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INDUCTION CHEMOTHERAPY (CISPLATIN + 5-FLUOROURACIL) AND RADIOTHERAPY IN ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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Abstract

A phase II study was made of 58 consecutive patients with previously untreated locally advanced squamous cell carcinomas of the head and neck. The induction chemotherapy consisted of 3 courses of cisplatin (100 mg/m^2) and a subsequent 120-h infusion of 5-fluorouracil (1 000 mg/m^2/24 h) repeated every 3 weeks. It was followed by radiotherapy to a median target dose of 66 Gy and surgery for residual tumour. A total of 91 per cent received all 3 courses of chemotherapy, which was well tolerated. Complete response (CR) was obtained in 20 patients (35%) after chemotherapy and in 40 patients (69%) after subsequent radiotherapy. The median observation time was 28 months (range 15–57). The actuarial survival at 2 years for complete responders to chemotherapy was 83 per cent, implying a prolonged survival ($p = 0.002$) compared to those with less than CR. Complete responders after chemotherapy had also a significantly longer recurrence-free survival, though 19 out of 20 did not undergo surgery. Complete response after this induction therapy is thus an important prognostic predictor.

Key words: Head and neck cancer, treatment, induction chemotherapy, radiotherapy, 5-fluorouracil, cisplatin, response, survival, recurrence, toxicity.

Patients with locally advanced (generally T3–T4 or N1–N3) squamous cell carcinoma of the head and neck, treated with radiotherapy and/or surgery, have a poor prognosis. More than 70% of these patients die within 2 years, mainly due to local recurrence (1–4). Since local failure is the main problem in these patients, achievement of local complete response is an essential predictor for disease-free survival. Clinical data from Wayne State University, Michigan, indicated a high local complete response rate (54%) after three courses of induction chemotherapy with 120-h 5-fluoruracil (5-FU) infusion preceded by cisplatin in previously untreated patients (5).

The aim of the present study was to evaluate tumour response, survival and toxicity after this type of induction chemotherapy in 58 consecutive patients with previously untreated locally advanced squamous cell carcinomas of the head and neck.

Material and Methods

Patients

The patients in the present phase II study included those with previously untreated, biopsy proven, unresectable locoregional squamous cell carcinoma of the head and neck region stage II–IV (UICC 1978) (6) and WHO performance status equal to or less than 2 (7). Patients with stage II ($n = 4$) were only included when the primary tumour was considered unresectable.

Patients with impaired hearing or renal function (s-creatinine > 130 μmol/l) or cardiac disease, that did not allow hydration, were excluded.

The series consisted of 58 consecutive eligible patients, who were referred during the period December 1983 to June 1987 to the University Hospital, Lund, Sweden. Hypopharynx and oropharynx were the most frequent primary sites (Table 1). The distribution of T- and N-stages (UICC 1978) is shown in Table 2. Follow-up was concluded in October 1988. The median survival time was 35 months (range 3–57).

Treatment

The treatment strategy followed the guidelines of Rooney et al. (5): Induction chemotherapy consisting of 3 courses

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Table 1

Patient characteristics

Patients (n)	58
Age (range)	28–80
median	61
mean	59
Sex	
male	48
female	10
Tumour site	
nasopharynx	7
hypopharynx	18
larynx	8
oropharynx	15
oral cavity	10
T- and N-stage (UICC 1978)	
II	4
III	24
IV	30
Degree of differentiation	
well-differentiated	5
moderately differentiated	30
poorly differentiated	23

Table 2

Distribution according to T- and N- category (UICC 1978). All patients were classified as M0

	T1	T2	T3	T4
N0		4*	7	10
N1	3	6	9	7
N2		1	1	1
N3	2	4	1	2

* Considered unresectable

of cisplatin (100 mg/m^2) and a subsequent 120-h infusion of 5-FU (1 000 mg/m^2/24 h) repeated every 3 weeks, followed by radiotherapy and, finally, salvage surgery, if indicated.

In order to diminish cisplatin nephrotoxicity, the agent was concomitantly administered with 500 ml mannitol and preceded by hydration (1 l i.v. 0.9% NaCl). Antiemetic treatment with 200 mg hydrocortisone (i.v.) and 20 mg dixyrazin (Esucos) (i.m.) was given before and during the administration of chemotherapy. Electrocardiography was performed at least every second day during the 5 days of cytostatic administration.

All patients were treated with radiotherapy (^{60}Co or 4-6 MV x-rays), which started 2–4 weeks after completion of induction chemotherapy. The target volume included the primary tumour and the cervical lymph nodes bilaterally. The prescribed target dose was 64–70 Gy given in daily absorbed doses of 2 Gy, 5 days a week with a split-course technique, so that two-thirds of the total absorbed dose was given in the first course with an interval of 3–4 weeks between the two courses. An exception to this split-course technique involved 6 patients with carcinomas of hypopharynx not being in CR after induction chemotherapy. These patients received preoperatively 24 Gy and postoperatively the rest of a planned absorbed dose of totally 64–70 Gy. The specification of absorbed dose agreed with the recommendations in the ICRU Report 29 (8). Surgery was considered for primary tumours or regional node metastases, still persisting after completion of induction chemotherapy and becoming resectable after radiotherapy.

Assessment of response

Tumour status was assessed 2–4 weeks after completion of chemotherapy, 2–4 weeks after completion of radiotherapy and then every third month during the first two years and after that at successively longer intervals. These evaluations included clinical examination, computer tomography of the head and neck region, a pan-endoscopy (comprising epi-, oro-, hypopharynx and larynx) supplemented with palpation during anaesthesia and biopsies from suspicious residual tumour lesions.

Complete response (CR) was defined as the disappearance of all clinically evident disease for at least 4 weeks or at start of radiotherapy; partial response (PR) as at least 50% reduction in the sum of the products of the largest perpendicular diameters of measurable lesions; and no response (NR) as less than 50% reduction but not more than a 25% increase in these measures (9). The response of the primary tumour and the regional node metastases were combined for each patient, and the lesser response was considered as the patient's response to treatment.

Recurrence-free survival (RFS) was designated for the interval between the patient considered being in complete response and the first recurrence. For patients dead without having any previous or current evidence of recurrence, the endpoint for the RFS was calculated as the time of death (viz resulting in the minimum value of RFS).

Survival was estimated by the actuarial method and differences in survival between groups were tested with the generalized Wilcoxon's test (10). The statistical package SPSS was used for computations.

Results

Of the 58 patients, 53 (91%) received three courses of induction chemotherapy. Dose reductions of 5-FU and/or cisplatin were only made in 4 cases in the beginning of the study period, due to moderate haematological toxicity.

Toxicity related to the chemotherapy is presented in Table 3 and graded according to the WHO-classification (9). The induction chemotherapy was well tolerated. Apart from mild and transient nausea and/or vomiting (despite prophylactic anitemetic treatment), mucositis, anaemia, and moderate leukopenia were the most frequent drug related side-effects encountered. Only one probable instance of

Table 3

Treatment toxicity of induction chemotherapy according to the WHO recommendations (1979)

	Total n	WHO grade I	II	II + IV
Mucositis	23	15	8	—
Anaemia	27	18	9	—
Leukopenia	26	15	11	—
Nephrotoxicity	10*	3	—	—
Cardiotoxicity	6	2	3	1
Ototoxicity	6	—	—	—

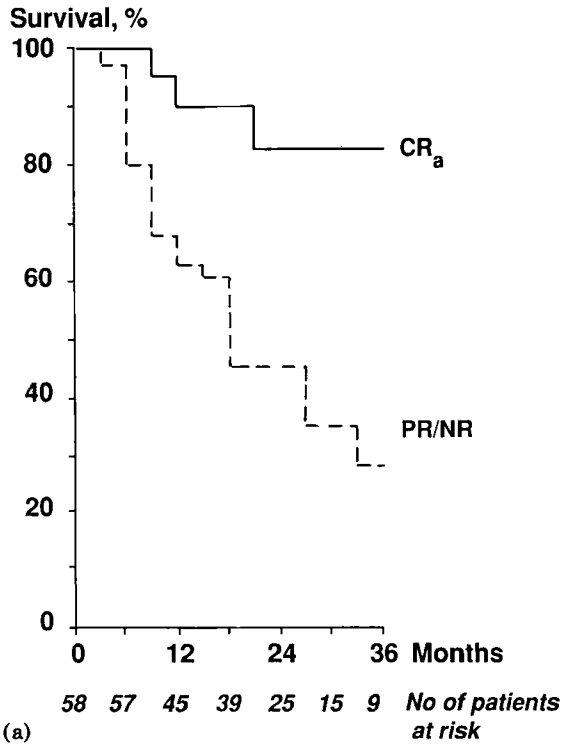
* In 7 patients S-creatinine exceeded 30% of pretreatment level, but was still grade 0

severe toxicity (grade 3–4) was observed; it was a myocardial infarction detected by electrocardiography at the start of the third course of chemotherapy.

Complete response after induction chemotherapy was obtained in 20 patients (35%) and partial response in 32 patients (55%). There was no significant association between primary site and rate of response or survival. The survival for all patients analysed according to response to induction chemotherapy, regardless of the following therapy, is given in Fig. 1a with a minimal follow-up of 15 months and a median follow-up of 28 months. The actuarial survival at a follow-up time of 2 years for complete responders to induction chemotherapy was 83% compared to 35% for non-complete responders (38% for PR and 17% for NR) (Fig. 1a). Patients with CR to induction chemotherapy had a significantly prolonged survival ($p = 0.002$) (Fig. 1a) compared to the combined group of partial and non-responders, regardless of the subsequent treatment.

The induction chemotherapy did not interfere with the subsequent radiotherapy, which could usually be accomplished according to the prescribed schedule. The radiotherapy increased the complete response rate to 69% ($n = 40$) and the total response rate to 91% ($n = 53$). CR achieved after chemotherapy only was also maintained during the radiotherapy. Of the patients with NR to chemotherapy only one obtained CR after subsequent radiotherapy. Patients with CR first after completed radiotherapy had significantly shorter survival ($p = 0.04$) than those who obtained CR already after the induction chemotherapy, but a longer average survival than the non-complete responders (Fig. 1b), although the last mentioned difference was not significant ($p = 0.19$).

Also the recurrence-free survival was significantly longer ($p = 0.03$) in patients with CR to induction chemotherapy than in patients obtaining CR first after radiotherapy (Fig. 2).



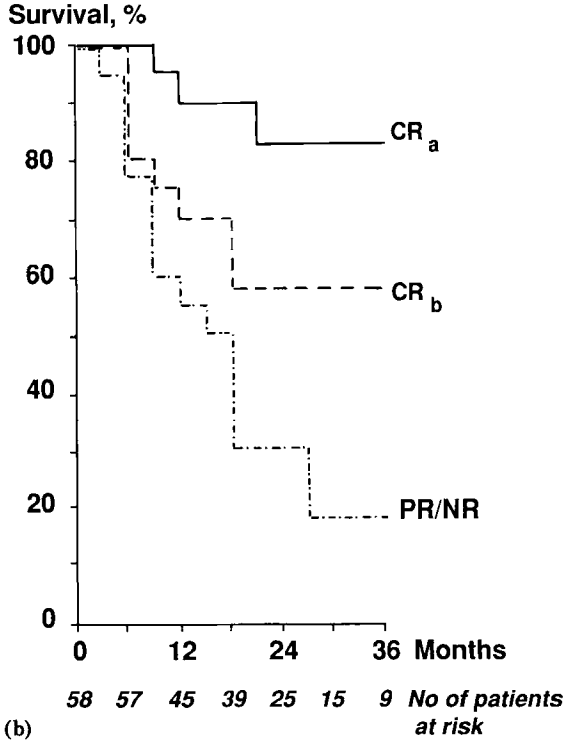


Fig. 1. Actuarial survival compared to degree of response after induction chemotherapy and after subsequent radiotherapy. All CR to chemotherapy was maintained during radiotherapy. a) Patients with complete response (CR_a) to induction chemotherapy showed significantly prolonged survival ($p = 0.002$) compared to patients with non-CR (PR/NR). b) Patients who achieved complete response only after radiotherapy (CR_b) had a poorer prognosis than patients with CR_a ($p = 0.04$).

Table 4

Analyses of local recurrence in 5 out of 19 patients with an initial local CR after induction chemotherapy, which was succeeded by radiotherapy only

Primary site and frequency of local recurrence	RFS (months)	Therapy of recurrence	Outcome
Nasopharynx (2/5)			
	4	—	Dead after 9 months due to M*
	20	—	Dead after 49 months due to L + M
Hypopharynx (1/5)			
	20	—	Dead after 25 months due to L + M
Larynx (1/3)			
	4	Cryo-surgery	Dead after 12 months due to L + M
Oropharynx (1/4)			
	8	Laser-surgery	Dead after 39 months due to IC.
Oral cavity (0/2)			

RFS = recurrence-free survival. L, M, IC = death attributed to local disease, metastases and intercurrent disease respectively. *Autopsy revealed microscopic local disease

Surgery of the primary tumour was not done in 19 of the 20 complete responders to chemotherapy, with the exception of neck node dissection, which was performed in 2 cases. Five patients (26%), had local recurrence later on and are presented in Table 4. Three of these 19 patients (16%), treated without surgical resection, finally succumbed to local failure.

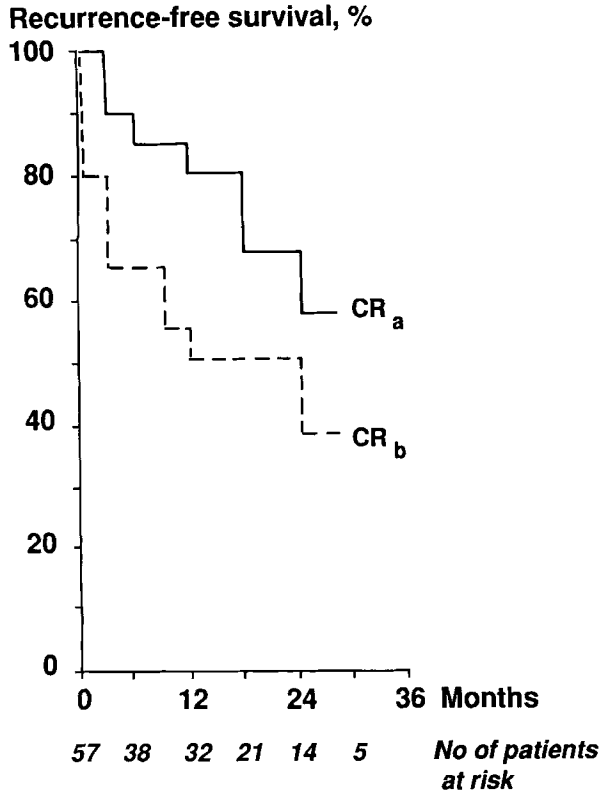


Fig. 2. Actuarial recurrence-free survival (RFS) in relation to time of complete response. CR after induction chemotherapy (CR_a) implied a significantly prolonged RFS ($p = 0.03$) compared to CR only after subsequent radiotherapy (CR_b).

Due to persistent cervical node metastases after radiotherapy, node dissections were performed in 8 patients. In these patients judgement of the response to radiotherapy was based on the histopathological findings. In 4 of these patients, residual carcinoma was found, and in one of these the node dissection was not considered radical.

Surgical resection of the primary tumour, usually combined with neck dissection, was performed in 14 out of the 38 patients without CR after the induction chemotherapy, but considered resectable after subsequent radiotherapy. A third ($n = 13$) of these 38 patients, of whom 10 did not undergo surgical resection, succumbed due to local failure.

Discussion

The present investigation demonstrated a complete response rate of 35% after 3 cycles of induction chemotherapy. In other series CR has been reported in 4–54% of the patients (5, 11–13). The differences in response to cisplatin and 5-FU are probably partly due to patient selection but may also be explained by differences in doses and treatment schedules. It has been shown that a 5-FU infusion administered during 120 h is superior to a 96-h infusion in inducing CR (5). The mode of administration of 5-FU is also of importance, viz continuous infusion is more effective and less toxic than a bolus injection (14). The primary tumour showed a better response to induction chemotherapy than the node metastases in the present study. Four partial or non-responders after radiotherapy

had complete disappearance of the primary tumour but persisting node metastases.

In the present study with a minimum follow-up of 15 months and a median follow-up of 28 months, complete responders to chemotherapy had a statistically superior survival (Fig. 1a) compared to partial and non-responders without considering the subsequent therapy. Also the recurrence-free survival (Fig. 2) was significantly longer in patients with CR after chemotherapy compared to patients with CR first after subsequent radiotherapy. Several previous investigations have also indicated that a CR is strongly associated with a prolonged disease-free survival (5, 12, 13, 15).

It should be noted that only one of the patients achieving CR after chemotherapy (n = 19), underwent surgical resection of the primary tumour. Elimination of surgical resection did not seem to adversely influence the survival (Fig. 1) or local recurrence rate (Table 4). These findings are in agreement with the reports of Jacobs et al. (12) and Demard et al. (16). By omitting large surgical resections the quality of survival may be improved without impairment of the prognosis.

The patients' compliance with this combination regimen was high. A total of 91% received all three courses of induction chemotherapy, mostly without dose reduction. In agreement with several other reports (11, 13) the toxicity of the chemotherapy was found to be tolerable (Table 3), and it did not interfere with subsequent radiotherapy and surgery. Continuous infusion of cisplatin, might further reduce toxicity (17). Nephro-, cardio- and ototoxicity are the most frequent serious side-effects reported after the present regimen (11, 18). However, only one patient had severe toxicity in the present study: a myocardial infarction. Adverse cardiac effects possibly related to 5-FU (19) consist of, besides chest pain, supraventricular tachyarrythmia and ST-T wave changes. These side-effects should be carefully observed with repeated ECG-recordings.

A high rate of CR to induction chemotherapy might be a selection phenomenon of a favourable subgroup, who might also respond to initial radiotherapy (20). Randomized trials are necessary to demonstrate a survival advantage. Such trials are on-going in Scandinavia and the USA and will hopefully answer this question.

Another argument against induction chemotherapy is the possible disadvantage to the subgroup of patients not achieving a CR, the start of whose radiotherapy or surgery is delayed by this regimen (12). Since there seems to be a strong correlation between the response to induction chemotherapy and subsequent radiotherapy, patients with a resectable carcinoma not responding at all to induction chemotherapy should probably be considered for an operation directly. On the other hand, induction chemotherapy can obviously save some patients with complete response from mutilating surgery.

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