A phase II study of concomitant boost radiation plus concurrent weekly cisplatin for locally advanced unresectable head and neck carcinomas

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Abstract

Background and purpose: This phase II study evaluated the efficacy and toxicity of weekly cisplatin along with concomitant boost accelerated radiation regimen in patients with locally advanced unresectable head and neck carcinoma.

Material and methods: A total of 94 patients (median age, 58 years) with UICC stage III (n = 19) and IV (n = 75) cancer of the oropharynx, larynx, hypopharynx and oral cavity were included. Patients received radiotherapy with a concomitant boost scheme (1.8 Gy on days 1-40 and 1.5 Gy boost on days 25-40 with a total dose of 72 Gy) and concurrent cisplatin, 40 mg/m² weekly, for the first 4 weeks.

Results: Most patients (95%) received both radiation and chemotherapy according to protocol. Toxicity was manageable with grade III mucositis and pharyngeal-oesophageal toxicity in 85 and 50% of patients, respectively. Haematological toxicity was mild. Four patients (4%) died due to complications. With a median follow of 41 months, median overall survival and time to progression were 27 and 25 months, respectively. The estimated overall survival at 4 years was 41%.

Conclusions: Concomitant boost accelerated radiation plus concurrent weekly cisplatin is a feasible schedule in patients with locally advanced unresectable head and neck carcinoma, with acceptable toxicity and survival data.

Keywords: Hyperfractionated; Accelerated; Radiotherapy; Squamous-cell; Head and neck

One of the main objectives in patients with locally advanced unresectable head and neck carcinoma (HNC) is to improve local control of the disease. At the present time, treatment fails at the locoregional level in 40-60% of cases, while systemic relapse occurs in 20-30% of cases [1,2].

In recent years, we have seen significant advances which have led to improvements in the local control of the disease and the survival of these patients. Several randomised clinical trials have shown an increase in local control using accelerated or hyperfractionated radiotherapy [3-6], while others have demonstrated an increase in survival when concomitant radio-chemotherapy schedules are administered [7-13].

According to two previous meta-analyses [14,15], if concomitant chemotherapy is added to locoregional treatment of advanced head and neck tumours, overall survival could be increased by 8-11% at 5 years. Another meta-analysis showed that altered radiotherapy with new fractionating schedules, achieved an increase of 7% in local control and 3% in survival at 5 years [16].

However, the concomitant use of chemotherapy and radiotherapy could increase acute severe toxicity which reduces the general performance of the patient. This fact could result in a temporary halt of the radiotherapy while the patient recovers from the toxic effects occurred at the mucosa. For this reason, some treatment schedules have programmed breaks to avoid toxicity, but these breaks could decrease the efficacy of the treatment by enabling tumour repopulation [9,17].

Tumour repopulation (which may occur during the third week of conventional radiotherapy), total treatment duration [9,18] as well as tumour duplication time during radiotherapy are key factors which determine a poor local control.

Taking into account these considerations, the use of a radiotherapy schedule such as concomitant boost, implies
a decrease in the total treatment duration by applying a second daily session to the macroscopic tumour, which should begin just when tumour repopulation is supposed to occur.

Cisplatin (CDDP) is a cytotoxic drug which is very active in squamous cell head and neck cancer (SCHNC), and also has a radiosensitive action [19]. It has been used simultaneously with radiotherapy in the treatment of digestive, upper respiratory and genitourinary tumours. Its toxicity profile, which is different to that of the radiotherapy, facilitates its combination.

When radiotherapy and full doses of CDDP are administered, the compliance could vary between 60 and 86% [20–22]. However, the weekly administration of low doses of CDDP allows to adjust the intensity of the treatment to the tolerance of the patient and therefore possibly to avoid interruptions of radiotherapy. A dose of 40 mg/m² per week was used by the Gynaecology Oncology Group (GOG) to test a radio-chemotherapy treatment of cervix cancer [23,24]. Another study demonstrated the efficacy of low daily doses of CDDP, together with radiotherapy in the treatment of advanced SCCHN [25].

The aim of this phase II study was to evaluate the efficacy and toxicity of combining concomitant boost accelerated radiation regimen (AFX-C) with concurrent weekly CDDP in the treatment of patients with locally advanced unresectable SCHNC.

**Patients and methods**

**Patient selection**

From February 2000 to September 2002, patients with positive histology of SCHNC, excluding nasopharynx, were evaluated by a multi-disciplinary team of surgeons, pathologists, medical and radiation oncologists. Patients with locally advanced (stage III or IV) squamous cell carcinoma, aged ≥18 years, staged as unresectable tumours by head and neck surgeons, measurable or evaluable disease, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 and with normal renal, hepatic and bone marrow function were enrolled. Baseline laboratory study requirements included neutrophils greater than 1.5×10⁹/L and platelets greater than 100×10⁹/L.

Patients were excluded from the study if they were pregnant or lactating, history of malignancy other than skin cancer or in situ cervical carcinoma, previous neuropathy or other severe concomitant disease.

This phase II study was conducted in compliance with the declaration of Helsinki and good clinical practice guidelines. All patients provided their written informed consent.

Prestudy evaluations included a complete clinical history and physical examination. The local tumour extension was evaluated with a complete fibre-endoscopy and CT or NMR scan of the head and neck. The metastatic screening included an X-ray of the thorax. Other tests were only done if there was clinical or analytical doubt of metastasis. Before treatment, routine haematology, blood electrolytes, liver enzymes and renal function tests (blood creatinine and creatinine clearance) were carried out. Dental treatment, including tooth extractions and hygiene care, was recommended before starting radiotherapy.

**Study treatment**

Patients were treated with three-dimensional conformal radiotherapy with fixation by a thermoplastic mask. The accelerated fractionation with concomitant boost scheme used in the RTOG 9003 study [5] was followed. The primary tumour, macroscopically affected lymph nodes and bilateral cervical plus supraclavicular lymph chains were treated with five fractions of 1.8 Gy per week during 6 weeks up to a total of 54 Gy. Spinal cord exclusion was carried out at 45 Gy and the posterior cervical lymph chains were boosted up to 50.4 Gy. When the forth week of treatment started, a second daily dose of 1.5 Gy per fraction (with at least a 6-h interval) was administered to the boost volume, including the primary tumour and involved cervical nodes for a total of 18 Gy in 12 treatment days. Six MV photons and electrons at different energies from a linear accelerator were used.

Chemotherapy was started the same day as radiotherapy, and consisted of the intravenous administration of 40 mg/m² weekly of CDDP for the first 4 weeks. Patients received antiemetic therapy (granisetron and dexamethasone), hydration and osmolar diuresis medication. The CDDP treatment was delayed or halted if the neutrophil counts were lower than 1000, the platelets less than 75,000 or the patient had grade III mucositis.

Patients were evaluated regularly during treatment and instructed in hygiene and preventive measures such as the regular use of mouthwash. Fungal infections were treated as soon as they appeared with nystatin or fluconazole. A nasogastric tube was used when swallowing liquids was difficult. Haemoglobin levels below 12 g/dl were corrected by the administration of erythropoietin. Analgesia with opiates (transdermal fentanyl) was used in all cases of mucositis > grade II.

**Patient follow-up**

At the end of treatment, patients had a physical examination and a fibre endoscopy 1 and 3 months after last radiotherapy, and a head and neck CT or NMR scan between the second and the third month from the end of treatment. During the first year, physical examination and fibre endoscopy were performed every 2 months, and laboratory analysis and cervical CT or NMR scan every 4 months. From that point, patients were regularly evaluated to detect any changes in their disease.

**Statistical analysis**

All patients were included in the efficacy and toxicity analysis. Primary objective of the study was response rate (RR). Secondary objectives included time to progression (TTTP), overall survival (OS), locoregional control and toxicity profile.

Criteria described in the Response Evaluation Criteria in Solid Tumours Group [26] was followed to evaluate response. No routine pathological confirmations of clinical responses were carried out. The WHO scale [27] was used to evaluate the toxicity coming from the use of CDDP, and RTOG [28] for that coming from radiotherapy.
OS, TTP and locoregional control were estimated for all patients by the Kaplan-Meier method, with the time to event beginning on the start of treatment.

Sample size was calculated following the Simon two-stage design method [29]. With a non-efficacy of \( P_0 = 40\% \), and an efficacy value of \( P_1 = 60\% \), both on complete responses, and with \( \alpha = 0.05 \) and \( \beta = 0.1 \), a total of 70 evaluable patients will be required. Taking into account a maximum of 10% of potential toxic deaths, and a 15% of non-evaluable, final recruitment should be 90 patients.

Results

From February 2000 to September 2002, 94 patients were included (male/female, 86/8). Main baseline characteristics are shown in Table 1. The median age was 58 years. At primary diagnosis, the majority of patients presented oropharynx tumours (44%) and stage IV disease (89%). Only one patient had surgery due to the disease before protocol. Another three patients went to surgery after study treatment. No other previous treatments were administered.

Treatment administration

Most patients (95%) received 4 weekly cycles of CDDP and reached the expected 72 Gy of radiotherapy planned per protocol.

Fourteen patients had interruptions during radiotherapy, six of them due to toxicity (four mucosal and two haematological toxicity), five patients died (four toxic deaths and one due to lung progression), two patients requested to leave the study protocol and another patient progressed at a local level. The length of treatment discontinuation ranged between 3 and 10 days, with a median of 6 days.

In one patient, the fractionation of radiotherapy was changed to a conventional one due to an early and severe acute toxicity.

Toxicity

The most common acute toxicity was mucositis, which reached grade III in 85% of patients. Grade III pharyngeal-oesophageal and dermatitis toxicity was observed in 50 and 17% of patients, respectively. Other severe toxicities were grade III anemia (3%), grade III neutropenia (5%) and grade III thrombocytopenia (3%).

Late toxicities observed following RTOG criteria were in bone (grade IV, 2%), larynx (grade III, 4%), oesophagus (grade III, 2%), and skin and/or subcutaneous tissue (grade III, 2%).

Four patients (4%) died during protocol, three of them due to treatment-induced sepsis pneumonia and the last one due to an acute renal failure. Also, it should be mentioned that two patients had mandibular radionecrosis, two gastrostomies were performed due to oesophageal stenosis, and four patients required tracheotomies due to laryngeal oedema. Additionally, the nasogastric tube had to be kept in place for more than 9 months after ending the treatment in three patients and two patients had severe neck fibrosis.

Efficacy

An overall response rate of 88% was achieved with 62 (66%) and 21 (22%) complete and partial responses, respectively. Five patients did not respond to treatment and six patients could not be evaluated for efficacy due to an early withdrawal, but they were included in the efficacy analysis.

Remote dissemination was observed in 12 patients (13%), being the lung the most common metastatic site (n=9), followed by bone (n=3). Six patients developed secondary tumours (three of the lung, one oesophagus, one oral cavity and one in prostate).

With a median follow-up of 41 months (range, 27-58 months) for surviving patients, median overall survival was 27 months (95% CI: 9-45). The estimated overall survival achieved at 4 years was 41% (Fig. 1).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline patient characteristics (n = 94)</th>
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<tbody>
<tr>
<td>Characteristics</td>
<td>Patients</td>
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<tr>
<td>Gender</td>
<td></td>
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<tr>
<td>Male</td>
<td>86</td>
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<tr>
<td>Female</td>
<td>8</td>
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<tr>
<td>Median age, years (range)</td>
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<td>ECOG performance status</td>
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<td>0</td>
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<td>1</td>
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<td>Initial UICC stage</td>
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<tr>
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<tr>
<td>Larynx</td>
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<tr>
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<tr>
<td>T and N stage (UICC 1997)</td>
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<tr>
<td>T1:T2:T3:T4</td>
<td>2:9:38:45</td>
</tr>
<tr>
<td>N0:N1:N2:N3</td>
<td>16:19:44:15</td>
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Fig. 1. Overall survival and time to progression (n=94).
The median time to progression was 25 months (95% CI: 10-40) with an estimated survival free of progression of 40% at 4 years (Fig. 1). Regarding locoregional control, an estimated local control of 59% at 4 years was observed.

At the time of the analysis, 46 patients were still alive (35 without disease and 11 alive with disease), 35 died of the disease, four died due to toxicity and nine patients died for other reasons without disease. Of these nine patients, three patients died due to a second primary tumour (two of the lung and one of the oesophagus), two due to a chronic obstructive pulmonary disease, two due to cardiovascular diseases, and the last two due to other causes.

Discussion
The most significant toxicity in our study was grade III mucositis in oral cavity and pharynx-oesophagus (85 and 50%, respectively). This incidence is about the same as other reported studies with similar schedules [2,20,30,31] and those where hyperfractionation was used [12]. The haematological toxicity of the chemotherapy was very low, with an excellent tolerance by the patient.

Most of patients (95%) completed the study treatment. This fact can be explained because the maximum mucosal toxicity was observed when the irradiation was already finished (between the fifth and the sixth week). The high rate of compliance was similar to that reported by Staar et al. [32] and higher than in other similarly designed treatments [2,20,21,33] and RTOG [22] radio-chemotherapy protocols.

On the other hand, it has to be pointed out that radiotherapy was interrupted due to toxicity in six patients, with a maximum of 10 days (median, 6 days). This data is similar to that obtained by Allal AS et al. [20] and better than other radio-chemotherapy studies, whether they were conventional or accelerated fractionation [34,35].

It is obvious that good compliance of treatment does not mean anything if the treatment is not efficient. In our study, the overall survival at 4 years was within the range (37-48%) of other reported radio-chemotherapy schedules, including altered fractionation and more aggressive chemotherapy treatments [8,9,12,25,30,32,36]. It should be noted that in many of these studies patients with resectable disease were included, and that could explain the better results there were obtained in some cases. When only patients with unresectable disease were included, the results reported were similar to or lower than those obtained in our study [9,30].

Another point to take into account is that in similar studies, more than 60% of the patients were suffering from oropharyngeal squamous carcinoma [2,21,32], which is a location with a better prognosis. In our study, less than a half of patients (43%) had oropharyngeal tumours.

In conclusion, treatment with AFX-C along with weekly CDDP in patients with locally advanced unresectable SCHNC is feasible, with an acceptable survival and toxicity profile and with a high rate of compliance. The optimal integration of chemotherapy with altered fractionation radiotherapy is not yet defined, and the results obtained in the present study support to carry out a randomised study which compares this type of schedule with more aggressive treatments. Future studies should incorporate quality of life evaluations according to standard questionnaires [37].

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