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Neoadjuvant and Adjuvant Chemotherapy in the Multidisciplinary Treatment of Oral Cancer Stage III or IV

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We performed a retrospective analysis on the effect of initial induction chemotherapy with two courses of cisplatin (each course 120 mg/m² cisplatin on day 1, then 20 mg/m² bleomycin (alone) per day for 5 days with 4 weeks between courses) in 75 consecutive patients with advanced cancer of the oral cavity or lip. Further local therapy consisted of surgery or radiation, depending on tumour location. In 18 resected patients adjuvant chemotherapy was added. This consisted of carboplatin, 400 mg/m² on day 1 then ftorafur alone, 500 mg/m²/day for 30 consecutive days, repeated every month for 4 consecutive months.

Among the patients treated in the neoadjuvant setting, complete response was observed in 10 out of 75 patients (13%), and partial response in a further 50 patients (67%) (partial plus complete rate 80%). Of all the patients, 43% in stage III and 26% in stage IV were long-term survivors. Improved survival was observed in surgical patients where adjuvant postoperative chemotherapy was added ($P<0.025$).

The main toxic effect was vomiting, observed in 71 patients. We noted a low rate of stomatitis (4%) and an important hearing loss (12%).

Neoadjuvant and adjuvant cisplatin-based chemotherapy as part of a multidisciplinary approach have a high overall response rate and low toxicity, and should increase survival in cancer of the oral cavity or lip.

Keywords: chemotherapy, oral cancer, prognosis, survival

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INTRODUCTION

The 5-year cure rate in patients with epidermoid carcinoma of the mouth treated with definitive surgery is 36% in stage III and 9% in stage IV [1].

Standard local treatment differences (surgery or radiation) may have prognostic significance [2]. Neoadjuvant chemotherapy might facilitate subsequent surgery and radiation therapy [3]. On the other hand, the positive effect of adjuvant chemotherapy in head and neck tumours because of the high relapse rate in stage III and IV tumours has been documented [4].

Trying to improve our results in oral cancer, we started a multidisciplinary treatment that consisted of neoadjuvant chemotherapy followed by local treatment (surgery or radiotherapy) and, in some patients, adjuvant chemotherapy. Active drugs have been used in head and neck cancer: cisplatin plus bleomycin for neoadjuvant and carboplatin plus ftorafur for adjuvant therapy [5, 6].

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The objectives of this multidisciplinary approach were to determine: (a) the rate and magnitude of tumour regression to induction chemotherapy; (b) the curative potential of subsequent surgery and/or radiotherapy, (c) the efficacy of adjuvant chemotherapy in the control of local relapses or distant metastases.

METHODS

Patients

75 consecutive previously untreated patients, with locally advanced cancer of the oral cavity or lip, were entered into a multidisciplinary therapeutic trial. Inclusion criteria consisted of biopsy-proven squamous cancer in stage III or IV [7]; age under 70; and performance status less than 4. A complete blood examination, including a platelet count, white blood cell and haemoglobin and serum creatinine level, was performed prior to therapy. Furthermore, an X-ray film of the chest and an audiometric study were performed before every course of chemotherapy and 1 month thereafter.

Informed consent was obtained from every patient before therapy.

Table 1. Patient characteristics and response to induction chemotherapy

	Number	Response		
		Partial (PR)	Complete (CR)	CR+PR
Primary site				
Cheeks	3	3 (100)		3 (100)
Retromolar area	9	6 (66)		6 (66)
Tongue	23	16 (69)	3 (13)	19 (82)
Lip	3	3 (100)		3 (100)
Floor of mouth	11	9 (81)	1 (9)	10 (90)
Hard palate	6	4 (67)	2 (33)	6 (100)
Tonsil	20	10 (50)	3 (15)	13 (65)
All sites	75	51 (67)	9 (13)	60 (80)
Treatment groups				
Surgery	20	1	17	18 (90)
Surgery + adjuvant chemotherapy	18	4	12	16 (88)
Radiation	37	5	21	26 (70)
Neoadjuvant chemotherapy	75	10	50	60 (80)

Percentages are shown in parentheses.

Primary therapy

All patients were given two courses of chemotherapy. This was followed by definitive surgery, if the tumour location was in the mucosal surface of the cheeks, retromolar area, tongue or lip. If the tumour was in the hard palate or tonsil, definitive radiation therapy (minimum of 65 Gy) was delivered over the primary lesion area (instead of surgery). Chemotherapy consisted of cisplatin, 120 mg/m^2 i.v. on day 1 then bleomycin (alone), 20 mg/m^2/day for 5 consecutive days in perfusion with dextrose 5%, 1000 ml/day. All patients were hospitalised for cisplatin and bleomycin therapy. If the audiometric study showed a decrease under 30 dB in frequencies lower than 8000 cycles/s, cisplatin was replaced by carboplatin, 400 mg/m^2 for 1 day then bleomycin as scheduled.

Anti-emetic therapy consisted of dexamethasone, 20 mg i.v. once before chemotherapy, then metoclopramide, 3 mg/kg i.v. every 3 h for the first day and continuing ever 6 h for 4 more days.

Adjuvant therapies

In 18 resected patients, adjuvant chemotherapy was added. This consisted of carboplatin, 400 mg/m^2 on day 1 i.v. then ftorafur, 500 mg/m^2/day for 30 consecutive days, repeated once a month for 4 consecutive months. Adjuvant postoperative radiation therapy (50–55 Gy) over cervical lymphatic chains was given for control of subclinical disease when positive nodes were found in the surgical specimen.

Therapeutic groups

Three therapeutic groups were considered: neoadjuvant plus surgery plus or minus radiation; neoadjuvant plus surgery plus adjuvant (postoperative) chemotherapy; and neoadjuvant chemotherapy plus radiotherapy (Table 1). All 75 patients were treated with neoadjuvant chemotherapy. 38 patients were also treated by surgery as local therapy; for 18 of these surgical patients, four courses of adjuvant carboplatin plus ftorafur were added.

Response and toxicity evaluations

Responses and toxicity criteria were evaluated according to World Health Organisation (WHO) criteria [8]. In the inner mucosal lesions of the mouth, the larger diameter and its perpendicular were measured by two or more members of a multidisciplinary team. Survival curves were performed by the Kaplan and Meier method [9]. Comparisons between curves were performed with the log rank test [10].

RESULTS

Patient characteristics

Of 75 patients, 68 were male and 7 female. The mean age was 54 years (range 38–68).

Original tumour sites were in the tongue (23 patients), tonsil (20 patients), floor of the mouth (11 patients), retromolar area (9 patients), hard palate (6 patients) and mucosal surface of the cheeks and lip (3 patients each) (Table 1).

Stage III was observed in 31 patients, stage IV in the 44 other patients (Table 2).

Therapeutic outcome

Complete resection was achieved in 32 out of 38 surgical patients, and in 6 more patients resection margins were invaded by the tumour.

Table 2. Staging in all patients

	T_0	T_1	T_2	T_3	T_4	Total
N_0	0	0	0	23	15	38
N_1	[illegible]	[illegible]	[illegible]	[illegible]	8	16
N_2	0	0	0	1	1	2
N_3 OR M_1	2	1	5	3	8	19
Total	2	1	6	34	32	75

Stage III Stage IV

The outcome of this treatment was as follows: regional node metastases were observed in 3 patients treated with adjuvant chemotherapy versus 4 in no adjuvant chemotherapy patients; local relapses were observed in 3 adjuvants versus 11 in no adjuvants. Pathological nodal staging was positive in 17 out of 38 surgical patients. In these 17 patients, postoperative adjuvant radiation was delivered over cervical lymph nodes. Adjuvant chemotherapy with carboplatin plus ftorafur was also given to 8 of them, while no further adjuvant chemotherapy was added to the other 9. 37 patients treated with chemotherapy followed by definitive external radiation over the primary tumour and ipsilateral neck lymph nodes.

Responses

Response rates to chemotherapy were as follows: 10 complete responses (13%) and 50 partial responses (67%), that are summarised as 60 complete plus partial responses (80%). The highest response rate was observed in the mucosal surface of the cheeks, in lips and in hard palate, followed by floor of the mouth and tongue sites (Table 1). After radiation therapy, 7 out of 21 chemotherapy definitive responders reached a complete response. At the end of definitive radiation, 12 complete responses (32%) and 16 more partial responses (43.5%) were achieved (overall response rate 75.5%).

Median duration of the time to relapse in all patients was 27.6 months (18 months for partial responders and 33.7 months for complete responders, $0.05 < P < 0.1$).

Survival

After a median follow-up period of 54 months, the overall median survival duration for all patients was 19.1 months, with a plateau in 30% of the patients after 31 months of follow-up (Fig. 1). There were no statistically significant differences between the survival curves of patients treated by definitive surgery versus definitive radiation. A trend towards better survival was observed in favour of stage III over stage IV patients (Fig. 2). Forty-three per cent of stage III and 26% of stage IV patients were long-term survivors. An improved survival was observed in surgical patients where adjuvant postoperative chemotherapy was added ($P < 0.025$) (Fig. 3). The median survival time (in months) according to the site of the primary tumour was as follows: 18.9 for mucosa surface of cheeks; 11 for tongue; 8.9 for retromolar area; 20.5 for hard palate; 6.7 for lips; 13.4 for tonsil; and 18.7 for floor of the mouth. Statistically significant differences in survival according to primary tumour sites were not observed. All patients died by local or regional progression of the disease and no case of distant metastases was seen.

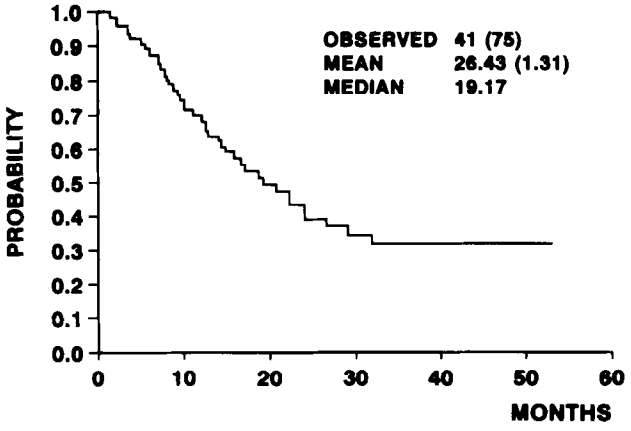

Fig. 1. Survival curve in all patients. A "plateau" after 31 months can be seen in 30% cases.

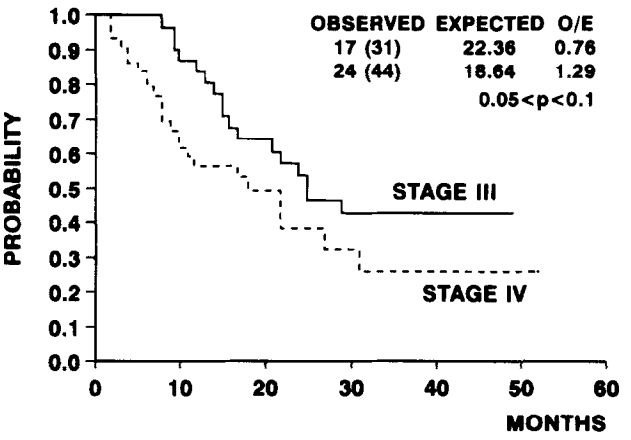

Fig. 2. Survival curves in stage III versus stage IV patients. There was a trend towards statistical difference in favour of survival of stage III over stage IV patients.

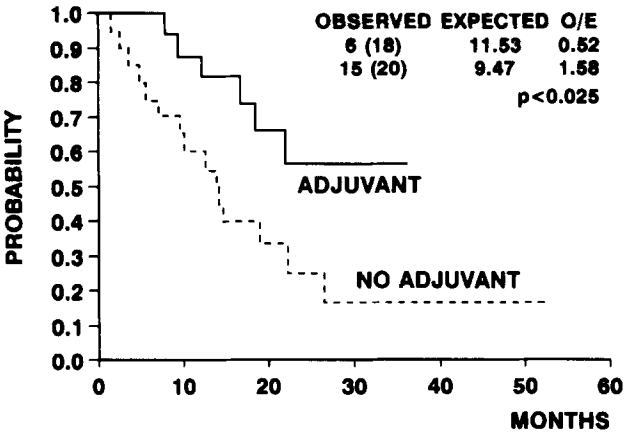

Fig. 3. Comparison in survival between patients treated by chemotherapy and definitive surgery plus or minus adjuvant chemotherapy. Statistical significant differences can be observed in favour of adjuvant treated patients.

Toxic effects

The main toxic effect was vomiting (mostly grade 1 or 2 of the WHO), observed in 71 patients. Low grade of reversal alopecia was observed in 19 patients, and mild anemia in 9 more patients. In 2 cases, chemotherapy was started with carboplatin instead of cisplatin because of an altered prior audiometry; hearing loss was observed in 9 patients. In 3 of them, audiometric loss was severe and affected the speaking frequency band. 5 out of 9 patients required a second course with carboplatin instead of cisplatin because audiometric changes were observed after the first course of chemotherapy.

Erythema related to bleomycin was seen in 8 patients, severe in one case.

Four patients had well-tolerated fever not associated with

chills. In some patients a light increase of basal temperature over 37°C was detected.

Other, less frequent, side effects were mild-grade stomatitis, anorexia, thrombocytopenia, increase 0.5 times the serum creatinine level, and a Raynaud phenomenon (one patient).

DISCUSSION

At the time of local treatment, patients with cancer of the oral cavity are generally debilitated, having poor performance status and a depressed immunological response. The administration of neoadjuvant chemotherapy leads to further general decline in the condition of these patients, even though there may be tumour regression [11]. A higher response rate is followed by an improvement in quality of life and in the general health of patients [12, 13].

In our series, focused on the oral cavity and lip, the overall response rate to neoadjuvant chemotherapy (80%) was similar to the results of cancer in other sites of the head and neck area, [14] but the complete response rate was lower (13%). In the survival curve we can observe a "plateau" of 30% after 31 months of follow-up. Frei *et al.* estimate that more than 50% complete response rate to induction chemotherapy is required before improved disease-free survival benefit will occur [15]. That could explain, in part, the poor effect on survival of this neoadjuvant therapy. The response rate with cisplatin plus bleomycin infusion was similar to that of cisplatin plus 5-fluorouracil reported by others [16]. Standard local treatment differences (i.e. surgery versus radiation) have been reported as prognostically significant in favour of surgery [16, 17]. However, our results support those of Rooney *et al.* [5], showing a 20–40% survival rate in a study that included both resectable and unresectable stage III and stage IV cases. Cure rate probability of stage III and stage IV patients appears better than that reported previously by authors not using neoadjuvant chemotherapy [1, 18]. We think that our results are due, in part, to a higher resection rate after induction chemotherapy which may facilitate subsequent surgery, and to a higher response to radiation.

The toxicity of induction cisplatin–bleomycin was acceptable. The low rate of oral mucositis permitted patients to complete all proposed courses of chemotherapy. Lung toxicity induced by bleomycin was not observed, probably because of the administration of only two courses of chemotherapy, giving a total dose of 200 mg/m^2 in patients with no previous lung disease. Audiometric changes are an important finding in cisplatin-treated patients. Performance of an audiometric study should be mandatory before every new course of cisplatin.

Chemotherapeutic relief of pain and asthenia may improve the quality of life and facilitate further local therapies of oral cancer patients.

Multidisciplinary programmes using neoadjuvant chemotherapy became our standard treatment in cancer of the oral cavity or lip. Such therapies may improve quality of life as well as survival time.

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