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COMBINATION CHEMOTHERAPY OF ADVANCED SQUAMOUS CARCINOMA OF THE HEAD AND NECK

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In Sweden squamous carcinoma of the cephalocervical region has a low incidence. Nevertheless, this tumor represents a therapeutic problem both in primary advanced diseases and in relapses, where the rate of curability and of palliation is distressingly low. Most of the patients have localized disease with a rather low tumor burden. Several cytotoxic agents are available with an objective response in 12 to 47 per cent as a monodrug therapy (GOLDSMITH & CARTER 1975, WASSERMAN et coll. 1975). Combination chemotherapy has resulted in an improved response rate (PRICE et coll. 1975). Favourable results have been obtained with regional intra-arterial infusion chemotherapy (OBERFIELD 1974, BERTINO et coll. 1975), but frequently complications have occurred. These results made it appear worthwhile to perform a preliminary trial of combination chemotherapy, if possible supplemented with an initial short-time regional intra-arterial chemotherapy of the bulk tumor.

Material and Methods

The material consisted of consecutive patients with measurable advanced squamous carcinoma of the cephalocervical region admitted July 1975–December 1976. Eleven patients where further treatment with surgery or irradiation was impossible were included; of these, 9 patients, 5 males and 4 females, were evaluable. Of the other two, one died early, not drug-related; the other did not cooperate. The median age was

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Table 1

Pretreatment features of the patients

Case No.	Sex	Age	Site	TNM	Radiation therapy (Gy)	Previous therapy		Recurrence after months
						Surgery	Chemotherapy	
1	M	59	Gingiva	T3N0M0	70	+	Bleomycin 225 mg	4
2	F	56	Gingiva	T3	70	+	Bleomycin 115 mg	—
3	F	74	Gingiva	T3N1BM0	70	−	Bleomycin 115 mg	—
4	M	56	Gingiva Maxillae	T3N0M0	64	−	Bleomycin 52.5 mg Vincristine 3 mg	—
5	F	49	Maxillae	—	70	−	—	—
6	M	58	Tongue	T3N0M0	70	−	Bleomycin 115 mg	4
7	F	29	Tongue	T2N0M0	40	+	—	3
8	M	62	Mouth	T2N1BM0	65	+	Mix 1 500 mg	4
9	M	69	Epi-pharynx	T2N2BM0	60	−	—	4

58 years (range 29–74 years). The site of the primary tumor, initial TNM-classification, previous therapy and disease-free interval appear in Table 1.

Before chemotherapy 8 of the 9 evaluable patients were treated with a maximum dose of irradiation, 4 with extensive surgery, and 6 with another type of chemotherapy (5 with Bleomycin, 1 with Methotrexate).

Two regimens of combination chemotherapy were used (Fig. 1). The treatment was repeated at intervals of 3 weeks until signs of progressive disease or a relapse. Adriamycin was withdrawn at the dose of 500 mg/m^2 body surface. The treatment was then continued with the other drugs as long as a response was observed. In the event of toxicity the dose was adjusted to a modification scale.

Four patients underwent selective angiography of the external carotid arteries. When the vascular supply of the tumor had been demonstrated, the catheter was advanced into or close to the main afferent artery where the chemotherapy was given as an infusion during 15 to 20 minutes. In 2 patients this was repeated after 2 weeks; in a third it was repeated twice with the same interval. Two patients were treated with Mitomycin C, each patient with Bleomycin and AMF-therapy.

Two patients (Nos 1, 9) were treated with Adriamycin-Methotrexate-Citrovorum factor rescue regimen (AMF), and 3 patients (Nos 2, 3, 8) with Vincristine-Adriamycin-Cyclophosphamide-Methotrexate-Citrovorum factor rescue regimen (VACMF). After initial intra-arterial chemotherapy one patient (No. 4) received AMF-therapy and 2 patients (Nos 6, 7) VACMF-therapy. One patient (No. 5) received only intra-arterial chemotherapy.

The results were assessed from regular physical examinations, Karnofsky's performance index and appropriate radiography and isotope examinations at least at two months' interval. Hemoglobin, leukocytes, and platelets were determined once

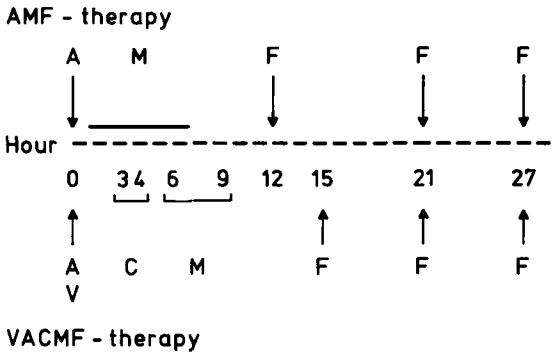


Fig. 1. Adriamycin-Methotrexate-Citrovorum and Vincristine-Adriamycin-Cyclophosphamide-Methotrexate-Citrovorum therapy. V = Vincristine 1 mg, A = Adriamycin 50 mg/m², C = Cyclophosphamide 600 mg/m², M = Methotrexate 300 mg, F = Citrovorum factor rescue 15–30 mg.

a week. Before each course reticulocytes, urate/serum, liver function tests and electrolytic status were determined.

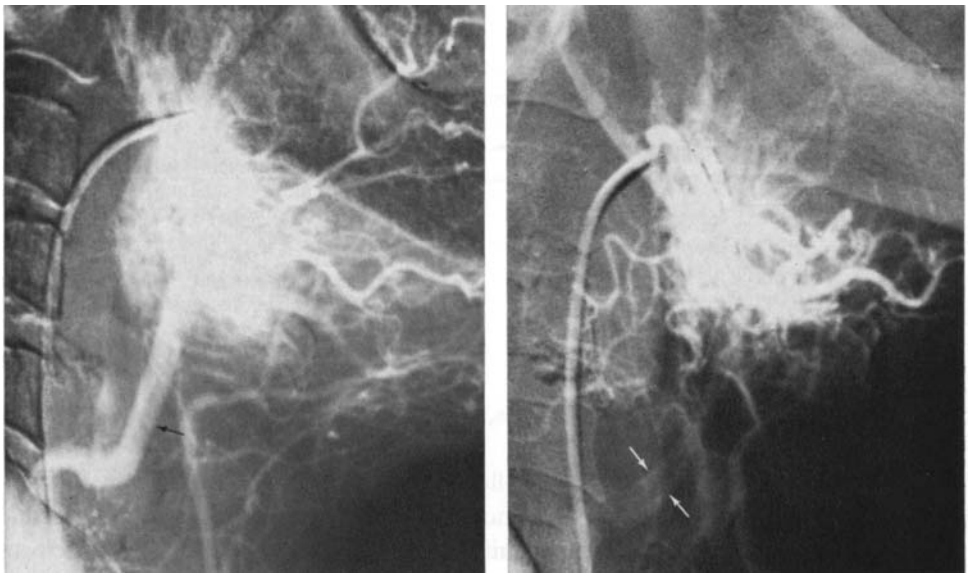
The response was classified in the following categories: Complete remission represents total disappearance of all tumors for at least one month and a normal Karnofsky's performance. A partial remission represents a decrease of 50 per cent or more in the product of diameters of lesions for at least one month. A static disease is defined as a below 50 per cent decrease of the product of diameters of measurable

Table 2

Site of recurrences, therapy and results

Case No.	Site of recurrence			Initial intra-arterial chemotherapy	Response		Chemotherapy	Response		Duration of remission (months)	Survival (months)
	Local	Lymph node	Other		Obj.	Subj.		Obj.	Subj.		
1	+	+	Skin	—			AMF	PR	Good	9	12
2	+			—			VACMF	CR	Good	6+	7+
3	+	+		—			VACMF	PD	None	—	3
4	+			A = 80 mg M = 200 mg	SD	Good	AMF	SD	Good	9	10
5	+			Bleomycin 15 mg × 2	SD	Good	—			—	4+
6	+	+		Mitomycin C 10 mg × 3	PR	Some	VACMF	PD	None	—	6+
7	−	+	Lung Bone	Mitomycin C 10 mg × 2	SD	Some	VACMF	PR	Some	4	7+
8	+	+		—	—	—	VACMF	PD	None	—	2
9	−	−	Lung	—	—	—	AMF	CR	Good	17	22+

Obj = objective, Subj = subjective, A = Adriamycin, M = Methotrexate, V = Vincristine, C = Cyclophosphamide, F = Citrovorum factor rescue, PR = partial remission, CR = complete remission, SD = static disease, PD = progressive disease.



a b

Fig. 2. a) Selective angiography of the lingual artery. Dense accumulation of contrast medium within tumor and rapid arteriovenous shunting. b) 2 weeks later. Tumor smaller. Less arteriovenous shunting.

lesions and no new lesions. Progressive disease represents more than 25 per cent increase of tumor mass or a new lesion. The duration of remission is calculated from the date of an objective response to a relapse. Survival is from the start of therapy to death.

Results

Intra-arterial chemotherapy. The intra-arterial chemotherapy resulted in one partial remission and three static disease. All patients achieved palliation. Relief of pain was good in 2 patients and fairly good in 2. As measured by Karnofsky's performance index, 2 patients improved 40 points, one 20 points, and one 10 points, respectively. The duration of remission could not be estimated as it was considered unethical to discontinue treatment with intravenous chemotherapy. One patient (No. 5) obtained such a good subjective improvement that she refused supplementary intravenous chemotherapy.

Intravenous chemotherapy. Five of eight patients treated with intravenous chemotherapy achieved objective remission. Of these 2 responded to VACMF-therapy (1 complete and 1 partial remission) and 3 to AMF-therapy (1 complete and 1 partial remission and 1 static disease) (Tables 2, 3). The median duration of remission was 9 months (range 4–17 months). The median survival for responders was 10 months (range 7+ to 22+ months) and for non-responders 3 months.

Table 3

Results of chemotherapy

	Intra-arterial	Vincristine-Adriamycin-Cyclophosphamide-Methotrexate-Citrovorum	Adriamycin-Methotrexate-Citrovorum
Complete remission	—	1	1
Partial remission	1	1	1
Static disease	3	—	1
Progressive disease	—	3	—
Total	4	5	3

One patient (No. 7) achieving a static disease with intra-arterial therapy experienced a partial remission with the subsequent VACMF-therapy. All metastases of the lung regressed. The metastases of the skeleton and of the regional lymph nodes became at least stationary for four months. Karnofsky's index increased by 20 points, and the subjective improvement made it possible for her to stay at home. One patient (No. 6) achieving a partial remission with intra-arterial chemotherapy (Fig. 2) did not obtain either objective or subjective improvement from subsequent VACMF-therapy.

Intra-arterial and subsequent intravenous AMF-therapy gave one patient (No. 4) an ameliorated quality of life (improvement of Karnofsky's index 40 points) and a static disease during nine months. The cause of death was an acute perforated stomach ulcer probably due to an alcoholic gastritis. On autopsy most of the remaining tumor was necrotic and no dissemination outside the cephalocervical region was found.

Two patients (No. 1, Fig. 3, and No. 9) obtained objective response with AMF-therapy (1 complete, 1 partial remission). Both patients had an increase of 30 points according to Karnofsky's performance scale. The duration of the complete remission was 17 months and the partial 9 months. At relapses both patients were treated with CCNU-Cyclophosphamide. The previous complete responder obtained a partial remission, but the other had a progressive disease and died from a carotic bleeding. On autopsy most of the tumor was vital but still located to the cephalocervical region.

With the VACMF-therapy one patient (No. 2) achieved complete remission; in 2 patients (Nos 3, 8) the disease progressed. The survival of these 2 nonresponders was 2 and 3 months, respectively.

Toxicity. The toxicity of the intra-arterial and intravenous chemotherapy was acceptable. No drug-related death occurred.

During the intra-arterial chemotherapy the patients experienced a transient burning pain but no other discomfort. No complications related to the technical procedure occurred. Neither myelosuppression nor mucosal ulcerations were observed.

Intravenous chemotherapy resulted in nadir values of leukocytes $3.9–2.0 \times 10^9/1$

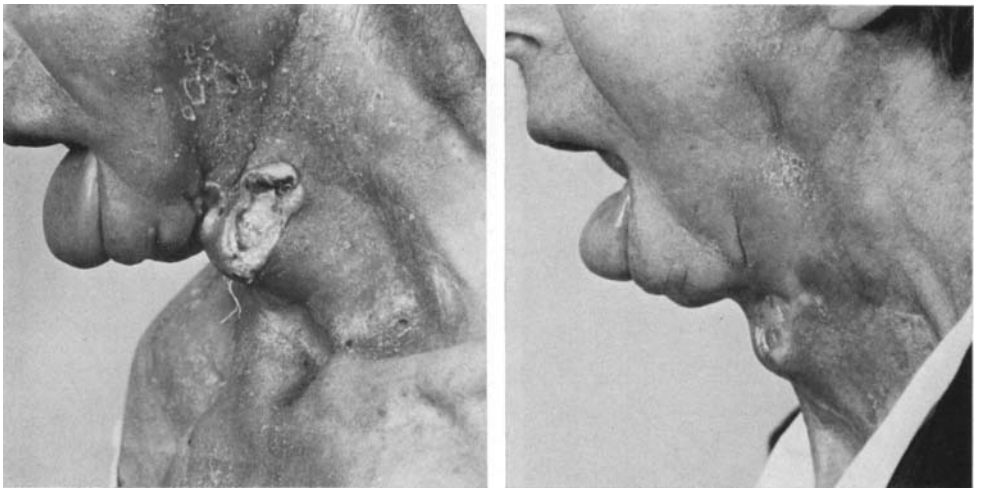


Fig. 3. Recurrent gingival carcinoma (Case No. 1) with metastatic skin lesion before and after 8 months of treatment.

and platelets 125–75 $\times 10^9$/l after 75 per cent of the courses. The myelosuppressions were always reversible and prolongations of the intervals were not needed. Dose modification was performed in 38 per cent of the courses. Mucosal ulceration requiring treatment was not observed. One patient had a secondary infection of candida in the mouth and lung, which responded to antimycotic treatment. Cardiotoxicity due to Adriamycin, cystitis due to Cyclophosphamide, nephrotoxicity due to Methotrexate did not occur. All patients treated with Adriamycin had reversible alopecia. During the first day of treatment all patients experienced nausea of varying severity but in no instance indicating a dose modification.

Discussion

As a monodrug the most effective drug is Methotrexate with or without subsequent Citrovorum factor rescue (BERTINO et coll. 1975). Other monodrugs with documented effects are Vincristine (BERTINO et coll. 1973), Adriamycin (BLUM & CARTER 1974), Bleomycin (YAGODA 1972, RYGÅRD & HANSEN 1975). Alkylating agents, such as Cyclophosphamide and Chlorambucil, and antimetabolics as 5-Fluorouracil, 6-Mercaptopurin probably have a place in the cytotoxic treatment of cephalocervical carcinomas (BERTINO et coll. 1975).

Combination chemotherapy has led to a higher response rate. GOLDSMITH and CARTER (1975) reported objective response for Methotrexate-Bleomycin therapy in 2 of 4 patients, for Methotrexate-Vincristine in 15 of 28, Bleomycin-Adriamycin in 4 of 8, and for Cyclophosphamide-Methotrexate-Vincristine-5-Fluorouracil in 8 of 10 patients. DOWELL et coll. (1975) achieved objective remission in 2 of 10 patients

and 6 of 12 by a four- and a five-drug combination, respectively, with a mean duration of remission of 3.5 months. Recently, in a randomized material, 7 of 14 patients and 8 of 20 responded to BACON (Bleomycin-Adriamycin-CCNU-Vincristine-Mechloretamine) and BACON plus immunotherapy, respectively, with a median duration of remission of 14 and 19.5 weeks and with a median survival of 21 weeks (RICHMAN et coll. 1976). In the present material objective response was obtained in 5 of 8 patients, which is in good agreement with these figures. The median duration of remission (9 months) and the median survival (10 months) corresponds favourably with other material. However, the most important result was a better quality of life.

The experimental findings of synergism between Adriamycin and Vincristine and Cyclophosphamide, respectively, (CARTER 1973, CORBETT et coll. 1975) and Adriamycin overcoming resistance to Methotrexate (HILL et coll. 1976) was the scientific basis when designing these regimens. Combined therapy based on cell kinetic concepts has yielded promising results. Thus, objective response has been obtained in 19 of 24 evaluable patients by a seven-drug combination (PRICE et coll. 1975) and in 10 of 17 by a three-drug combination (COSTANZI et coll. 1976). However, the median duration of remission was still short. As several cytotoxic agents with objective effects are available, an exploration of these drugs in appropriate cell kinetic combinations might improve the results in the future.

Intra-arterial regional cytotoxic chemotherapy seems logical as these tumors have a tendency even in advanced diseases to be located in the cephalocervical region. Metastases outside the cephalocervical region were present in only 2 of the 9 cases. By intra-arterial infusion chemotherapy with a single drug, about 50 per cent of the patients have obtained objective response with Methotrexate (BERTINO et coll. 1975) and with 5-Fluorouracil (DONEGAN & HARRIS 1976). The duration of these remissions was 2 to 13 months. Furthermore, intra-arterial combination chemotherapy has shown encouraging results. Remission from a combination of 5-Fluorouracil, Methotrexate, and Bleomycin occurred in 14 of 15 patients (DONEGAN & HARRIS). Using a Methotrexate-Bleomycin combination, STEPHENS (1974) achieved objective response in 5 of 8 patients, and BILDER & HORNOVA (1974) in 5 of 5 patients.

A drawback with prolonged intra-arterial infusion chemotherapy is the complicated technical procedure, which limits its wider use. Furthermore, a rather high rate of complications has been reported. Therefore the justification of this approach has been questioned (GOLDSMITH & CARTER 1975). On the other hand, the short selective intra-arterial infusion used in the present patients is a simpler procedure. It can be performed as an adjuvant therapy in connection with angiography both as a preoperative examination and as a means to demonstrate the extent of the disease. For over a year this method was also used in the bronchial arteries in patients with bronchial carcinoma with good results (BOIJSEN et coll. 1977). As cytotoxic agents antibiotics (Mitomycin C, Adriamycin, Bleomycin) were used with a presumtive effect during the whole cell cycle. The initial results suggest that this approach might be of

value as a supplementary therapy. The most important result is the striking palliative effect in all patients, however.

A further evaluation of chemotherapy both intra-arterially and intravenously seems to be indicated. As HILL et coll. (1975) and WOODS (1976) have stated, chemotherapy should be administered not only in advanced diseases, but above all as adjuvant therapy at the initial diagnosis in patients considered as high risks for development of recurrences.

SUMMARY

Combination chemotherapy in advanced squamous carcinoma of the head and neck resulted in objective remission in 5 of 8 patients, with a median duration of 9 months. In 4 patients, the intravenous chemotherapy was supplemented by regional intra-arterial short-time infusion chemotherapy, by which one patient obtained a partial remission and 3 a static disease. The most important results of the methods used were the subjective improvements of the patients. The side-effects were acceptable, and no serious complications were observed.

ZUSAMMENFASSUNG

Die kombinierte Chemotherapie führte bei fortgeschrittenen Fällen von Plattenepithel-Karzinomen des Kopfes und Nackens zu objektiven Remissionen bei 5 von 8 Patienten mit einer mittleren Dauer von 9 Monaten. Bei 4 Patienten wurde die intravenöse Chemotherapie durch regionale intra-arterielle Kurzzeit-Infusions-Chemotherapie ergänzt, wobei bei einem Patienten eine partielle Remission erreicht wurde und bei drei die Erkrankung stationär wurde. Die wesentlichsten Resultate der verwendeten Methoden waren die subjektive Verbesserung der Patienten. Die Nebenwirkungen waren akzeptabel und es wurden keine ernsten Komplikationen beobachtet.

RÉSUMÉ

Une chimiothérapie combinée a donné une rémission objective chez 5 malades sur 8 avec une durée médiane de 9 mois dans des carcinomes épidermoïdes avancés de la tête et du cou. Chez 4 malades la chimiothérapie intraveineuse a été complétée par une chimiothérapie en perfusion artérielle régionale de courte durée grâce à laquelle un malade a bénéficié d'une rémission partielle et 3 autres d'une stabilisation de leur affection. Les résultats les plus importants des méthodes utilisées sont l'amélioration subjective des malades. Les effets secondaires ont été acceptables et on n'a pas observé de complication sérieuse.

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