Pergamon

European Journal of Cancer Vol. 33, No. 7, pp. 1152–1155, 1997

Printed in Great Britain
0959-8049/97 $17.00 + 0.00

PII: S0959-8049(97)00099-3

Short Communication

Chemo-radiotherapy for Locally Advanced Head and Neck Cancer—Long-term Results of a Phase II Trial

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The feasibility and effectiveness of a combined chemo-radiotherapy treatment modality for locally advanced head and neck cancer was tested in a phase II trial. Between 1990 and 1993, 74 patients (20 female/54 male) with head and neck cancer stage III ($n = 12$) and IV ($n = 62$) were treated with accelerated radiotherapy (72 Gy) and simultaneous chemotherapy (5-FU, folinic acid, mitomycin C). The median follow-up time was 43 months (1–72). Complete remission (CR) was absent in 76% (56/74) of patients and, after subsequent resection of residual lymph nodes, another 8 patients achieved CR. The cumulative local control rate was 72% and disease-specific survival rate was 59% at 4 years. Two patients died with treatment-related conditions (pancytopenia, larynx oedema). By multivariate analysis, only lymph node status was an independent parameter for local control ($P = 0.04$). This treatment was feasible and toxicity was not a treatment-limiting factor. As a consequence, a German multicentre phase III trial was initiated in 1995. © **1997 Elsevier Science Ltd.**

Key words: head and neck neoplasms, radiotherapy, drug therapy, combination, clinical trials, phase II

Eur J Cancer, Vol. 33, No. 7, pp. 1152–1155, 1997

INTRODUCTION

IN PATIENTS with locally advanced, unresectable head and neck tumours, stages III and IV (UICC 1987), the 5-year survival rates range from 10 to 30% despite high-dose, conventionally fractionated radiotherapy. These disappointing results have led to several therapeutic strategies either using altered fractionation schedules [1–5] or combination with chemotherapy [6–8]. 5-Fluorouracil (5-FU) (740 patients) or mitomycin C (120 patients) in combination with radiotherapy have shown encouraging results in four phase III trials [9–12]. Simultaneous 5-FU infusion (120 h continuously) in the first week leads to an additive cytotoxic effect for the tumour and mucosa. This early stem cell depletion of the mucosa acts as a strong stimulus for regeneration and possibly reduces mucositis during the phase of accelerated radiotherapy. The rationale for combining mitomycin C in the first and sixth treatment week is to kill the hypoxic tumour cells. In this phase II study, we used a similar approach, but with an accelerated radiotherapeutic regimen to reduce stem cell repopulation.

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Received 22 Aug. 1996; revised 20 Jan. 1997; accepted 19 Feb. 1997.

PATIENTS AND METHODS

Between January 1990 and March 1993, 74 patients with inoperable and locally advanced head and neck cancer, stages III and IV (UICC 1987), of the oral cavity, naso-, oro-, hypopharynx and larynx were treated with combined radiochemotherapy. Ten nasopharyngeal tumours were included in this study because of advanced (T4) primary tumours or excessive lymph node involvement. Karnofsky index was at least 70%. Initially, radiotherapy was conventionally fractioned with 2 Gy per day for 15 fractions for 3 weeks. Thereafter, an accelerated regime was used, with twice-daily 1.4 Gy to a dose of 42 Gy applied in 3 weeks (30 fractions) to the primary tumour and macroscopically involved lymph nodes. The overall dose was 72 Gy in 6 weeks (45 fractions). The twice-daily fractionation

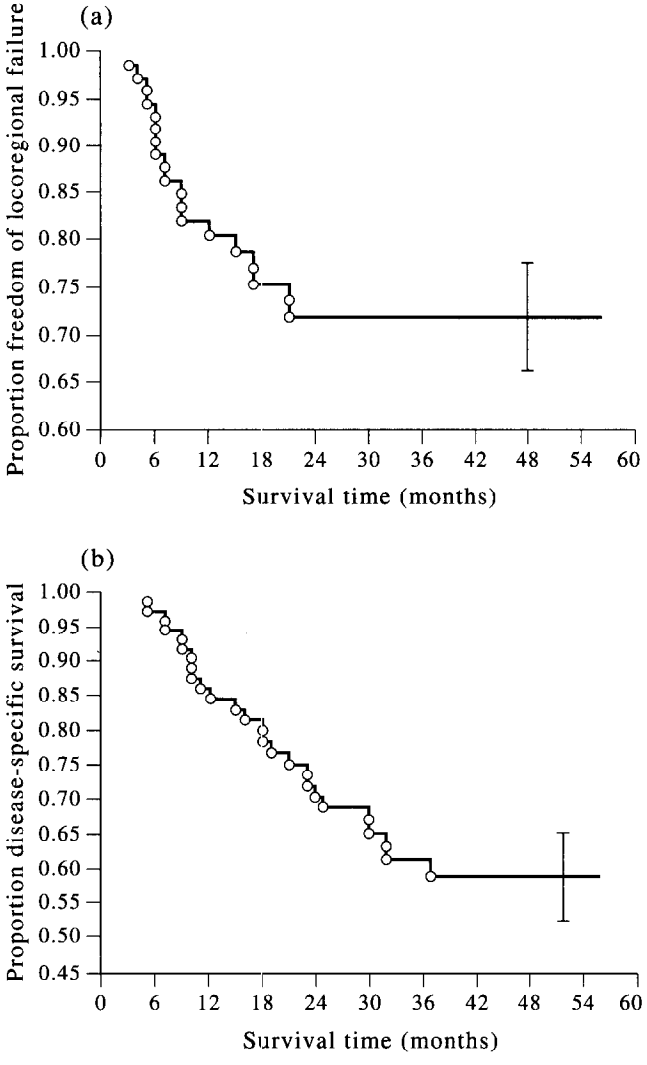

Figure 1. (a) Locoregional tumour control (salvage resection included); (b) disease-specific survival.

was given only to a partial treatment volume. Cervical and supraclavicular lymph nodes with a high or low risk of metastatic disease received a total target dose of 60 Gy in 6 weeks (30 fractions) or 50 Gy in 5 weeks (25 fractions), respectively. The total dose to the myelon did not exceed 39.6 Gy to avoid radiation myelitis. A three-field technique, two lateral opposed fields for the upper target volume and one anterior field for the lower cervical and supraclavicular lymph nodes, with telecobalt or 10–15 MV photons in a shrinking field technique, was used. If there was involvement of the base of the skull, the chiasma was shielded after 60 Gy to prevent severe late side-effects.

Table 1. Multivariate analysis (proportional hazard (Cox) regression)

	Local control	Disease-specific survival
Age	0.19	0.43
Tumour localisation	0.09	0.05
T-stage	0.36	0.11
N-stage	0.04	0.02
Radiation dose	0.22	0.16
Overall time	0.21	0.14

5-FU (350 mg/m^2) and folinic acid (50 mg/m^2) were given on day 1 intravenously (i.v.) as a bolus and thereafter from days 1 to 5, and 35–39 by continuous infusion (5-FU 350 mg/m^2 and folinic acid 100 mg/m^2). An i.v. bolus of mitomycin C (10 mg/m^2) was given on days 5 and 36. The second course of 5-FU had to be cancelled after the first 20 patients because of acute side-effects.

The survival and time to local failure analysis was carried out according to the Kaplan–Meier product-limit method with standard software. The multivariate analysis was performed according to the proportional hazard (Cox) regression model to identify prognostic factors for the outcome of the patients.

RESULTS

The median age of the 74 patients (20 female, 54 male) was 53 years (range 26–81 years). The median follow-up interval was 43 months (range 1–72 months). There were 10 primary tumours located at the nasopharynx only, 40 at the oropharynx with or without involvement of the tongue or floor of the mouth, eight tumours at the oropharynx infiltrating the hypopharynx/larynx, 12 tumours involving both the hypopharynx and larynx, and four tumours were very advanced tumours, involving the naso-, oro- and hypopharynx.

Complete remissions (CR) were seen in 76% (56/74) of patients treated by radiochemotherapy. In addition 11% (8/74) other patients achieved CR after resections of residual neck nodes, giving a total CR rate of 86%. The cumulative local control rate was 72% (one salvage resection for node recurrence included Figure 1a) after 4 years. The 4-year disease-specific survival was 59% (Figure 1b). By multivariate analysis, only node status was an independent parameter for local control ($P = 0.04$; Table 1). Age, tumour localisation, T-status, radiation dose and overall time had no prognostic significance. For disease-specific survival, tumour localisation and node status were significant, whereas age, T-stage dose and overall time were not (Table 1).

Table 2. Acute side-effects according to the RTOG-EORTC score except weight

Grade	0	1	2	3	4
Skin	6 (8%)	19 (26%)	23 (31%)	19 (26%)	0
Mucositis	0	1 (1%)	14 (19%)	52 (70%)	1 (1%)*
Dysphagia	1 (1%)	15 (20%)	44 (59%)	7 (9%)	
Xerostomia	3 (4%)	14 (19%)	38 (51%)	11 (15%)	
Weight	0	2 (3%)	37 (50%)	22 (30%)	4 (5%)
	(> + 10Kg)	(> + 5Kg)	(±5Kg)	(> − 5Kg)	(> − 10Kg)

*Not tumour related.

Table 3. Late side-effects

Grade	0	1	2	3	4
Skin	43 (58%)	16 (22%)	5 (7%)	1 (1%)	1 (1%)
Subcutis	11 (15%)	25 (34%)	21 (28%)	7 (9%)	–
Oedema	17 (23%)	24 (32%)	15 (20%)	5 (7%)	–
Mucosa	36 (49%)	17 (23%)	–	1 (1%)	9 (12%)
Xerostomia	3 (4%)	17 (23%)	34 (46%)	11 (15%)	
Trismus/fibrosis		4 (5%)	3 (4%)	4 (5%)	
Arterial stenosis or venous thrombosis				4 (5%)	2 (3%)
Osteoradionecrosis					2 (3%)
Cranial nerve lesions			4 (5%)		
Lhermitte syndrome			2 (3%)		

Acute toxicity is shown in Table 2. Mucositis grade 3 and 4 was seen in 70% and 1%, respectively. Nutritional support was provided by a liquid diet (dysphagia grade 2) in 57% (42/74) and via percutaneous endoscopic gastroduodenostomy (PEG) or parental nutrition (dysphagia grade 3) in 16% (12/74) of the cases. Acute skin reactions were not therapy limiting. 5 patients developed an acute serotympanion lasting for more than 6 months after the start of the treatment. One patient developed a pancytopenia after the second course of mitomycin C and died because of sepsis and central nervous bleeding 10 months after therapy.

Late side-effects occurring 6 months or more after the start of treatment are shown in Table 3. One patient developed an oesophageal stenosis with a fatal larynx oedema 8 months after treatment.

DISCUSSION

Overall, in head and neck cancer, accelerated treatment is believed to improve local control rates because of the observed reduction in local control due to prolongation of treatment [13]. Maciejewski and associates [14] deduced that accelerated repopulation of squamous cell carcinomas of the head and neck occurs towards the end of treatment which, in our study, was the rationale for the acceleration being provided in the latter phases of the treatment. The 4-year local tumour control rate of 72% and 4-year disease-specific survival rate of 59% for advanced tumours of the head and neck region demonstrate the effectiveness of this treatment approach. In a meta-analysis of the published results from 54 randomised controlled trials of adjuvant chemotherapy in head and neck cancer, Munro [6] demonstrated an increase in survival by 12.1% with single-agent chemotherapy given synchronously with radiotherapy. Lymph node status was an independent parameter for local control, whereas tumour localisation and lymph node status were significant in terms of disease-specific survival. These observations are in agreement with other published series [15, 16].

Assuming an α/β-ratio of 3 Gy for late and 10 Gy for acute reacting tissue, respectively, the dose of this treatment approach was biologically isoeffective at 66.9 Gy_3 and 69.9 Gy_{10}, respectively, in a conventionally fractionated regimen. The protection for peripheral nerves with a calculated α/β-ratio of 2 Gy was even better (65.7 Gy_2). The incidence of 5.4% of peripheral neuropathies (nerve lesions) is adequate for this dose level and is in agreement with the data reported from the literature [17]. The relative higher rate of vessel obliterations is probably due to a combined chemotherapy-induced toxicity.

The acute and late toxicities were high, but tolerable, and in good agreement with those reported by other authors for such a combined treatment modality. Haraf and associates [18] observed one case of brain necrosis, one of bone necrosis and two deaths during treatment out of 26 patients after concomitant chemoradiotherapy with cisplatin, 5-fluorouracil and hydroxyurea. Azli and associates [17] reported, from a study of 30 nasopharyngeal carcinomas, grade 3 and 4 mucositis in 13 and 5 cases, respectively, and a weight loss of 5–10% in one-half of the patients for acute side-effects. Xerostomia, trismus, fibrosis of cervical tissues, velar atrophy, cranial nerve palsy and radiation myelitis were also reported in 30, 3, 3, 3, 2 and one case respectively for late side-effects [17]. Sanchiz and associates compared a combined treatment with radiotherapy alone in a total of 859 patients, and observed a major incidence of grade 3 toxicity in the combined group [11]. Similar observations were made by studies from Abitbol and associates [19] and Wendt and associates [20].

In conclusion, as a consequence of the encouraging results in terms of local control and overall survival in our poor prognostic patient group, a German Mulitcentric Study was launched in 1995.

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