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BLEOMYCIN, METHOTREXATE AND VINCRISTINE BEFORE IRRADIATION OF STAGE III AND IV LARYNGEAL AND PHARYNGEAL SQUAMOUS CELL CARCINOMA

A study initiated by the Danish Society of Head and Neck Cancer

DAHANCA I

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Abstract

Primary treatment with bleomycin, methotrexate and vincristine for two weeks followed by curatively intended ^{60}Co irradiation was administered to 153 patients consecutively referred to the three main treatment centres in Denmark over more than a two-year period. Seventy-one laryngeal and 82 pharyngeal squamous cell carcinomas were evaluated. According to the TNM classification (UICC) 76 patients had stage III and 77 patients stage IV disease. The immediate response (complete + partial) to chemotherapy was 20 per cent. Judging from frequency of local recurrence, metastases as well as survival the treatment results were not obviously improved. A high frequency of complications was observed after this combination of chemotherapy and irradiation, and it was often impossible to fulfil the irradiation to the planned dose in appropriate time.

Key words: Therapeutic radiology; laryngeal and pharyngeal cancer, preoperative chemotherapy.

Carcinomas in the head and neck region usually remain locoregional for a long time. Local treatment results in a high cure rate, 70 to 80 per cent 5-year survival, for patients with small tumours. For advanced tumours the treatment results are much less satisfactory. In 1976–1977 a study-subgroup under the Danish Head and Nech Oncology Society decided to examine the effect of chemotherapy before irradiation for stage III and IV laryngeal and pharyngeal carcinomas.

In all oncology centres in Denmark the treatment policy for these tumours is primary irradiation with salvage surgery for residual or recurrent tumours. In the mid-seventies single chemotherapeutic agents such as methotrexate (MTX), bleomycin (BLM) and 5-fluorouracil (5-FU) had shown a response in 20 to 30 per cent of the tumours, and especially MTX and BLM had been proved to be effective in patients with squamous cell carcinomas of the head and neck, according to LIVINGSTON & CARTER (14) and WASSERMAN et coll. (25).

Bleomycin is most active towards highly differentiated squamous cell carcinoma; RYGÅRD & HANSEN (22) found a 38 per cent response rate in patients with head and neck carcinomas. MTX is active against all squamous cell carcinomas, and sequential application of MTX before irradiation was demonstrated to be valuable by VON ESSEN et coll. (4), KLIGERMAN et coll. (12) and RICHARD et coll. (20). Better response and less secondary effects are often achieved by a combination of two or more agents, as shown by PRICE et coll. (19) and ISRAEL et coll. (9).

Alternating multi-agent chemotherapy and irradiation offer a cell kinetic advantage (2). Experiments reported by FREI (6) have indicated enhanced effect of BLM after injection of vincristine.

Material and Methods

In 1977 the oncologic treatment centres in Copenhagen, Aarhus and Odense agreed upon the following treatment programme: All histologically proven squamous cell carci-

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Table 1
Chemotherapy schedule

Drug	Day			
	1	4 or 5	8	11 or 12
Vincristine* 1 mg/m² intravenously	x		x	
Methotrexate 20 mg/m² intravenously	x		x	
Bleomycin 13 mg/m² intramuscularly	x	x	x	x

*Vincristine was given 4 to 5 hours before MTX and BLM.

Table 2
Patients grouped according to localization of tumour, sex and treatment centre

Region	Copenhagen (n=84)		Odense (n=44)		Aarhus (n=25)		Total			
	M	F	M	F	M	F	M	F	M + F	Per cent
Supraglottis	23	7	9	3	8	2	40	12	52	34
Glottis	11	0	7	0	1	0	19	0	19	12
Hypopharynx	6	3	2	1	0	2	8	6	14	9
Oropharynx	20	4	12	2	7	2	39	8	47	31
Rhinopharynx	9	1	8	0	2	1	19	2	21	14
Total	69	15	38	6	18	7	125	28	153	

nomas in stage III and IV with primary tumour in larynx or pharynx were eligible, if the patient had no other malignant disease except carcinoma cutis, had normal white blood cell (WBC) and platelet count and normal liver function as measured by ASAT, alkaline phosphatase and LDH; had plasma creatinine below twice the upper limit, and no pulmonary fibrosis as demonstrated by chest radiography.

Radiation therapy was given according to previously used schedules except that it was preceded by two weeks of chemotherapy (Table 1). On day 1 and day 8 the patients received an injection of vincristine, 5 hours before methotrexate and bleomycin. In Copenhagen, however, the drugs were for practical reasons given as one injection on days 1 and 8, thereby omitting the time interval of 4 to 5 hours.

The irradiation was given as ^{60}Co teletherapy to a CRE value of 1750 reu. The total dose aimed for varied between 60 and 64 Gy given with 5 fractions weekly in a total treatment time from 6 to 7 weeks. The treatment fields included the primary tumour and at least the first regional lymph nodes; if neck nodes were palpable the whole neck and usually also the supraclavicular lymph nodes were included in two lateral opposed treatment fields.

The study included all eligible patients with laryngeal and pharyngeal squamous cell carcinomas, stage III and IV, referred consecutively through two and a half years from 1977 to 1979. Excluded from the study were patients not thought to tolerate the drugs—mostly patients over 70 years of age and patients with obstructive lung diseases or liver, blood or kidney diseases. A few patients with histology other than squamous cell carcinoma, patients having had a primary operation (tonsillectomy) and patients living outside the country if close follow-up was impossible, were also omitted from the study.

The localization of the 153 primary tumours and their distribution on the participating oncologic centres, which covered around 90 per cent of the whole country, are shown in Table 2.

A total of 125 males and 28 females entered the study. The females constituted 17 per cent of the laryngeal and 19.5 per cent of the pharyngeal cases. Most patients were in their sixties (39%) and the age ranged from 18 to 84 years. A total of 76 patients had stage III and 77 patients had stage IV disease. The TNM classification according to the UICC classification was utilised for the study and reclassified according to guidelines from 1978 (Table 3). A rough outline of the tumours was drawn in the case records before treatment commenced, after a fortnight of

Table 3
TNM classification according to UICC 1978

	N0	N1	N2	N3	Total
Larynx*					
T1a	0	1	0	1	2
T1b	0	6	1	1	8
T2	0	2	1	0	3
T3	22	3	3	3	31
T4	15	7	1	4	27
Total	37	19	6	9	71
Pharynx**					
T1	0	6	0	2	8
T2	0	10	4	5	19
T3	11	15	5	14	45
T4	2	2	0	6	10
Total	13	33	9	27	82

* Stage III n=34, stage IV n=37.
** Stage III n=42, stage IV n=40.

Table 4
Response to chemotherapy

Region	CR	PR	NC	NR	No data	Response (CR + PR) (per cent)
Larynx	1	12	31	22	5	18
Hypopharynx	0	1	2	8	3	7
Oropharynx	0	10	15	16	6	21
Nasopharynx	0	6	6	8	1	29
Total	1	29	54	54	15	20

chemotherapy, after irradiation therapy, and again two months after treatment.

Results

The treatment effect was evaluated for chemotherapy alone, and for the combined treatment by chemotherapy and irradiation.

The effect of chemotherapy was analysed at the start of radiation therapy, typically on the 15th to 18th day after commencement of the treatment. The usual criteria were used

where

CR means a total absence of tumour
PR, a more than 50 per cent decrease in tumour size, measured as maximum diameter (cm) × the transverse diameter, at a right angle to the first one
NC, a 25 to 50 per cent decrease in tumour size, and
NR equals a zero to 25 per cent decrease of the primary tumour.

The results appear in Table 4. The overall response rate to chemotherapy was 20 per cent, measured immediately after the course of treatment. In all, 90 per cent received the full course of chemotherapy, whereas only 8 per cent received half the course or less. Eight patients got skin reactions from bleomycin and received only 75 per cent of the course. The response rate to chemotherapy was 19 per cent for tumours larger than 2 cm and 38 per cent for the 8 patients with tumours less than 2 cm.

The irradiation was planned and carried out according to the usual treatment policy of each institution, aiming at an equal CRE value of 1750 reu administered in less than 52 days. All patiens were accepted for curatively intended treatment on referral. All patients received the intended irradiation, except for 3 patients who died before radiation therapy commenced and 6 patients who died before the course of radiation therapy was completed. However, 30 per cent (46 patients) did not attain the predetermined dose of ≥60 Gy and thus received insufficient radiation therapy. The tolerance to irradiation was distinctly reduced. Of the 16 patients not completing the full course of chemotherapy 9 (56%) received an incomplete radiation dose.

Seventy-four patients had a treatment period in excess of 8 weeks due to unavoidable interruption of the radiation treatment caused either by oedema or by mucositis.

Table 5
Local recurrence after primary treatment according to response to chemotherapy

	Larynx		Pharynx		Total		All	Per cent
	St. III	St. IV	St. III	St. IV	St. III	St. IV		
CR	0/0	0/1	0/0	0/0	0/0	0/1	0/1	0
PR	1/5	5/7	2/8	2/9	2/13	7/16	10/29	34.5
NC	7/15	13/16	5/12	4/11	12/27	17/27	29/54	53.7
NR	8/11	9/11	7/16	10/16	15/27	19/27	34/54	62.9
No data	2/3	0/2	4/6	3/4	6/9	3/6	9/15	60.0
Total	18/34	27/37	18/42	19/40	36/76	46/77	82/153	53.6
	53 %	73 %	43 %	48 %	47 %	60 %		

These symptoms were slight in 30 patients and severe in 20 patients. The longest treatment period was 86 days. Sixteen patients received irradiation for more than 10 weeks. After treatment 2 patients had a temporary tracheostomy, oedema reaction was noted in 20 cases and one patient had chondronecrosis.

The long-term results were analysed with regard to local tumour response and the frequency of local recurrence. Just over half the number of patients developed local recurrence (Table 5). In all, 63 per cent (45/71) of the laryngeal tumours and 45 per cent (37/83) of the pharyngeal tumours evolved local recurrence. The frequency of recurrence among the 30 patients responding favourably to chemotherapy was 33 per cent, whereas patients responding less favourably (NC, NR, ND) showed a recurrence rate of 59 per cent ($p<0.05$). The BMV dose seemed to have no influence on the recurrence rate.

Treatment of the first recurrence was surgical, if possible. Thirty-two patients had to have a total laryngectomy and a total of 47 patients were operated upon for residual or recurrent tumours. The complication rate was high, as 17 patients suffered pharyngocutaneous fistulae, and a further 6 patients had postoperative complications of which 3 got necrosis of the skin, 2 got haemorrhages and one protracted infection in the wound area.

Within the follow-up period, which was 5 years or more for all patients, a total of 80 patients had recurrences, either locally, regionally or in 10 patients, as distant metastases. Twenty-four patients showed complete remission after secondary treatment, but another 24 patients never achieved a disease-free status in spite of treatment.

At referral, 67 per cent (103/153) of the patients had lymph node metastases, and 23 patients developed lymph node metastases during the further course.

The 5-year survival. In October 1984, 52 patients were still alive. Twenty-two per cent of the patients who died had no evidence of cancer at the time of death, this being attributed to other diseases than cancer of the larynx or pharynx.

The 5-year survival for all patients was 45 per cent, calculated according to the cumulative life table method.

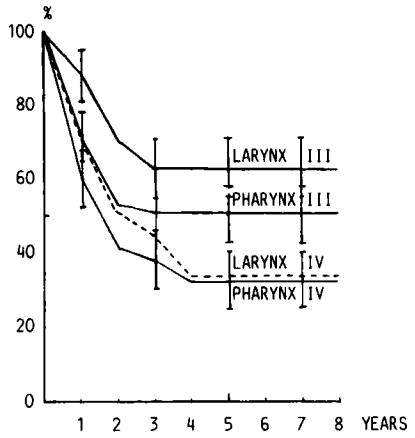

Fig. 1. Actuarially calculated survival for patients with laryngeal and pharyngeal tumours, shown for stage III and IV separately. One standard deviation is indicated on the curves.

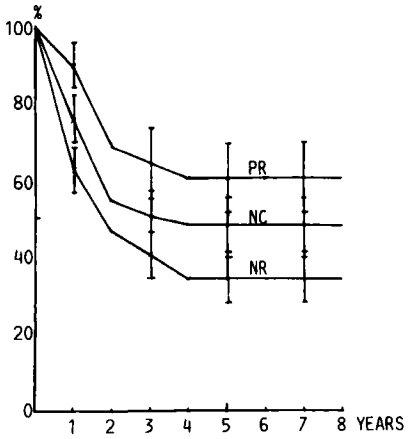

Fig. 2. Actuarially calculated survival for patients, according to the primary response to the initial chemotherapy. One standard deviation is indicated on the curves.

The 5-year survival for all stage III patients was 56 per cent and for stage IV patients 33 per cent.

According to localization, the 5-year survival was 55 per cent for patients with glottic stage III and IV tumours, 44 per cent for supraglottic stage III and IV, and 42 per cent for pharyngeal tumours stage III and IV. In Fig. 1 the 5-year survival for patients with laryngeal and pharyngeal stage III and IV tumours is depicted graphically.

Response to chemotherapy seemed to be an important prognostic factor concerning survival. For patients with total or partial response to two weeks of chemotherapy, evaluated less than one week after the last injection, the 5-year survival was 61 per cent (Fig. 2). The 5-year survival for patients with 25 to 50 per cent tumour response was 48 per cent, for patients with no response 34 per cent and for the few patients on whom no information about chemotherapy response was available 32 per cent.

Discussion

The treatment philosophy behind induction chemotherapy before radiation treatment is a better drug delivery to a previously untreated tumour bed with good vascularity.

Induction chemotherapy has been evaluated by MOLINARI et coll. (16) and RUFFMANN et coll. (21) after a 48-hour infusion schedule with the same 3 drugs as in the present study (VCR, BLM and MTX). RUFFMANN et coll. (21) reported a response rate of 69 per cent (9/13) after 4 series, with 38 per cent CR (5/13).

The RTOG trial (15) used the same agents, but with higher doses and with BLM infusion over a period of 2 days, without any enhanced morbidity. The response to chemotherapy was 61 per cent for the tumour and 37 per cent for nodes, but only 33 and 27 evaluable patients were included, respectively.

LACCOURREYE et coll. (13) used BLM given over 6 days in 3 cycles over 5 weeks as preoperative treatment with less than a 10 per cent response rate (CR + PR) with no obvious change in survival rate.

As noted by others, the side effects during irradiation increase considerably when induction chemotherapy has been administered. The treatment period had often to be extended in our series and like FRIEDMAN & DALY (7) we found a greater frequency of severe radiation epithelitis.

In contrast to the effect of irradiation, the effect of chemotherapy can be evaluated soon (weeks) after the treatment. SCHULLER et coll. (23) could not show enhanced response rates after 3 series of vincristine, methotrexate, bleomycin and cis-platinum, as compared with 2 series, contrary to the Michigan group. DECKER et coll. (3) obtained better results than others. They reported even better response after 3 series of cis-platinum and 5-fluorouracil infusion than after 2 series.

In the present series the response of radiation therapy was positively correlated to the response of induction chemotherapy. SNOW (24), WEAVER et coll. (26) and others have reported similar findings.

When chemotherapy is administered as induction treatment its long-term effects can only be evaluated by randomised studies. Some patients who obtain CR after induction chemotherapy experience recurrence of the tumour, usually within the first year, and in most cases within 6 months. Even when response rates to chemotherapy are high, the survival benefit thus remains to be proved.

Comparison with historical materials does so far not suggest that induction chemotherapy increases long-term survival rate. The RTOG randomised trial, including 638 patients treated with radiation or MTX + radiation, does not suggest that the combined treatment should be adopted for routine clinical usage. The conclusion from our study is identical: the gain in survival is dubious and the treatment morbidity is greater in patients treated with chemotherapy for a fortnight before radiation therapy.

Another method of enhancing the response to treatment of advanced head and neck tumours would be to use drugs combined with radiation. Drugs known to sensitize tumour cells to irradiation will be used in an attempt to obtain a synergistic and cytocidal effect against the tumours. This study is described in a preliminary report, DAHANCA II, by OVERGAARD et coll. (17).

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