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CONCOMITANT RADIOTHERAPY AND DAILY LOW-DOSE CARBOPLATIN IN LOCALLY ADVANCED, UNRESECTABLE HEAD AND NECK CANCER

Definitive results of a phase I–II study

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The combination of daily low-dose carboplatin and radiotherapy was studied in 55 patients with inoperable head and neck cancer. All patients were planned to receive 70 Gy plus carboplatin i.v. daily, 45–60 min before radiotherapy. A starting schedule of 30 mg/m^2 on days 1 through 5, weeks 1, 3, 5 and 7 was administered to 17 patients; an escalating daily dose, up to 55 mg/m^2, was given to 38 additional patients. Up to a daily dose of 45 mg/m^2, only 4.4% of the patients developed grade 3 leukopenia; on the contrary, grade 3 and 4 leukopenia was seen in 62.5% of patients receiving 50 mg/m^2 or more. Mucositis was the major nonhaematologic toxicity and seemed to be dose-dependent. At the end of the loco-regional treatment there were 33 (61.1%) CR and 17 PR; the most effective total carboplatin dose seemed to be 40–45 mg/m^2. After surgical salvage the number of CRs increased to 37 (68.5%). One- and 2-year loco-regional control rates were 64% and 53% respectively. One- and 2-year actuarial survival rates were 71% and 53% respectively; the corresponding rates of disease-free survival were 60% and 43%. There was a strong correlation nodal status and both survival and disease-free survival.

The results of conventional radiation therapy (RT) for locally advanced head and neck cancer are far from satisfactory, with the majority of patients dying of persistent or recurrent disease (1). In attempts to improve the results, several investigators have added single agent chemotherapy (CT) to the irradiation (2). All the major drugs potentially enhancing radiotherapy have been used. Several clinical studies have shown that the addition of chemotherapy to irradiation is beneficial in terms of initial response, local control and disease-free survival rates (3–10); unfortunately, most of the trials have reported severe stomatitis and other major side-effects and, consequently, interruptions and suboptimal delivery of the RT. Among the drugs selected, cisplatinum has shown a high degree of activity with less mucosal toxicity than most other drugs (9). Similar advantages are possessed by carboplatin (11). The combination of this drug and conventional or accelerated RT has been evaluated in several uncontrolled trials (12–15); encouraging results have been reported, but the optimal timing and dosage for the combined treatment have probably not been established. Preclinical studies suggest that both carboplatin and cisplatin, enhances the radiation effect (16). This enhancement seems to be maximal when the drug is present in the target cells at the moment of irradiation (17) and when the combined treatment is fractionated over a long time (18). Consequently, the greatest tumoricidal effect should be obtained when the drug is given with a prolonged daily schedule, before each irradiation (19). Based on these observations we started a study on daily low-dose carboplatin, used basically as a radiosensitizer, and conventional RT with curative intent

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in a group of patients with inoperable, locally advanced head and neck cancer. Preliminary data on a limited number of patients have already been published elsewhere (20, 21). In the present report the definitive results are assessed in the whole series of 55 admitted patients.

Material and Methods

Patients. The patients eligible for the study had locally advanced, inoperable, histologically confirmed squamous cell carcinoma of the head and neck, or recurrent disease after previous primary surgery. Additional inclusion criteria were: no prior CT or RT, no distant metastases, age >18 and $\leqslant 70$ years, ECOG performance status $\leqslant 2$, white blood count (WBC) $\geqslant 4 \cdot 10^9/l$, platelet count $\geqslant 100 \cdot 10^9/l$, haemoglobin $\geqslant 100$ g/l, bilirubin <20 g/l, SGOT, SGPT, Aph <3.0x's upper limit of normal value, adequate renal function (creatinine clearance >50 ml/min), informed consent. The tumor mass had to be measurable. Adequate nutritional and liquid intake was required. All patients were staged by clinical examination, panendoscopy, head and neck CT scan, chest-x-rays, and abdominal ultrasound.

Treatment. All patients were irradiated by cobalt-60 beam or 6 MV x-rays and with electron beams for additional boost; the planned total radiation dose was at least 70 Gy to the involved areas, given with 2 Gy/fr/d, 5 frs/wk. Carboplatin was given daily, as i.v. bolus 45–60 min before the irradiation. A starting schedule of 30 mg/m^2 on days 1 through 5, weeks 1, 3, 5 and 7 of the combined treatment (total dose: 600 mg/m^2 in 7 weeks) was administered to 17 patients; an escalating daily carboplatin dose was given to 38 additional patients: 35 mg/m^2 (5 pts; total: 700 mg/m^2), 40 mg/m^2 (5 pts; total: 800), 45 mg/m^2 (19 pts; total: 900), 50 mg/m^2 (5 pts; total: 1 000) and 55 mg/m^2 (4 pts; total: 1 100) (Table 1). They rested from treatment up to 2 weeks if grade 3 and 4 myelodepression or mucositis occurred. For patients in whom tumor shrinkage allowed resection of the residual mass, salvage surgery was planned to be performed approximately one month after chemoradiotherapy.

Evaluation of response and toxicity. Response and toxicity were evaluated according to the WHO criteria. Tumor assessment was carried out from 4 to 6 weeks after completion of radiochemotherapy by clinical and radiological examination, including CT scan; acute toxicity was assessed weekly (daily in patients with severe myelosupression). During the follow-up period, patients were observed at 2-month intervals.

Patient characteristics. Between February 1990 and December 1991, 55 consecutive patients fulfilling the eligibility criteria were treated. The patient compliance was very good and only one was regarded as not evaluable because of treatment refusal after 3 weeks from the start. Thus 54 (98.2%) patients could be evaluated for toxicity and response. The patient characteristics are shown in Table 2.

Statistics. The statistical analysis of toxicity and response was performed using Fisher's exact test and the Kaplan-Meier method was used for actuarial loco-regional

Table 2

Patient characteristics

Enrolled (February 1990/ December 1991)	55 patients
Evaluable for toxicity and response	54 (98.2%)
Median age, years (range)	58 (32–70)
Sex (male/female)	43/11
Performance status 0/1/2 (ECOG)	12/31/11
Previously untreated/recurrent tumour	49/5
Histologic grade G1/G2/G3/GX	11/13/18/12
Stage III/IV	7/47
Patients (%) with T4 primary tumour	39 (72.2%)
Patients (%) with N2/N3 neck nodes	24 (44.4%)/10(18.5%)
Primary site	
Oral cavity	17 (31.5%)
Oropharynx	15 (27.8%)
Nasopharynx	7 (14.3%)
Larynx	5 (9.2%)
Hypopharynx	4
Other	6

Table 1

Carboplatin and standard radiation therapy. Planned carboplatin dose associated with WHO toxicity grade

Daily dose carboplatin	Patients n	WHO toxicity grade														
		Leukocytes					Thrombocytes					Mucositis				
		0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
30 mg/m^2	17	10	4	2	1	0	14	2	1	0	0	0	3	10	4	0
35 mg/m^2	4*	2	2	0	0	0	2	0	2	0	0	0	0	2	2	0
40 mg/m^2	5	0	3	2	0	0	4	0	0	1	0	0	0	2	3	0
45 mg/m^2	19	6	7	5	1	0	15	4	0	0	0	0	2	9	7	1
50 mg/m^2	5	0	1	2	2	0	1	2	2	0	0	0	0	1	3	1
55 mg/m^2	4	0	0	1	1	2	2	2	0	0	0	0	1	1	2	0

* plus one refusal

control, disease-free survival and survival. Comparisons were made by the log-rank test. In order to individualize some prognostic variables influencing survival, a multivariate analysis was achieved according to the stepwise logistic regression model by Cox (BMDP Statistical Software, Inc, Los Angeles, CA, 1990). The follow-up analysis started at the completion of radiochemotherapy. The final evaluation was made with February 28, 1993 as deadline. No patients were lost to follow-up. The minimum follow-up time was one year or up to the time of death and the maximum follow-up 36 months (median: 708 days).

Results

Toxicity. No treatment-related death occurred. Patients were treated with 6 dose levels of carboplatin. Hematologic toxicity mainly consisted of leukopenia. Nadir count of leukocytes occurred between the 6th and 7th week of the combined treatment, with recovery within 10 days. Up to a daily dose of 45 mg/m^2, only 2 of 45 (4.4%) patients developed grade 3 leukopenia (WBC count $<1.5 \cdot 10^9$/l) whereas grade 3 and 4 leukopenia was seen in 5 of 8 (62.5%) patients receiving 50 mg/m^2 or more. This difference was statistically significant ($p < 0.01$). In the 2 patients with febrile leukopenia (granulocyte count $<0.5 \cdot 10^9$/l) the drug administration was discontinued after 960 and 990 mg/m^2 respectively. Only one patient manifested grade 3 thrombocytopenia. Coagulation tests revealed prolongation of prothrombin time in 3 patients (5.5%). Hemoglobin values were steady. Mucositis was the major non-hematologic toxicity. The degree of mucositis seemed to be dose-dependent, although the differences between different carboplatin doses were not statistically significant ($p = 0.08$). Grade 3 or 4 mucositis was observed in 6 of 21 (28.6%) patients receiving 35 mg/m^2 or less and in 16 of 33 (48.5%) patients planned to be given at least 40 mg/m^2; in this group we observed the 2 cases of grade 4 mucositis. There was a high incidence of local infection: oral and oropharyngeal candidosis occurred in 23 patients (42.6%). No other significant acute side-effects occurred: grade 1 nausea and vomiting was observed in 3 of 54 patients (5.5%) and transitory moderate paresthesias were seen in 4 patients (7.4%). The cumulative acute toxicity of the chemoradiotherapy did not necessitate reduction of the RT dose (all but one evaluable patients received the planned total dose of 70 Gy) or significant prolongation of the treatment course. Forty-one of 49 patients (83.7%) received the whole treatment course without delay; 5 patients required an interruption for 2–5 days and another 3 patients had an 8–15 days' delay. An adequate feeding support (nasogastric tube mainly) was furnished to the great majority of patients. Supportive care was administered on an outpatient basis for the great majority of cases. Only 3 patients required hospital care. The incidence of late damage was not significantly higher than that observed with standard RT alone. Up to now, 3 patients have developed necrosis of the mandibular bone at 5, 11 and 14 months; two of them had T4 lesion of the floor of the mouth. Salvage surgical treatment was conducted without obvious additional toxicity.

Table 3

Carboplatin and standard radiation therapy. Response according to the planned carboplatin dose

Daily dose carboplatin	Patients n	CR		PR	NR
30 mg/m^2	17	10 (58.8%)		6	1
35 mg/m^2	4*	1		3	0
40 mg/m^2	5	4 (80.0%)	$p = 0.09$	0	1
45 mg/m^2	19	14 (73.7%)		3	2
50 mg/m^2	5	2 (40.0%)		3	0
55 mg/m^2	4	2 (50.0%)		2	0
Total	54*	33** (61.1%)		17	4

* plus one refusal

** total number of CR patients after salvage surgery: 37 (68.5%)

Response and loco-regional control. At the end of the loco-regional treatment there were 33 (61.1%) CR (complete response) and 17 PR (partial); 4 patients (7.4%) had minimal response or stable disease. With respect to the possible role of carboplatin to increasing the efficacy of the RT, our results suggest that the most effective dose was 40–45 mg/m^2 (Table 3). A favourable statistical trend ($p = 0.09$) was observed for patients treated at this dose level compared to lower dosage. No additional advantages seemed to result from further escalation of the daily dose, probably due to the increased acute toxicity (in 2 patients the drug administration was discontinued).

The CR rate was statistically correlated with nodal status (N3: 25.0% versus $N < 3$: 68.3%; $p < 0.05$). Variables that in this study were not significantly correlated to the CR rate were T-category (T4 versus $T < 4$; $p = 0.13$) and stage of disease (IV versus III; $p = 0.20$). Out of 17 patients with PR, 5 were considered for the salvage surgery. Of these patients, one refused while 4 were successfully operated with wide resections of residual disease at the primary site (3 cases) or radical neck dissection (one case). Thus, after surgery the total number of CR increased to 37 (68.5%). Loco-regional relapse occurred in 6 (16.2%) of 37 CR patients. Four patients had their recurrence at the site of the primary tumor, and 2 in the neck. The median time to recurrence was 15 months, with a range from 5 to 22 months. The estimated probability of having a loco-regional relapse for CR patients was 12% at one year and 26% at 2 years. Two patients with resectable

local recurrence were successfully cured with salvage surgery. Therefore, in the whole series of patients, the one- and 2-year loco-regional control rates were 64% and 53% respectively. The prognostic significance of the nodal status was also confirmed for loco-regional control rates (N3 versus others, $p < 0.05$). The favorable statistical trend of the carboplatin dose level for CR rate was not confirmed for local control. Seven patients (13%) developed distant metastases of whom 6 had local or regional persistent or recurrent disease. The only patient with local control and disseminated disease (lung) was alive at 24 months. Three patients had a second primary tumour (2 oral cavity, 1 lung). In 2 cases the second cancer was the cause of death.

Survival. One- and 2-year actuarial survival rates were 71% and 53% respectively; the corresponding disease-free survival rates were 60% and 43% (Fig. 1). The one- and 2-year cause-specific survival rates were 71% and 65%. Multivariate analysis of different prognostic factors (performance status, T and N-categories, stage of disease, site of primary tumour, total carboplatin dose) revealed a strong correlation between N-category only and survival and disease-free survival. Plots in Fig. 2 show that the estimated probability of survival was significantly higher for patients with N0–2 disease than for those with N3 ($p < 0.005$). A similar trend was observed for disease-free survivors ($p < 0.01$). A statistically significant difference was also found in the probability of survival between CR patients and the others (at 2 years 72% versus 0%; $p < 0.001$).

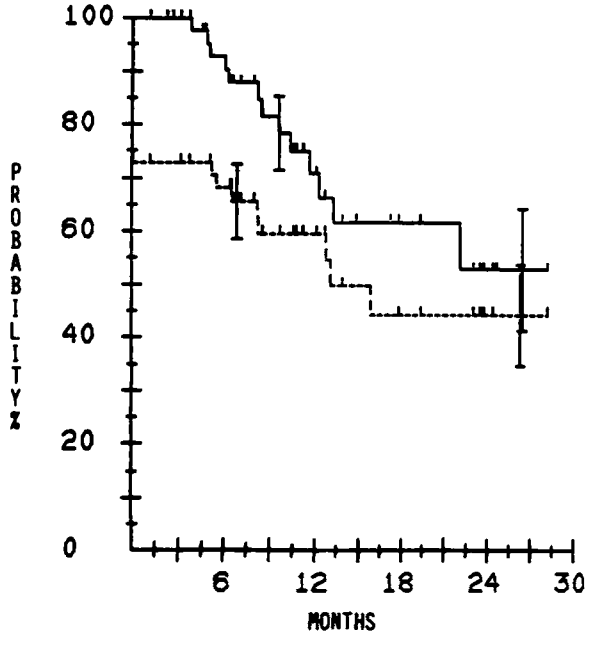

Fig. 1. Survival (—) and disease-free (- - -) survival in the whole series of patients (Kaplan-Meier method).

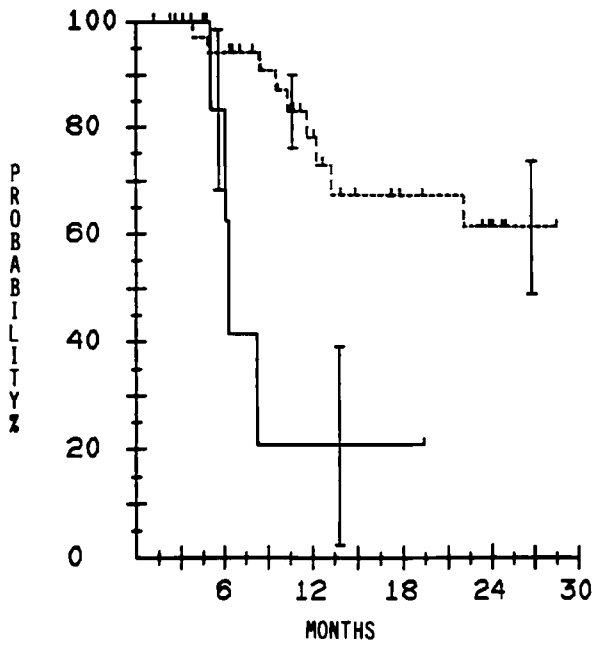

Fig. 2. Survival according to N-category (Kaplan-Meier method): N3 (—), N0–2 (- - -), $p < 0.005$.

Discussion

Our data suggest that a daily carboplatin dose between 40 and 45 mg/m^2 (corresponding to a cumulative dose of 800 and 900 mg/m^2 respectively, in a period from 7 to 9 weeks) can be administered on an outpatient setting with tolerable and reversible toxicity. As compared with reported data on cisplatin used in a similar way, the tolerance of carboplatin was remarkable (22). Leukopenia was the only dose-limiting side-effect. From this point of view, the actual treatment schedule was noticeably better tolerated than monthly carboplatin doses (13) and well comparable with other fractionated schedules in which the total dose of the drug was 15–25% lower than in our trial (10, 13–15). Oral and pharyngeal mucositis were moderate in the majority of patients. Grade 3 and 4 mucositis occurred in about 40% of the patients and a statistical trend ($p = 0.08$) was found between the incidence of severe mucositis and the carboplatin dose level. No such correlation could be observed in the other published series (10, 18).

In order to reduce bone marrow toxicity and degree of mucositis, G-CSF could be employed, as recently suggested in a preliminary report (24).

The observed complete response rate of 61% and the one- and 2-year rates of survival and disease-free survival suggest that the combined treatment may be more effective than standard RT (1). Other investigators have obtained similar results in locally advanced head and neck cancer using concomitant conventional RT and weekly injections of carboplatin (10, 13, 14). No additional advantages seem to have been observed by using other fractionated carbo-

platin schedules and irradiation with 2 fractions daily (15, 25). In our series, surgical resection of residual tumor mass played an important role; after salvage survery the CR rate increased considerably with minimal complications.

Due to differences between our patient population and that of other series, a comparison between results after different schedules of drug administration is not justified. Laboratory studies have indicated a therapeutic potentiation when a single dose of the platinum complexes was combined with a single dose of radiation (16). Few data are available evaluating the fractionated use of drug and radiation; some of them suggest that most enhancement is obtained with a daily administration of the drug, before each irradiation (17–19, 23). This suggestion has recently been supported by clinical data of the Radiotherapy and Lung Cancer Cooperative Groups in a randomized study on a large series of patients with inoperable non-small cell lung cancer (26).

With the limitation of a small number of patients, our results are encouraging and show that low-dose carboplatin in a daily prolonged schedule, concomitant with conventional RT can be safely used in an outpatient setting for the treatment of locally advanced and inoperable head and neck cancer. The present study was the basis for a randomized study which is now ongoing at the Radiation Therapy and ENT Clinics at the University of Turin comparing the reported chemoradiotherapeutic approach with standard radiation therapy.

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