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Vinblastine, Methotrexate, Bleomycin, in the Management of Head and Neck Cancer*

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Abstract—*Fourty-three patients with head and neck epidermoid carcinomas were treated with combination chemotherapy consisting of vinblastine (VLB) 4 mg/m² i.v., methotrexate (MTX) 60 mg/m² i.v. and bleomycin (BLM) 15 mg i.v. day 1 and 8, q 28 days.*

Dose limiting toxicity was clearly hematological: leukopenia was more severe than thrombopenia and 5 patients died of septicemia associated with WBC <1000. Other toxicities included mucositis, skin rash, fever, nausea and vomiting. Alopecia was rare. Treatment was stopped in two patients because of reversible pulmonary toxicity. There was no significant hepatic or renal toxicity. Ten patients were inevaluable: because of loss of follow-up or refusal of treatment (9) or intercurrent radiation therapy (1). Out of 33 fully evaluable patients, there were 9 (27%) responders: 3 complete responses lasting 8, 16+, 18+ months and 6 partial responses (>50% decrease in tumor size) for a median duration of 4 months. Stabilisation of disease (no change or regression <50%) was seen in 8 (23%), progression of disease in 8 (23%), early death in 3 (9%) and toxic death in 5 (15%) patients.

Although some long lasting complete remissions were seen in head and neck cancer patients treated with this regimen, it appears too toxic to be recommended.

INTRODUCTION

THIS paper reports on a phase II study of the combination of methotrexate (MTX), vinblastine (VLB) and bleomycin (BLM). These agents were combined because of proven activity and experimental evidence of synergism. Methotrexate is the best single drug in the treatment of head and neck carcinoma [1]. Vinblastine has given 29% response in the single published series [1]. Although bleomycin has shown only moderate activity [1, 2] it was chosen because of its lack of hematological toxicity, which confers it a unique value in combined therapies. Furthermore, VCR is known to synchronize cells in M and G phases, between 4 and 6 hr after administration in man [3]. Vinblastine has the same stathmokinetic properties and was assumed to have the same synchronizing properties, enhancing the cytocidal effects of BLM, most effective in phases M and G_2 [2, 4]. There are moreover experiments pointing to some synergism between MTX and BLM [5]. Finally VLB as vincristine have been shown to increase the intracellular content of MTX probably by blocking the excretory pathways [6].

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MATERIALS AND METHODS

Drug administered

Vinblastine (4mg/m²) was given at the same time that methotrexate (60mg/m²): both i.v. on days 1 and 8 of each cycle of 28 days. Bleomycin (15mg total dose) was given i.v. 6 hr later on days 1 and 8.

Reduction schedule

A new course was delayed if white blood cells counts were below 4000/μl and/or plate-

lets below 100,000/μl. After 2 weeks of delay, or on the 8th day of the course, treatment was administered with the dose reduction schedule shown on Table 1. In case of buccal mucositis, drug administration was postponed until all lesions were healed.

Patients

Forty-three patients with head and neck epidermoid carcinoma were selected: all fulfilled the criteria shown on Table 2. Ten were inevaluable: 9 because they were lost to follow-up or refused further treatment after a single course; 1 was excluded because the only evaluable lesion was included in a field of radiation therapy during treatment. Thirty-three patients were thus fully evaluable (28 males, 5 females, mean age was 58, range from 38 to 77). Primary sites are shown on Table 3. Before the present trial, 6 patients received single agent chemotherapy [anhydro arafluorocytidine (1 patient); chlormethine (1 patient); preoperative intra-arterial bleomycine (4 patients)]. Thirty patients underwent surgical procedures, multiple in some cases and 32 had been heavily irradiated on the region of primary lesion (over 6000 rad). Local recurrence was present in all 33 cases and was the only evidence of disease in 20 (60%).

Criteria of remission

A complete remission is defined as disappearance of all evidence of disease during at least 1 month.

A partial response means a 50% reduction in the product of the two largest perpendicular diameters of at least one lesion while no other lesion increases in size and no new lesion appears, during at least one month.

No change means a reduction of less than 50% of the initially measurable lesions without increase or appearance of any other lesion.

Progession means any increase in tumor size or appearance of one or more new lesions.

Duration of remission is defined from the first day of treatment to first day of progession.

Follow-up

Before each course of chemotherapy the patients had a physical examination and a complete blood count. Every 2 months renal and liver function were tested. A chest X-ray was done every month in the presence of lung metastases, once every 2 months otherwise.

RESULTS

Responses

There were 9 responses (27%), 3 complete remissions lasting 8, 16+, 18+ months and 6 partial responses for a median duration of 4 months. No change was seen in 8 (23%),

Table 1. *Dose reduction schedule*

	WBC > 4000 Platelets > 100,000 (%)	4000 > WBC > 3000 Platelets > 100,000 (%)	3000 > WBC > 2500 100,000 > Platelets > 75,000 (%)	WBC < 2500 Platelets < 75,000
VLB	100	50	25	0
MTX	100	50	25	0
BLM	100	100	100	0

Table 2. *Criteria for selection of patients*

Epidermoid carcinomas of head and neck (histology proven)
Recurrent disease, unresponsive to radiotherapy and surgery
Evaluable lesions
Consent of patients
Life expectancy over two months
Karnofsky index better than 30
Platelet counts over 100,000 mm^3 and WBC over 3500/mm^3
Serum creatinine under 1.3 mg/dl
Absence of other cancer

Table 3. *Primary sites of disease*

Larynx	8
Tongue	7
Floor of the mouth	5
Hypopharynx	4
Epiglottis	3
Gum	3
Recurrent epid. cervical adenopathy	1
Ethmoidal mucosa	1
Salivary gland	1

progression of disease was observed in 8 and 8 patients died in the course of treatment. In 5 of these, death was possibly related to hematological toxicity of treatment.

Considering the small number of cases in each category it is not possible to find any correlation between histological type and response rate.

Toxicity

The dose limiting toxicity was hematological as shown in Table 4. Severe leucopenia

Table 4. Hematological toxicity in head and neck carcinoma treated with MTX-VLB-BLM

Leucopenia	over	2500	11
	over	1000	2
	over	500	2
	below	500	7
Thrombocytopenia	over	75,000	10
	over	30,000	3
	below	30,000	6

(WBC less than 1000/μl) was observed in 9 patients and severe thrombocytopenia (platelets less than 30,000/μl) in 6. Mild hematological toxicity was present in 11 patients. Anaemia was never severe. Other toxic manifestations include mucositis (16 patients), fever (12 patients), infection (10 patients), nausea (4 patients), fine crepitant rales at pulmonary bases (2 patients) compatible with incipent bleomycin fibrosis [7] and reversible after discontinuation of the drug, hyperkeratosis or pigmentation (4 patients), hypotension, alopecia, bullous erythema associated with major methotrexate toxicity (1 patient of each).

DISCUSSION

Cancer of the head and neck accounts for 5 of all malignant tumors [1]. Although there is no figure on the recurrence rate, a reasonable approximation seems to be that two thirds of the patients will recur within 5 yr [8, 9], most of them in the first year following the first treatment [9].

The medical treatment of those tumors has remained neglected and disappointing.

Only methotrexate and bleomycin have been extensively evaluated. The cumulative response rate was 39% for MTX and 15% for BLM. Vinblastine has a response rate of 29% which is close to cyclophosphamide (36%) and hydroxyurea (39%) but these three drugs have not been adequately evaluated according to the present criteria [1].

Combination regimens are few and the results difficult to analyse in view of the poor methodology used [1]. Most of them will not produce more than 25% responses with the exception of one series with a five drug regimen of fluorouracil, methotrexate, vincristine, cyclophosphamide and prednisone [10] which has not been confirmed.

Our regimen has an unexpected high toxicity, especially if compared with similar combinations in the other neoplasms (cyclophosphamide, methotrexate, and fluorouracil in breast cancer [11] or the combination of BLM, VLB and cis-platinum used in testicular cancer) [12]. Possible explanations could be either that the synergism acts on the medullary level as it is expected to act on the tumor, or that previous treatments and the disease itself led to severe debilitation of our patients. This has previously been correlated with a deficiency in folic acid which enhances the hematological toxicity of methotrexate [13].

Our protocol, although too toxic to be recommended as such, is encouraging, as, in an unselected heavily treated population, and with more severe criteria of response, it produces a similar rate of response than that of methotrexate and moreover has induced three long lasting complete remissions.

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