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COMBINED BLEOMYCIN TREATMENT AND RADIATION THERAPY IN SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK REGION

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Abstract

Forty-six patients with squamous cell carcinoma of the head and neck region were randomized to either irradiation or irradiation plus bleomycin. If possible, the patients later underwent radical surgery. In the bleomycin group, significantly fewer patients had remaining tumour cells in the tissue removed at operation, and a longer time elapsed before recurrences occurred. However, bleomycin had no significant effect on the 3-and 5-year survival rates, and it did not significantly reduce the incidence of local recurrences.

Bleomycin is widely used in malignant lymphoma, squamous cell carcinoma of the head and neck, and testicular carcinoma. Its particular advantage is the lack of myelotoxicity. Bleomycin is bound to DNA (10), and RNA and protein syntheses are somewhat less sensitive to bleomycin than DNA synthesis (3, 11).

Studies on bacteria, mammalian cell cultures, and tumour bearing animals suggest that bleomycin and radiation therapy used in combination have an additive if not synergistic antitumour activity (1, 2). Encouraged by the favourable effects of bleomycin in advanced head and neck carcinoma, a randomized trial was started in order to study the influence of bleomycin combined with radiation therapy on regression of the tumour, the disease-free interval, survival time, and side effects.

Material and Methods

Forty-six patients (35 males, 11 females, aged 31–87, mean age 62 years) with squamous cell carcinoma of the head and neck region were included in this investigation during 1975–1978. Irradiation was given to 25 patients before radical operation and 21 patients received radiation therapy only. Using an envelope method, the patients were randomized to bleomycin and non-bleomycin groups. The classification, histologic grading, and location of the tumours are indicated in Tables 1, 2 and 3, respectively.

^{60}Co irradiation was given in 5 fractions/week to a total dosage of 30 to 32 Gy during three weeks, to a region including the primary tumour and the regional lymph nodes on both sides of the neck. Bleomycin (7–15 mg) was injected intramuscularly 30 to 60 min before each irradiation during the first and third week, reaching a total dose of either 75 or 150 mg.

The final decision about the operation was made immediately after the administration of 30 to 32 Gy, and in positive cases the operation was performed three weeks later. The operation was omitted in 11 cases, due to advanced age, and in 6 cases due to poor general condition. In addition, 4 patients refused the operation. These patients received an additional course of radiation therapy after an interval of 3 weeks, up to a total dose of 55 to 60 Gy.

The patients were examined both by an otorhinolaryngologist and a radiotherapist before treatment, after preoperative irradiation, after surgery, and at the end of the radiation therapy. Control visits were carried out at intervals of three to four months. The

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mean observation time was 70.4 months (range 46–86 months).

Results

Effect of irradiation on clinical findings. Eight of the 23 tumours treated with irradiation combined with bleomycin disappeared clninically after the preoperative dose of 30 to 32 Gy. In 13 cases remaining tumour was clearly detectable while in 2 cases oedema made clinical judgement impossible. Also in 8 cases out of 23 given radiation therapy only, the tumour disappeared clinically.

Effect of treatment on histologic findings. In 7 cases out of 13 in the bleomycin group, no viable tumour cells could be detected in the tissue removed at operation (Table 4). In the non-bleomycin group, this was the case in only one patient out of 12 ($p<0.05$). Degenerating, severely damaged tumour cells were seen in 2 specimens in both groups. One specimen in the non-bleomycin group could not be evaluated.

Local recurrence. The mean recurrence-free observation time in the bleomycin group was 64 months. Four out of 13 patients in this group did not show any local recurrence, whereas in 9 patients the recurrence appeared within an average time of 19 months; two of the last-mentioned patients lived for more than 65 or 86 months after the therapy.

Six out of 12 patients in the non-bleomycin group had an average recurrence-free interval of 58 months. Two of these died of an intercurrent disease 75 and 10 months, respectively, after the therapy, and one patient died after development of distant metastases 15 months after treatment. The mean survival time for the remaining six patients with local recurrences was 12 months: one was alive 80 months after the initial therapy. No statistically significant difference existed between the incidence of local recurrence in the two groups.

Survival. The 3-year survival rate for all patients was 54 per cent (25/46; Table 5), and 15 out of 41 patients (36%) were alive after 5 years. Recurrence usually appeared during the first year after therapy. The longest disease-free interval, 44 months, was observed in a patient operated upon after combined irradiation and chemotherapy. Some delay in the fatal outcome was seen in the bleomycin group, but the difference was not statistically significant.

Toxicity. No essential difference in the toxicity existed between the treatment groups. Twelve out of the 23 patients in the bleomycin group had an intermission during the preoperative treatment due to mucositis, as compared with 14 out of the 23 patients treated with irradiation alone.

Table 1

TNM classification of the patients

	Bleomycin and irradiation	Irradiation
T1N0	1	4
T2N0	7	5
T3N0	9	5
T4N0	2	1
T1N1-3	1	2
T2N1-3	2	1
T3N1-2	1	4
T3N1	–	1
Total	23	23

Table 2

Histologic differentiation of the tumours

	Bleomycin and irradiation	Irradiation
Grade 1	11	12
Grade 2	9	9
Grade 3	3	2
Total	23	23

Table 3

Location of the tumours

		Bleomycin and irradiation	Irradiation
Larynx	24	14	10
Tongue	11	5	6
Buccal mucosa	6	3	3
Tonsil	2	1	1
Gingiva	1	–	1
Nose	1	–	1
Hypopharynx	1	–	1
Total	46	23	23

Discussion

A favourable effect from the combination of bleomycin and preoperative irradiation in the treatment

Table 4

Histologic findings in specimens from operated patients after radiation therapy with 30 to 32 Gy

	Bleomycin and irradiation		Irradiation
No malignant cells	7	$p<0.05$	1
Dead malignant cells	2		2
Vital malignant cells	4		8
No diagnosis	–		1
Total	13		12

Table 5

Three- and five-year survival

	3 years	5 years
Patients treated with radical surgery after preoperative		
Bleomycin and irradiation	8/13	4/11
Irradiation	5/12	4/11
Patients not treated with radical surgery		
Bleomycin and irradiation	6/10	3/9
Irradiation	6/11	4/10
Total	25/46	15/41

of head and neck tumours was demonstrated in patients given surgery: 7 patients out of 13 (54%) showed no malignant cells in the removed tissue six to eight weeks after combined chemotherapy and irradiation, in contrast to only one out of 12 cases (8%) given preoperative irradiation alone. The favourable effect was not always clinically apparent, due to concomitant radiation oedema. The findings reported by KAPSTAD et coll. (5) were different. They demonstrated a clinically more prominent effect on the tumour regression after combined therapy than after irradiation alone, while no difference was noted in the histologic findings at the operation.

Although the favourable effect could to some extent be attributed to the combination of bleomycin with preoperative irradiation and surgery, no major improvement in recurrence or mortality rates could be demonstrated in this analysis. It would perhaps be more advisable to deliver the chemotherapy a couple of weeks before the preoperative irradiation (8). Another possibility would be to combine bleomycin with other agents effective in squamocellular tumours (4).

It was indicated in the present investigation, that the response of the tumour during the preoperative radiation therapy should not induce essential changes in the treatment schedule, and the same has been suggested by other authors (7, 9). The fact that malignant cells are not histologically demonstrable after preoperative treatment does not exclude later recurrence (6).

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