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A Randomized EORTC* Trial Comparing Intra-arterial Infusion with Methotrexate vs Bleomycin as Initial Therapy in Carcinoma of the Oral Cavity

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Abstract—*Either intra-arterial infusions of MTX* (500 mg *over* 10 days) *or intra-arterial infusions of BLM* (95 mg *over* 13 days) *were administered as initial treatment to* 85 *patients with untreated squamous cell carcinomas of the oral cavity. Tumour regression was assessed* 10–15 days *after the end of chemotherapy. A sequential analysis was used, and BLM demonstrated a significantly greater local efficacy after the* 32*nd matched pair was assessed. The same results were observed when tumour response rates were compared, ignoring the matching, on the* 85 *patients,* ($P < 0.001$). *The response rate for patients with neck nodes was low* (10/38). *Catheter management problems, toxic effects and lethal reactions were* 2.5 *times more frequent in the MTX group.*

INTRODUCTION

IN RECENT years, chemotherapy has proved to be a powerful preliminary means for achieving regression in head and neck cancer before application of major local–regional treatments.

Its contribution seems to be comparable to that of preoperative radiotherapy, with the advantage of a lower incidence of post-operative complications. In both treatment sequences a direct relationship seems to emerge between the importance of the immediate remission achieved by the first treatment and the long-term result of the combined therapy [1–3]. From numerous reports, both methotrexate (MTX) and bleomycin (BLM) were considered in the early 1970s as the most active single agents against disseminated epidermoid carcinomas of the head and neck [4, 5], but as an adjuvant treatment, systemic chemotherapy has not yet been demonstrated to be very active.

Methotrexate was the usual drug for adjuvant intra-arterial chemotherapy in head and neck carcinoma [6–8]. Adjuvant BLM given either systemically [9] or by intra-arterial infusions [10, 11] demonstrated its activity in cases of advanced head and neck carcinoma. After a preliminary study [12], the EORTC Head and Neck Cooperative Group decided to compare MTX and BLM when delivered by the same intra-arterial infusion method to invasive carcinoma of the oral cavity.

This anatomical localization was chosen because it is well irrigated by the external carotid arterty and is very accessible to accurate measurement.

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MATERIAL AND METHODS

Selection of patients

All patients with a histologically proven squamous cell carcinoma of the mobile portion of the tongue, the floor of the mouth, the oral mucosa or the hard palate with tumour greater than 3 cm or infiltrating, with or without neck nodes and without distant metastates, were included in the trial.

Patients over 70 years of age, female patients, diabetic patients, those who had received previous treatment and those with a second primary tumour other than skin basal cell carcinoma were excluded from the trial. Patients were also excluded if they had a general contra-indication to chemotherapy such as kidney failure, bone marrow depletion or chronic pulmonary disease. Local contra-indications to intra-arterial infusion were the presence of neck nodes preventing catheterization or absence of coloration of the tumour area after

introduction of Evans blue dye through the catheter.

Treatments

Patients received one of the two following treatments: (1) intra-arterial MTX infusion: 50 mg per day over 8 hr for 10 days, combined with intramuscular leucovorin 6 mg every 6 hr, beginning 2 hr after the infusion of MTX; (2) intra-arterial BLM infusion: 15 mg per day over 12–20 hr for 13 days.

The route used for intra-arterial infusion was the superficial temporal artery or, if necessary, the superior thyroid artery. In the case of a midline tumour, bilateral catheters were inserted, each delivering half the total dose.

In both groups, the i.a. infusion course was followed by external irradiation or by surgery depending on the routine protocol of each participating centre. The regression of the tumour was evaluated before initiating radiotherapy or surgery.

Randomization

Patients were randomized after the catheter had been placed and after the irrigation of the tumour area had been checked with Evans blue dye. Patients were paired by age (to within 5 yr), primary tumour site (floor of mouth, tongue, gingiva, oral mucosa, hard palate), tumour extension (one, two, more than two sites) and clinical nodes (NO + N1a + N2a, N1b + N2b, N3). A treatment was allocated randomly to the first patient of each pair. The first new patient with same pairing characteristics was given the other treatment. Randomization and pairing were done by telephone.

Evaluation of the response to chemotherapy

The size of the tumour, i.e. product of the largest diameter by its perpendicular, was measured before treatment and 10–15 days after the end of chemotherapy.

Toxicity was recorded and patients were to be followed up for five years. Tumour regression expressed as a percentage of initial tumour size was chosen to evaluate the result of the treatments. An open sequential design was used [13]. The analysis is based on the cumulative sum, which will be denoted by d, of differences between the pairs of tumour regressions. The variance of d was estimated to be 15 from a previous study [12]. The boundaries were calculated ([14] eq. (5) p. 154) for a design with a significance level of 0.001 under H_0: $d = -10\%$, and power $1-\beta = 0.999$ under H_1: $d = +10\%$.

RESULTS

Patients

Between 1973 and 1977, 90 patients were accrued and 36 pairs formed. Five patients were excluded from the analysis: four patients, two in each group, were ineligible because they had oropharynx tumours, and one patient was given the wrong treatment by mistake. Thus 85 patients can be evaluated, 42 in the group receiving MTX and 43 treated with BLM.

Table 1 gives the distribution of patients by institution and treatment. The distribution of the main prognostic factors by treatment is given in Table 2. There were no significant imbalances between the groups.

The most frequent sites are the floor of the mouth (52%) and the mobile portion of the tongue (27%). Only 21% of the patients had a tumour limited to one site and 46% of the cases presented with clinically involved neck nodes. The average ages in both the MTX group and

Table 1. Distribution of cases by institution and treatment

Institutions	MTX	BLM	Total
Institute J. Bordet	7	8	15
Centre L. Bérard	3	2	5
Centre J. Paoli	6	6	12
Hôpital Régional Lille	4	5	9
Centre A. Lacassagne	3	2	5
Istituto dei Tumori	10	14	24
Centre H. Becquerel	4	1	5
Institut Curie	5	5	10
Total	42	43	85

Table 2. Distribution of cases by treatment and prognostic factors

	MTX	BLM	Percentage
Site			
Floor of mouth	22	23	52
Mobile part of tongue	12	8	27
Gingiva	5	8	13
Oral mucosa	1	3	5
Hard palate	2	1	3
	42	43	100
Extent			
One site	9	9	21
Two sites	17	17	40
More	16	17	39
	42	43	100
Cervical nodes			
N_0, $N_{1,2a}$	22	24	54
$N_{1,2b}$	14	16	35
N_3	6	6	11
	42	43	100
Mean age (S.D.)(yr)	54 (2.5)	55 (2.5)	

the BLM group are similar: 54 (± S.D. = 2.5) and 55 yr (± S.D. = 2.5).

Complications due to treatment

In the MTX group significantly more patients ($P < 0.001$) could not receive the complete dose of chemotherapy (43 vs 16% respectively) when compared with the BLM group (Table 3). The interruptions of treatment were mostly due (15 out of 25) to catheter complications, with the rest due to toxicity. Detailed reasons for these interrupted treatments are given in Table 4. Lethal complications occurred once in the BLM group due to an arterial embolism and twice in the MTX group due to thrombosis of the carotid artery.

Table 3. Distribution of administered doses of chemotherapy

MTX(mg)	Patients		BLM(mg)	Patients	
50–100	6		15–75	4	
150–300	9	43%	135–150	3	16%
350–400	3		180–195*	24	
450–500*	24		210–300	12	
	42			43	

*Protocol dose scheduled.

The overall incidence of catheter problems (Table 5) reached 36% in patients receiving MTX and only 21% in those treated with BLM. Drug-related toxicities were also more frequent in the patients treated with MTX (59 vs 32% respectively, as shown in Table 5) than in those receiving BLM.

Second degree mucositis and local bleeding were encountered equally; skin reactions were more frequent with MTX than with BLM, but dyskeratosis of the extremities was not systematically searched for in the BLM group. Haematological complications were also more frequent in the MTX group. Two pneumopathies occurred in the BLM group but only one was considered as a consequence of BLM. Other reactions noted during chemotherapy, all of them reversible, were one haemiplegia, one CNS seizure, one facial palsy, one anaemia, one headache and two shivering in the MTX group, and two skin keratoses and one hyperuricaemia in the BLM group.

Tumour response

Figure 1 shows the sequential analysis of tumour regression in the 36 matched pairs. The trial could have been terminated in favour of BLM after the 32nd pair. However, there were time lags between randomization and

Table 4. Reason for interruption of chemotherapy

	MTX	BLM	No. of patients
Lethal displacement of catheter	2	1	3
Obstructed or displaced catheter	9	3	12
Toxicity	7	3	10
Total	18	7	25

Table 5. Complication due to chemotherapy

	MTX	BLM	No. of patients
Catheter problems			
Catheter displaced	15	7	22
Catheter obstructed	0	2	2
			24
Toxicity			
Leucopenia or thrombocytopenia	8	1	9
Pneumopathy	1	2	3
Second degree mucositis or local bleeding	6	6	12
Skin rash	8	2	10
Fever, weakness	6	0	6
Other reactions	7	3	10
Total	25*	14	39*

*Some patients experienced two or three types of toxicity.

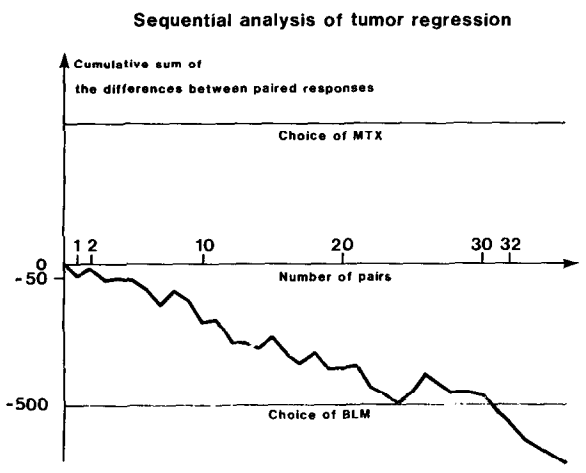

Fig. 1. Sequential analysis of tumour regression.

measurement of tumour regression, and in communication between the clinic and the statistical office, which explains the extra four pairs.

This sequential analysis includes only 72 of the 85 included patients. When one compares tumour regression with MTX and BLM in all 85 patients, regardless of matching (Table 6), the results are similar (non-parametric $P < 0.001$). The response rate (at least 50% of tumour regression) is 26% in the MTX group and 60% in the BLM group.

Restricting the comparison to the 60 patients who received more than 400 mg of MTX or more than 150 mg of BLM leads to the same conclusion, with a 67% response rate (defined as above) for BLM and 37% for MTX.

Analysis of neck node response is based on a total of 38 patients with palpable neck nodes. Table 7 shows that the response rate on nodes is low (10/38: 26%), with no significant difference by treatment.

DISCUSSION

Fifty-three per cent of the patients in this trial have tumours of the floor of the mouth, whereas tumours of the tongue are reported to be more frequent in our countries.

This selection is due to the exclusion from the trial of small tumours (T_1) which are more frequent on the mobile part of the tongue.

Patients in the trial are also 4–5 yr younger than patients generally observed for these tumours. This phenomenon is a consequence of the exclusion of older patients, with their increased contra-indication to chemotherapy, from the trial.

In the patients of our study we observed that intra-arterial BLM at the dosage used in the trial is superior to MTX as regards both feasibility and efficiency. With BLM, the full dose was administered in 85% of the cases, whereas only 60% of the cases were able to support the full dose of MTX.

The toxic effects observed in one third of the patients with BLM were mostly mild or moderate and anyway less numerous and less important than the toxic effects observed with MTX. In the latter group, 60% of the patients experienced some toxic symptoms, 17% of which were major.

From other reports, the overall incidence of side effects in i.a. chemotherapy is about 50%, with major complications in 5–20% of the cases [12, 15, 16], but only a randomized trial is able to demonstrate a difference between drugs.

Table 6. Tumour regression by treatment

Treatment group	No regression	Regression <50%	Regression ≥50%	Complete regression	No. of patients
MTX					
Total	16	15	9	2	42
Dose ≥ 400 mg	4	11	7	2	24
BLM					
Total	7	10	26	0	43
Dose ≥ 150 mg	5	7	24	0	36

(Wilcoxon test for the total population: $P < 0.001$.)

Table 7. Neck node response by treatment

Treatment group	No regression	<50%	≥50%	No.of patients
MTX	11	3	3	17
BLM	11	3	7	21
Total	22	6	10	38

In the literature, catheter complications vary widely in their incidence and importance. Sealy [17] mentioned 3 deaths out of 84 cases (4%), a figure comparable with our data. At the beginning of his experiment, Molinari [16] reported a high mortality rate which was soon reduced to a 3% rate. The relatively high incidence of technical problems with catheter observed in our study (28%) illustrates some consequences of clinical trials: firstly, the incidence of problems seems higher because they are noted prospectively, and so are not underestimated as in retrospective studies, and secondly, new treatments may not be similarly managed in the various participating centres because some of the centres may not yet have much experience with these therapies. The tumour regression rates observed in this trial are different than those generally reported in the literature. However, most of the studies published are not controlled trials and include various categories of patients in terms of staging, tumour sites, etc., and exclude patients considered as 'inevaluable', thus leading to generally over-rating the responses.

Bertino [18] reported a 50% or more tumour regression in 44% of 800 cases of head and neck carcinomas treated with MTX. The general response rate to this therapy varies from 37 [15] to 60% [19] in the literature. However, in these studies MTX is generally not used as a single drug, and it is given at lower doses. Concerning the data on the use of BLM by i.a. infusion, we refer again to Bertino[18], who reported a 25% response rate ($\geqslant 50\%$ reduction in tumour size) in a series of 24 head and neck cases, while Goldsmith and Carter[15] reported a 31% overall response rate, with 15% of cases achieving a tumour regression of more than 50%. Richard [8] controlled study on oral cavity carcinoma gave an identical low response rate. Japanese authors such as Inuiyama [20] come up with higher rates (66–70% of responses exceeding a 50% regression) in the better responding category of maxillary antrum carcinoma.

Nevertheless, it is worth noticing that the results quoted by Bertino and Goldsmith referred to experiences gathered from the literature which concerned a small number of miscellaneous cancers (not always squamous carcinomas) in various locations. When delivering BLM intra-arterially to epidermoid carcinoma of the oral cavity and oropharynx, Molinari [1] found a regression rate greater than 50% in 39% of 43 cases, including 8 previously treated patients. Therefore, the better results achieved by BLM in this study are not surprising, considering that our patients had potentially curable lesions and had not received previous treatment.

Finally, there were few complete tumour regressions (3/85) in our study and their incidence is identical to those published by others [1, 12, 16]. On the other hand, more impressive results were achieved recently by using multiple drug chemotherapy, associating both BLM and MTX with vincristine [1], vinblastine or 5-fluorouracil. Complete tumour regressions rates were reported in 25–30% of patients.

This trial was not undertaken to answer the important question of possibly increased survival for patients treated with these adjuvant therapies. Therefore, a new randomized trial has been designed by the EORTC Head and Neck Cooperative Group to evaluate the efficiency in terms of survival of i.a. chemotherapy (using BLM and vinblastine before surgery) for patients with a carcinoma of the oral cavity.

REFERENCES

1. MOLINARI R. Experience with intraarterial chemotherapy prior to surgery or radiotherapy for advanced cancer of the oral cavity. *Rev Sudam Oncol (Buenos Aires)* 1979, **3**, 18–25.
2. SULLIVAN RD. Protracted arterial infusion chemotherapy in head and neck cancer. *Med Sci* 1967, **18**, 35–40.
3. NERVI C, ARCANGELI G, CASALE C, CORTESE M, GUADAGNI A, LE PERA V. A reappraisal of intraarterial chemotherapy. *Cancer* 1970, **26**, 577–582.
4. FRIEDMAN M, DENARVAES FN, DALY JF. Treatment of squamous cell carcinoma of the head and neck with combined methotrexate and irradiation. *Cancer* 1970, **26**, 711–721.
5. JESSE RH, GOEPFERT H, LINDBERG RD, JOHNSON RH. Combined intraarterial infusion and radiotherapy for the treatment of advanced cancer of the head and neck. *Am J Roentgenol Radium Ther Nucl Med* 1969, **105**, 20–25.
6. DESPREZ JD, KIEHN CL, KRIZED TJ, DAMN H. Histological and biochemical considerations in the treatment of oral cancer with preoperative methotrexate infusion. *Plast Reconstr Surg* 1966, 336–341.

7. COUTURE J. Evaluation of the intraarterial infusion therapy for oral carcinoma. *Ann R Coll Phys Canada* 1968, **1**, 61–68.
8. RICHARD JM, SANCHO H, LEPINTRE Y, RODARY M, PIERQUIN B. Intraarterial MTX chemotherapy and telecobalt in cancer of the oral cavity and oropharynx. *Cancer* 1974, **34**, 491–496.
9. RYGARD J, HANSEN HS. Combined bleomycin and irradiation. *Can J Otolaryngol* 1975, **4**, 209–212.
10. MAYER M, COLON J. La chimiothérapie par voie intraartérielle dans les cancers de la région "téte et cou". *Acta Chir Belg* 1971, **70**, 337–350.
11. EORTC CLINICAL SCREENING GROUP. Study of the clinical efficiency of bleomycin in human cancer. *Br Med J* 1970, **2**, 643.
12. RICHARD JM, SANCHO H. La chimiothérapie intraartérielle des tumeurs de la tête et du cou: étude statistique portant sur 129 cas traités à l'Institut Gustave-Roussy. *Biomedicine* 1973, **18**, 429–435.
13. WALD A. *Sequential Analysis*. New York, Wiley, 1947.
14. SCHWARTZ D, FLAMANT R, LELLOUCH J. *Clinical Trials*. London, Academic Press, 1980.
15. GOLDSMITH MA, CARTER SK. The integration of chemotherapy into a combined modality approach to cancer therapy. *Cancer Treat Rev* 1975, **2** 137–158.
16. MOLINARI R, DE PALO GM, PREDA F. La chemoterapia regionale endoarteriosa palliativa nei tumori del distretto cervico-faciale in fase avanzata. *Tumori* 1971, **57**, 111–127.
17. SEALY R, HELMAN P, GREENSTEIN A, SHEPSTONE B. The treatment of locally advanced cancer of the head and neck with intraarterial cytotoxics, cobalt and hyperbaric oxygen therapy. *Cancer* 1974, **34**, 497–500.
18. BERTINO JR, MOSHER MB, DECONTI RC. Chemotherapy of cancer of the head and neck. *Cancer* 1973, **31**, 1141–1149.
19. SINDRAM M, SNOW GB, VAN PUTTEN M. Intraarterial infusion with methotrexate in the rat. *Br J Cancer* 1974, **30**, 349–354.
20. INUIYAMA Y, MUKAYAMI Y, KOHNO N. Clinical effects of NK 631 (Pe bleomycin) in the treatment of malignant tumors of the head and neck. *Pract Otol (Kyoto)* 1978, **71**, 1517–1523.