budapest, between January 1977 and November 1980 who had stage III or IV measurable recurrent squamous cell carcinoma of the head and neck and had received no previous chemotherapy were the subjects of this study. Eligibility criteria also included age < 70 years, a performance status of > 50% (Karnofsky), and normal serum bilirubin, SGOT, BUN (< 30 mg/dl), serum creatinine (< 1.7 mg/dl), WBC (> 4,000/μl) and platelets (> 100,000/μl). A 2 : 1 ratio of patient allocation in favor of the combination therapy was used, since considerable experience with BLM as a single agent was historically available.

Bleomycin was initially administered at a dose of 15 μ/m² by IV bolus three times weekly to a total dose of 360 μ/m², to the first 24 patients entered in the study. This was subsequently reduced to 15 μ/m² twice weekly to a total dose of 240 μ/m², after the higher dose was found to result in unacceptable stomatitis. Dibromodulcitol was administered throughout the study at a dose of 10 mg/kg PO weekly for 8 consecutive weeks.

Response was defined as a tumor regression of 50% or greater of the sum of the products of the largest diameters of all measurable lesions.

Results

Two of the 64 eligible patients entered into the study died of causes unrelated to their cancer or treatment after only 1 week of therapy and were considered inevaluable. Of the remaining 62 evaluable patients, 44 were randomized to the combination treatment and 18 to single-agent BLM. The characteristics of patients entered into each study arm are outlined in Table 1 and demonstrate that patients were comparable in terms of age range, sex, tumor site, prior radiotherapy or surgery, and performance status.

Table 2 details response to therapy according to treatment. Measured tumor regressions of > 50% were seen in four of 18 patients (22%) receiving single-agent BLM and 12 of 44 patients (27%) receiving BLM combined with DBD. Response durations were relatively short for both therapies,

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Table 1. Patient characteristics

	BLM	BLM/DBD
Total patients	18	44
Median age (range)	54 (42–69) years	56 (36–69) years
Male/female	17/1	41/3
Performance status		
Karnofsky 90–100	3 (17%)	8 (18%)
Karnofsky 70–80	7 (39%)	22 (50%)
Karnofsky 50–60	8 (44%)	14 (32%)
Site of disease		
Primary only	11 (61%)	23 (52%)
Nodes/metastases	7 (39%)	21 (48%)
Prior therapy		
Surgery	5 (28%)	9 (20%)
Radiotherapy	13 (72%)	35 (80%)

Table 2. Response to therapy[a]

	Total patients	Responders	Response duration (months)
Single-agent BLM			
All patients	18	4 (22%)	3–8
High BLM induction	7	3 (43%)	
Low BLM induction	11	1 (9%)	
DBD + BLM			
All patients	44	12 (27%)	2–16
High BLM induction	17	7 (41%)	
Low BLM induction	27	5 (19%)	

[a] Response = > 50% measured tumor regression

Table 3. Toxicities

	Percentage of patients with toxicity		
	All patients (n = 62)	BLM patients (n = 18)	BLM/DBD patients (n = 44)
Pulmonary	16	11	18
Skin	79	72	84
Alopecia	84	72	89
Stomatitis	35	33	36
Nausea/vomiting	18	33	11
Fever	9	11	7

ranging from 3 to 8 months for patients responding to BLM alone and from 2 to 16 months for patients responding to BLM plus DBD. There was a higher response rate for patients who received BLM on the initial intensive three-times-weekly schedule (Table 2), but insufficient numbers are available to determine the statistical significance of this. Also, insufficient data are available to determine whether an increased duration of response resulted from the more intensive BLM administration, which was poorly tolerated by patients due to excessive stomatitis and had to be reduced.

Toxicities for all patients were as anticipated for BLM, and are outlined in Table 3. Stomatitis and alopecia were the most frequent toxicities reported. Fifteen percent of all patients experienced some degree of pulmonary toxicity. There were no drug-related deaths. Sixteen percent of the patients randomized to the DBD-containing therapy also experienced mild leukopenia. Apart from this, however, there was no clear evidence of added toxicity imparted by DBD administration. The incidence and severity of stomatitis was increased in the thrice-weekly BLM schedule compared with the twice-weekly schedule (62% versus 13%, respectively). However, other toxicities did not appear to be significantly increased in patients receiving the intensive BLM schedule.

Discussion

Methotrexate is the drug that has been most thoroughly evaluated in recurrent head and neck cancer patients, with an overall response rate of 20%–30% in most larger series of tolerable single-agent therapy. Bleomycin and cisplatin are the second most studied single agents in this condition, and appear to give comparable results to methotrexate. A variety of combinations have been reported, but there is no evidence from phase II studies that suggests a superiority over single-agent therapy in recurrent disease [3]. Since myelosuppression is the dose-limiting toxicity of DBD, non-myelosuppressive BLM was the drug chosen for this study.

Within the limitations of this study, the addition of DBD did not appear to significantly increase the benefit of BLM alone. The low frequency of myelosuppression for patients in the combination arm suggested that a higher dose of DBD might have been more appropriate, although there are no published data to suggest that a dose-response relationship would exist in this setting. The dose used was that recommended from the initial clinical trial with the weekly schedule [4]. Our results are corroborated by Ohnuma et al. [5], who investigated the addition of DBD 3 mg/kg/day for 6 weeks to BLM 15 μ/m^2 twice weekly and reported five responses in 20 evaluable patients. They also concluded that there was no evidence of a superiority for this combination

over either drug given alone. It is, therefore, doubtful that DBD will have a significant future role in the management of recurrent head and neck cancer.

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