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Results of a Low-Dose Combination Chemotherapy with Vincristine, Bleomycin and Methotrexate (V-B-M) Based on Cell Kinetics in the Palliative Treatment of Head and Neck Squamous Cell Carcinoma

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Abstract—*A low dose combination chemotherapy with VCR, BLM and MTX (V–B–M) in a theoretically double synchronizing sequence was administered for palliative purpose to* 84 *patients with advanced squamous cell carcinoma of the head and neck. The treatment started with a weekly* 3 days *regimen (VCR* 1 mg *i.v., BLM* 15 mg *i.m. after* 6 *and* 24 hr, *MTX* 20 mg/m^2 *p.o. after* 48 hr *for* 4 weeks). *BLM was then reduced according to two different regimens in order to protract the treatment avoiding cumulative toxicity of the drug.*

In 60 *assessable patients, a good response was observed in* 46 *patients* (76%), *with* 62% *of regressions greater than* 50% *and* 32% *of complete responses; regressions greater than* 50% *were more frequent in patients not previously treated* (88 *v* 51%).

The duration of response was correlated with the degree of the regression: in the responders its median duration was 4.1 months.

V–B–M was effective in reducing or eliminating pain in the great majority of the cases, and this result was often protracted after interruption of the chemotherapeutic treatment. No important toxicity was observed and no patient required hospitalization or specific treatment to control side effects.

INTRODUCTION

DURING the past 10 yr chemotherapy was increasingly applied in the treatment of squamous cell carcinoma of the head and neck, both for palliative and as a part of therapeutic combinations involving also radiotherapy or/and surgery. Almost all the known drugs were tested on this type of cancer: methotrexate (MTX), bleomycin (BLM), cyclophosphamide (CTX), hydroxyurea (HU) and recently cis-platinum proved to be the most effective drugs when used alone, but frequency and importance of the responses and their duration can be defined as quite disappointing [1–3].

Polychemotherapy combining different drugs at various doses was also tested by several authors, showing a significant improvement of results but also of toxicity [2, 3]. More consistent improvements were achieved by schedules based on a theoretical manipulation of the cell cycle by means of certain sequences of different drugs, mainly using vincristine (VCR) and vinblastine (VLB) with the purpose of blocking cells in phase M [4–6].

Of many killing agents tested, practically only BLM given 6–12 hr after VCR proved to be effective in cancer of the head and neck [7, 8].

Studies made by Barranco *et al.* [9] suggest that BLM, after the effect of VCR, besides killing cancer cells blocked in G_2 and M phases, reduces their passage from phase S to G_2. A S-phase specific agent administered at this time should kill all these cells. Costanzi *et al.* [10] applied these experimental findings on a series of 17 patients with head and neck epidermoid cancer, giving sequentially BLM and MTX. Regressions greater than 50% were observed in 59% of the patients, and these results are better than that achieved by either drug when used alone and by both drugs administered concomitantly.

The sequence VCR–BLM–MTX (V–B–M)

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was included into a certain number of polychemotherapy schedules [11–13] in association with several drugs or with radiotherapy, so that its activity as single unit has not yet been clearly established.

The purpose of this phase II study was to evaluate the effectiveness of a low-dose sequential administration of VCR, BLM and MTX, specifically devised for palliation, to allow the most protracted treatment with the lowest toxicity. The chronology of administration was established in order to achieve a theoretical double sequential cell cycle modification.

MATERIALS AND METHODS

Patients

V–B–M was prescribed with palliative purpose to 84 patients with far advanced squamous cell carcinoma of the oral cavity, oropharynx, retromolar space and laryngopharynx. Most of them had recurrent disease after previous RT and/or surgery, or other kind of chemotherapy. Taking into account the low doses of drugs to be administered, the selection of the patients for the trial was not very restrictive as for the biologic parameters. Patients were excluded only if evidence existed of important renal impairment (serum creatinine greater than 1.7 mg%) or of serious bronchopneumopathy. A mild hepatic impairment was biochemically documented in 58% of the patients, but this was not considered a reason of exclusion.

The mean age of the patients was 57 yr (range 41–77) male to female ratio was 5 : 1. The first patient entered the study in May 1976 and the last in December 1977.

VCR was given i.v. at the dose of 1 mg, BLM was administered i.m. at the dose of 15 mg, 6 and 24 hr after VCR, MTX was given orally at the dose of 20 mg/m^2 48 hr after VCR. This regimen (regimen A) was repeated once in a week for 4 weeks; in patients showing a regression greater than 50% the dosage of BLM was then reduced to only 15 mg after 6 hr (regimen B) for the other 4 cycles; if regression was maintained, the same schedule as in regimen B was administered every 10 days (regimen C). In patients with regression of less than 50% and in non responders, regimen A was continued for a total of 8 cycles before changing to regimen B or to another type of chemotherapy. In long responders, after 6–8 months of regression, V–B–M regimen B was administered every 15 days, intercalated with MTX alone (20 mg/m^2) every 15 days. All patients were controlled monthly at our out-patient clinic.

Since 14 patients were living far away and could not be regularly controlled and 10 received surgery or radiotherapy after chemotherapy, 60 patients are available for a complete evaluation.

RESULTS

As far as the clinical response is concerned, the patients are divided into 5 groups, according to the site of the tumor: anterior oral cavity (floor of the mouth, anterior tongue, anterior gum, cheek mucosa); posterior oral cavity (retromolar space, anterior pillar, faucial arch); oropharynx proper (tonsil, base of tongue, pharyngeal walls); larynx and hypopharynx; miscellaneous sites.

Results are reported in Table 1. The most impressive results were observed in patients with cancer of the oral cavity, specially in its posterior part, with 83% of regressions greater than 50%, and 41% of complete regressions. Oropharyngeal and laryngopharyngeal lesions showed less important responses. On the whole, 37 cases of 60 (62%) showed regression greater than 50% of the initial size, and in 19 patients (32%) a clinically complete disap-

Table 1. Type of response to treatment with V–B–M according to the tumor site

Site	No. cases	Response rate 0–25%	25–50%	>50%	CR
Oral cavity (post.)	12	0	2 (17%)	5 (41.5%)	5 (41.5%)
Oral cavity (ant.)	22	6 (27%)	3 (14%)	4 (18%)	9 (41%)
Oropharynx	11	2 (18%)	3 (27%)	4 (37%)	2 (18%)
Larynx–hypopharynx	12	5 (41%)	1 (8%)	4 (34%)	2 (17%)
Lips skin	3	1 (33%)	0 —	1 (33%)	1 (33%)
Total	60	14 (23%)	9 (15%)	18 (30%)	19 (32%)
		23(38%)		37(62%)	

pearance of the tumor was observed.

The malignancy histological grading of the tumor slightly influenced the results, with better responses in poorly differentiated carcinoma. Patients who had not received radiotherapy showed markedly better responses than those previously treated with this modality alone or combined with surgery: 88% of regressions greater than 50 vs 51%.

In most of the responsive patients (45/48, 94%) the maximum regression was observed after the first four courses. In three cases, a further decrease of the tumor size took place during the second month. In many patients (19/45, 42%) the maximum regression was observed after only two courses (2 weeks).

Duration of regression was measured from the beginning of chemotherapy to the appearance of relapse. This is reported in Table 2 by degree of initial response.

Table 2. Duration of response according to the degree of regression

Regression	No. cases	Median duration of response (months)
<50%	23	1.9
>50%	18	3.9
CR	19	6.9

Results on the pain were almost constant in responders: antalgic drugs assumption was rapidly reduced or eliminated. Among non-responders a reduction of the pain was sometimes achieved in spite of the absence of objective regression; nevertheless this improvement was transient and of short duration.

Toxicity is summarized in Table 3. Forty patients of 60 (66%) did not show any kind of toxicity. Fever higher than 38°C (8 cases) and weakness (7 cases) were the most common side effects, followed by vomiting (4 cases) and diarrhea (3 cases).

Table 3. Side effects observed during the treatment with V–B–M

Side effects	No. of cases
None	40
Hyperpyrexia (>38°C)	8
Weakness	7
Vomiting	4
Diarrhea	3
Paresthesia	2
Myelosuppression	2
Stomatitis	1
Skin hyperpigmentation	1

DISCUSSION

The results achieved by V–B–M seem to be considerably better than those of any monochemotherapy treatment applied to head and neck squamous cancer up to today.

Results of V–B–M are also satisfactory when compared with some polychemotherapeutic regimens. Furthermore, these treatments gave relatively high toxicity, so that they look hardly applicable for palliative purpose.

On the contrary toxicity of V–B–M was remarkably low. Hematologic, neurologic and pulmonary damage were practically negligible: in particular, toxicity of VCR did not exist and pulmonary fibrosis was never detected in this group of patients. MTX caused only transient and mild hematologic toxicity in 2 cases.

Effectiveness of V–B–M as palliative treatment comes out from the evaluation of the length of response: the median remission time of the whole group was 4.1 months, which is longer than that observed in previous phase II studies, using every kind of chemotherapy. Among the patients who showed a regression greater than 50% the duration of response approached the median survival of a historical group of untreated patients (3.9 months); among complete responders this duration was decisively longer (6.6 months) than survival in untreated patients. V–B–M also seems to be a very useful means for reducing the need for analgesic drugs.

In conclusion, V–B–M seems to represent a particularly active sequence, whose results, inspite of low doses, are nearly comparable to those of polychemotherapy regimens including it together with several other drugs. In clinical practice, it seems to be recommendable as palliative treatment of squamous cell carcinoma, due to its simplicity, lack of toxicity and no need of hospitalization.

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