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Combined Chemotherapy of Head and Neck Squamous Cell Carcinomas with Methotrexate, Bleomycin, and Hydroxyurea

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Summary. *Thirty-two patients with squamous cell carcinoma of head and neck not amenable to surgery or radiotherapy were treated with a combination of methotrexate 0.6 mg/kg IV weekly, bleomycin 15 mg IV weekly, and hydroxyurea 1,000 mg/m^2 three oral doses weekly. Eleven complete responses and ten partial responses of more than 50% were observed. The mean duration was 43 weeks for complete responses and 35 weeks for partial responses. Toxicity consisted in leukopenia, thrombocytopenia, nausea, vomiting, stomatitis, and cutaneous alterations. Only one patient suffered reversible lung toxicity.*

These results suggest that a combination of three drugs in squamous cell head and neck cancer may be more effective than a combination of bleomycin and methotrexate only.

Introduction

Two previous studies of combined chemotherapy of disseminated head and neck squamous cell carcinomas were carried out at the University Hospital in Geneva from 1972–1975, with the aim of improving the insufficient results of monotherapy in this type of tumor. The first study, carried out in 15 patients, demonstrated the efficacy of a bleomycin (BLM) and methotrexate (MTX) combination [1]. In this study the doses of BLM and MTX were 30 mg twice a week IV and 0.4 mg/kg twice a week IV, respectively. Treatment lasted 5 weeks only, so as not to exceed a total dose of 300 mg BLM.

A partial remission was observed in 60% of the patients and its average duration was 9 weeks. This result was obtained at the price of serious toxic effects, mainly hematological and pulmonary. This study showed that a high-dose combination of MTX and BLM can produce a satisfactory percentage of remissions, but that these cannot be prolonged by maintenance chemotherapy because of the risk of irreversible lung damage if BLM is given at a high dosage for more than a few weeks.

The aim of the second study was to try to avoid the problem mentioned above by using a lower dosage of both agents, and also to investigate the effect of a reduced dosage on the remission rate and on the duration of treatment and remission [4]. In this study, 26 patients received a weekly dose of 15 mg BLM and 0.6 mg MTX/kg IV. After 4 weeks a first evaluation was carried out. In the case of remission or no change the same treatment was maintained, but in the case of progression the high-dosage treatment of the first study was substituted. Maintenance therapy was an injection of BLM-MTX at the same dosage as during induction, every 1 or 2 weeks. Half the patients showed a partial remission of 35 weeks average duration since the first signs of response. The mean duration of treatment was 17 weeks.

These results suggest that a low-dosage treatment can be maintained longer. This could explain the longer remissions. As anticipated, treatment was tolerated better at low than at high dosage.

The aim of the present study was to try to improve the efficiency of low-dose BLM-MTX by adding a third agent. Hydroxyurea (HU) was chosen as the third agent because of its activity as a single agent in the treatment of head and neck squamous cell carcinomas [2, 3, 5].

Materials and Methods

Thirty-two patients with head and neck squamous cell carcinoma were entered into this study between 1975 and 1977 (Table 1). All

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Table 1. Patient characteristics

	MTX + BLM + HU	Low dose MTX + BLM	High dose MTX + BLM
Number of patients	32	26	15
Mean age	56 years	62 years	58 years
Previous treatment[a]	21 cases	18 cases	11 cases
None	11	8	4
Surgery	10	2	1
Radiotherapy	6	9	5
Surgery + radiotherapy	5	7	5
Tumor location			
Piriformis	8	4	3
Mouth floor	6	4	2
Tonsils	4	3	2
Tongue	5	8	3
Epiglottis	3	3	2
Larynx	3	2	1
Vocal cords	2	2	1
Other	1	0	1

[a] Before chemotherapy

Table 2. Total doses and duration of treatment and tumor response as a function of type of response

Type of response	No. of patients	Average doses (extreme doses)			Average duration in weeks of	
		BLM (mg)	MTX (mg)	HU (g)	Treatment	Tumor response
Complete response	11	360 (180/660)	1,625 (400/2,850)	126 (54/198)	24	43
Partial response	10	295 (135/450)	850 (350/1,350)	87 (40/135)	19	35
No change	7	185 (120/360)	480 (240/860)	55 (36/99)	12	–
Tumor progression	4	90 (145/420)	220 (180/260)	21 (18/25)	6	–
Total	32	265 (145/420)	1,100 (320/1,450)	65 (32/110)	16	39

these patients had a histologically proven tumor that was disseminated, progressive, or recurrent, inoperable and not amenable to radiotherapy, as well as measurable tumor locations, which were regularly monitored by clinical and endoscopic examination. Twenty-one patients had received prior therapy: ten had undergone surgery; six had received radiotherapy (4,500–7,000 rads); five had undergone surgery followed by radiotherapy. Eleven patients had received no prior treatment. Primary tumor locations are shown in Table 1. Of the 32 patients, 17 had a history of chronic alcoholism, smoking, or chronic bronchitis, or had clinical or biological signs of malnutrition or liver disease.

Therapy consisted in a weekly IV injection of BLM 15 mg and MTX 0.6 mg/kg, along with three oral doses of HU 1,000 mg/m^2 a week. Maintenance treatment consisted of MTX and BLM at the induction dosage twice a month, with 2,500 mg HU m^2 every 2 weeks.

All patients were hospitalized when treatment was begun and then were usually followed-up as out-patients with weekly check-ups. Tumor locations were measured and controlled or evaluated weekly. If serious digestive toxicity, a white cell count below 2,000/mm^3 or a platelet count below 100,000 occurred, MTX and HU were temporarily stopped, but BLM was continued.

Disappearance of all tumor locations, as confirmed endoscopically and histologically, was considered to be a complete response. Partial response was defined as a 75% or more reduction of the tumor mass diameter, or, in non-measurable but evaluable cases, a greater than 75% shrinkage of tumor volume. Duration of response was counted from the beginning of treatment to recurrence.

The following toxic effects were monitored: hematological, digestive, cardiac, pulmonary, cutaneous, mucous membrane, urogenital and neurologic. Complete blood count, serum iron and TIBC, liver function tests, and LDH were monitored. Blood creatinine and urea along with diuresis and urinary sediment were also followed.

Results

Antitumor Effect (Table 2)

Eleven patients of the 32 showed a complete response. Six of these patients had received no previous treatment, four surgical treatment, and one radiotherapy only. These patients received a total dose of BLM of 180–660 mg (mean 360 mg). For

MTX the total dose was 400–2,850 mg (mean 1,625 mg). For HU, the total dose was 54,000–198,000 mg (mean 126,000 mg).

A partial response was seen in ten patients. Three of these patients had no previous treatment, four surgery, two radiotherapy only, and one combined surgery and radiotherapy. The total dose of BLM was 135–450 mg (mean 292 mg), the total MTX dose 350–1,350 mg (mean 850 mg), and that of HU 40, 500–135,000 mg (mean 87,750 mg).

In seven patients the tumor showed no change. One of these patients had undergone no previous treatment, one surgery, three radiotherapy only, and two combined surgery and radiotherapy. The total dose of BLM was 120–360 mg (mean 185 mg), that of MTX 240–860 mg (mean 480 mg), and that of HU 36,000–99,000 mg (mean 55,000 mg). In four patients the tumor progressed during treatment. One of these patients had received no previous treatment, one surgery, and two combined surgery and radiotherapy. The total dose of BLM was 60–120 mg (mean 90 mg), the total dose of MTX was 180–260 mg (mean 220 mg), and the total dose of HU was 18,000–25,000 mg (mean 21,000 mg) (Tables 1 and 3). Twenty-six patients experienced significant relief of pain after as little as 2 weeks of treatment.

The mean duration of treatment was 16 weeks (Table 2). The mean duration of complete response was 43 weeks in 11 patients (range 11–86 weeks). The mean duration of treatment in these patients was 43 weeks. Four of them abandoned treatment after 8, 12, 17, and 18 weeks respectively; 3–5 weeks after cessation of treatment they suffered relapse. Three patients underwent a surgical intervention after 22, 26, and 28 weeks chemotherapy, respectively. They relapsed after 24–49 weeks. Two patients, after 29 and 33 weeks of chemotherapy, received complementary radiotherapy and relapse occurred 20 and 28 weeks later. In one patient, because of a suspicion of pulmonary toxicity, chemotherapy was stopped after 30 weeks, with relapse 4 weeks later. In one patient, treatment had to be stopped after 41 weeks because of BLM toxicity and cutaneous lesions. The remission was long and lasted for 45 weeks before relapse.

Partial response was observed in ten patients with a mean duration of response of 35 weeks, ranging from 8–48 weeks. The mean duration of treatment was 19 weeks. Four of these patients abandoned treatment after 6, 9, 13, and 19 weeks and suffered relapse after 9–27 weeks. Two patients underwent surgery after 22–25 weeks; relapse appeared 17–21 weeks later. Two patients received complementary radiotherapy after 14–18 weeks of chemotherapy, suffering relapse after 15–19 weeks. In one patient the treatment had to be stopped after 30 weeks due to hematologic toxicity, and relapse occurred 16 weeks later. In one patient, treatment was stopped after 34 weeks because of cutaneous signs and BLM toxicity; relapse occurred 14 weeks later.

Table 3. Therapeutic response in relation to previous treatment

Previous treatment	No. of patients	CR	PR	NC	P
None	11	6	3	1	1
Surgery	10	4	4	1	1
Radiotherapy	6	1	2	3	0
Surgery + radiotherapy	5	0	1	2	2
Total	32	11	10	7	4

Table 4. Toxicity

Number of patients	32		
Average duration of treatment	16 weeks		
Type of toxicity	None	Moderate	Severe
Hematological	18	11[a]	3[a]
Digestive	24	7	1
Pulmonary	31	1	0
Muco-cutaneous	26	4	2
Urogenital	31	1	0
Neurological	31	1	0
Other	30	1	1

[a] Hematological toxicity: moderate if the white cell count was between 2,000 and 3,000/mm^3 and the platelet count between 80,000 and 100,000/mm^3, and severe if the white cell count was below 2,000/mm^3 and platelet below 80,000/mm^3

Toxicity

Eleven patients suffered hematologic toxicity (Table 4), which was severe (WBC counts below 1,500/mm^3 and platelet counts below 50,000/mm^3) in three. There was no death due to toxicity. In eight patients hemoglobin was lowered by more than 1.5 g%. Of the 11 patients in complete remission, six had hematologic toxicity, which was severe in two. Amongst the 21 other patients we observed only eight cases of hematological toxicity, one being severe.

Three patients developed bleeding buccal aphthae, which disappeared 15 days after discontinuation of MTX. Eight patients complained of nausea and vomiting. Two patients developed a fever of more than 38.5° C 2 h after BLM injection, but the course of treatment was not modified. Cutaneous toxicity, evidenced by a cutaneous necrosis of the fingertips

and soles of the feet and by pigmented indurations of the palms, was noted in three patients. In each case the total dose of BLM exceeded 400 mg. Two patients had skin toxicity apparent in skin dryness and desquamation along with dark striae appearing after scratching.

Pulmonary toxicity developed in one patient after 450 mg BLM and led to its permanent discontinuation. This toxicity was evidenced by progressive dyspnea and, radiologically, by nodular infiltrations. It was reversible with 100 mg prednisone a day for 15 days. We found no changes in liver function tests, renal tests, or signs of neurological toxicity.

Discussion

In a previously published series, 60% of 15 patients treated with a high dosage of BLM (30 mg IV twice a week) and MTX (0.4 mg/kg IV twice a week) showed partial responses marred by considerable hematological and pulmonary toxicity, with a very short duration of response, recurrence during the first weeks after the end of treatment, which was determined by the maximal dose of BLM usually admitted as tolerable.

In a later series, a combination of rather low doses of BLM (15 mg IV/week) and MTX (0.6 mg/kg IV/week) induced an objective response in 50% of 26 patients. The mean duration of treatment was 17 weeks, and the mean duration of response was 37 weeks, counting from the first day of treatment. These results suggest that a dosage at the upper limit of tolerance in this category of patients in poor general health does not improve therapeutic efficacy over that of a lower dosage. They also suggest that a lower-dose treatment can be maintained for a longer time, which could explain the longer duration of response observed. As could explain the longer duration of response observed. As could be foreseen, mean tolerance of low-dose treatment in the second study was better than that of higher doses.

The addition of HU to the low-dose BLM and MTX combination in this new series of 32 patients with squamous cell head and neck carcinoma produced a 70% objective response rate, half these responses being complete. The best results were obtained with patients who had not had previous radiotherapy treatment. There is no difference in response rates between patients who had no previous treatment and those who had undergone surgery. This result is encouraging, considering that most of the patients had advanced and recurrent conditions and that they were in bad general condition due to alcoholism, smoking, chronic bronchitis, and malnutrition. In the present series, the mean duration of treatment was 16 weeks, the mean duration of complete response was 43 weeks, and that of partial response 35 weeks, counting from the first day of treatment (Table 5). Among 11 patients who experienced complete response, three were submitted to complementary surgery and two to complementary radiotherapy. This second therapeutic intervention induced a prolongation of the complete response duration, the patients relapsing 20–49 weeks later. These results are relatively encouraging, considering that the cessation of chemotherapy was followed by early relapse in all except one patient, in whom relapse occurred only 49 weeks later. Among ten patients with partial response, two were submitted to complementary surgery and two to radiotherapy. This did not prolong the duration of response. Thus, only a complete response, obtained by chemotherapy and completed by surgery and radiotherapy, allows a prolonged response duration in our patients with advanced head and neck tumours. It is important to note that no complete response occurred in the two previous studies combining only MTX and BLM, while in the present study the rate of complete response was 35%. The duration of response in this series was equal to that obtained with low-dose MTX and BLM. Tolerance of the treatment was not different from that observed without HU. This low toxicity is probably due to the experience acquired in the use of MTX and BLM combination therapy with patients in poor general condition. As expected, hematological toxicity was more pronounced in patients with complete response, probably due to

Table 5. Comparative results of three successive pilot studies

	No. of patients	CR	PR	NC	P	Average duration of treatment (weeks)	Average duration of response (weeks)
High-dose BLM + MTX	15	0	9	1	5	5	9
Low-dose BLM + MTX	26	0	13	7	5	17	35
BLM + MTX + HU	32	11	10	7	4	16	39

longer treatment. Only one case of reversible lung toxicity occurred, against four in 26 patients receiving low-dose BLM and MTX, and three in 15 receiving high-dose BLM and MTX. Here also, acquired experience plays a major role.

The comparison of three pilot studies with limited numbers of patients and in which therapeutic effect can vary with the location of the tumor studied, is open to justified criticism. The data presented here suggest, however, that the addition of HU to the BLM-MTX combination increases therapeutic efficacy in disseminated squamous cell head and neck carcinoma. With this combination given at dosages that do not entail serious toxicity a complete response was obtained in about one-third of patients, lasting an average of 43 weeks. These results are encouraging, compared with those previously obtained in comparable patients.

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