Concomitant adjuvant chemoradiotherapy with weekly low-dose cisplatin for high-risk squamous cell carcinoma of the head and neck: a phase II prospecitve trial

Concomitant Adjuvant Chemoradiotherapy with Weekly Low-dose Cisplatin for High-risk Squamous Cell Carcinoma of the Head and Neck: a Phase II Prospective Trial

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ABSTRACT

AIMS

Several randomised trials have tested adjuvant regimens using concomitant high-dose cisplatin and radiotherapy to improve outcome in high-risk locally advanced squamous cell head and neck cancer (HNSCC), showing a substantial increase in locoregional control and disease-free survival, despite a higher and eventually detrimental toxicity profile. The aim of the present phase II single-stage prospective study was to investigate whether a weekly cisplatin-based chemoradiotherapy regimen might be able to improve patients' compliance compared with standard-dose cisplatin with similar outcome results.

MATERIALS AND METHODS

Between January 2004 and November 2008, 54 patients with high-risk locally advanced HNSCC were enrolled on to this phase II trial. Patient characteristics were: median age 59.7 years, Eastern Cooperative Oncology Group performance status 1 in 72% of patients and stage IV disease in 82%, extracapsular nodal spread in 67% and positive/close surgical margins in 37%. Patients received cisplatin (30 mg/m^2) once a week for 7–8 weeks concurrent with external beam radiotherapy delivered with a median dose of 66.6 Gy (1.8 Gy each day; five fractions/week) on the primary site and 50 Gy (2 Gy each day) for the lower neck.

RESULTS

Major acute toxicity of the combined treatment, defined as grade 3–4 mucositis, was observed in 35.2% of patients. No fatal complications occurred, with 81.5% of patients completing the planned regimen. Late reactions were mild (total 16% with a grade 3 dysphagia rate of 12%). The locoregional control rate was 82%; 5 year overall and disease-free survival were 63 and 62%, respectively.

CONCLUSIONS

Concomitant adjuvant chemoradiotherapy with weekly cisplatin seems to be a feasible and well-tolerated therapeutic approach in 'unfit' patients. Clinical results seem to be at least comparable with those previously reported. However, to draw any definitive conclusion, large confirmatory phase III randomised trials are demanded.

INTRODUCTION

Adjuvant external beam radiation therapy (EBRT) after surgical excision is considered the standard therapeutic option towards resectable locally advanced squamous cell carcinoma of the head and neck region (HNSCC) [1] and [2]. Nonetheless, locoregional failure and distant metastatic spread often occur in this subset of patients, particularly when high-risk features are present, leading to 5 year survival rates not exceeding 40% [3]. Several prognostic factors have been recognised to affect outcome, such as nodal extracapsular extension (ECE), oral cavity localisation of the primary tumour, the dimension and number of involved lymph nodes, close to positive resection margins, perineural invasion, vascular embolism and prolonged radiation overall treatment time [4].

In the attempt to improve clinical results, several randomised trials have investigated the association of chemotherapy concomitant to radiation within a postoperative setting in high-risk locally advanced head and neck cancer [3], [5] and [6]. In recent years, two randomised trials reached satisfactory evidence of improved outcome with adjuvant cisplatin-based chemotherapy concurrent with EBRT, namely the Radiation Therapy Oncology Group (RTOG) trial 9501 and the European Organization for Research and Treatment of Cancer (EORTC) trial 22931 [7] and [8]. Apart from a substantial difference concerning inclusion criteria, both studies used the same chemotherapy regimen consisting of cisplatin 100 mg/m^2 of body surface area on days 1, 22 and 43 concomitant with EBRT up to a conventionally fractionated total dose of 60–66 Gy delivered over a 6–6.5 weeks. These two trials achieved a substantial improvement in terms of locoregional control and disease-free survival (DFS), but registered a high percentage of acute adverse effects (respectively, 77 and 41% of grade 3 or higher acute toxicity) in the combined modality arm, which might be detrimental, causing eventual treatment delay and even occurrence of toxic deaths [8]. In order to explore whether a weekly low-dose cisplatin-based chemoradiotherapy concurrent approach might be able to improve patients' compliance, reducing the treatment-related toxicity profile with comparable outcome results than the high-dose regimen, we conducted this prospective phase II trial in high-risk locally advanced HNSCC. The schedule of weekly cisplatin in a dose of 30 mg/m^2 of body surface area for 8 weeks was chosen, representing a slight reduction in planned dose intensity with respect to a high-dose 3 week cisplatin regimen; a treatment delivery improvement without detrimental effect was expected.

MATERIALS AND METHODS

Eligibility Criteria

Between January 2004 and November 2008, 54 consecutive patients affected with high-risk locally advanced HNSCC were enrolled on to this prospective phase II single-stage trial. The Clinical Research and Ethical Review Board of our institutional hospital approved the present study. Written informed consent was obtained from all patients. Eligibility criteria consisted of age $\geq$ 18 years, Eastern Cooperative Oncology Group performance status $\leq$ 1, no prior history of chemotherapy or radiotherapy, medical fitness to receive weekly low-dose cisplatin, stage III or IV histologically

proven HNSCC, previous macroscopically radical surgery and high-risk features at pathological examination. Patients with distant metastasis at the time of diagnosis were excluded. Major histological features deemed of high-risk were the presence of extracapsular nodal spread and positive to close (<5 mm) resection margins; minor risk factors considered were the presence of foci of poorly differentiated cells within the pathological specimen (grade 3 according to the World Health Organization classification), multiple positive cervical lymph nodes, perineural invasion, vascular invasion and finally primary lesion size.

Clinical Assessment and Follow-up

Pre-treatment evaluation consisted of an accurate medical history and physical examination, clinical measurement of detectable masses, plan chest X-rays or chest computed tomography and magnetic resonance imaging or computed tomography of the head and neck region; moreover, complete blood cell counts, liver function tests, blood urea nitrogen, creatinine, albumin, calculated creatinine clearance and a dental examination were obtained. Surgical approaches varied according to the site of presentation of the primary lesion and included an 'en block' neck dissection when needed, specifically radical or functional, bilateral or monolateral strictly depending on the clinical assessment of cervical node status at diagnosis. Ninety days after the completion of the whole combined modality treatment approach, patients were re-evaluated by the head and neck board of our institutional hospital with a fibroscope otorhinolaryngology examination, computed tomography or magnetic resonance imaging scan of the head and neck in order to assess local control. Subsequently, patients were regularly followed up with an otorhinolaryngology examination every 3 months and radiological imaging every 6 months for the first 2 years and thereafter with a clinical examination and radiological assessment twice a year.

Surgery

Surgical approaches were very heterogeneous: eight patients (15%) underwent a total laryngectomy, seven (13%) a partial laryngectomy, six (11%) a partial hemiglossectomy, five (9.5%) a wide resection, five (9.5%) a partial pharyngectomy, four (7%) a hemiglossectomy, four (7%) a pharyngo-laryngectomy, two (4%) a partial glossectomy and two (4%) a pharyngectomy. Surgical procedures different from those listed above involved six patients and in five cases (9%) the combined surgical modality was accomplished.

Fifty patients underwent a surgical strategy towards the neck region: seven (14%) bilateral radical neck dissections, 17 (34%) bilateral functional neck dissections, 11 (22%) omolateral radical neck dissections (one undergoing controlateral functional neck dissection) and 15 (30%) omolateral functional neck dissections were carried out.

Radiotherapy

Adjuvant EBRT was delivered to all patients using a megavoltage source of 5 MV, starting no later than 8 weeks after surgical excision. For set-up purposes, patients were mainly immobilised within a thermoplastic mask; in some cases a shoulder fixation device was used. A three-dimensional conformal treatment planning approach was used. Nevertheless some patients were treated with two block-shaped lateral parallel-opposed fields encompassing the primary site and upper neck for the first part of the treatment: a supplemental boost dose was delivered to high-risk regions using two or more oblique fields. A single anterior field arrangement (with a shield for the larynx when necessary) was used to treat the lower neck and supraclavicular areas; two shaped direct electron beam fields were used to boost spinal nodes when necessary. The planned total dose was delivered over 7.5 weeks, using a conventionally fractionated schedule in all patients, with a daily 1.8 Gy

fraction. For the primary tumour site, the median delivered dose was 66.6 Gy (range 54–68.40 Gy), whereas the average dose was 65 Gy; conversely, for the lower neck region, the average dose was 50 Gy (2 Gy/day, range 44–56 Gy) and for spinal nodes a boost of 10 Gy (2 Gy/day, range 6–16 Gy).
For the primary site we chose a daily dose of 1.8 Gy (instead of 2 Gy as in RTOG and EORTC trials), based on a published French study [9] and [10] to further reduce toxicity. Moreover, when the study was designed, 1.8 Gy/day was our standard fractionation; later we decided to maintain this schedule in order to offer a homogeneous treatment in this series.
Finally, seven patients (13%) were given amiphostine in order to reduce salivary gland injury.

Chemotherapy

Patients were scheduled to receive cisplatin (30 mg/m^2) once a week for 7–8 weeks, given concurrently with EBRT on an outpatient basis. Cisplatin was infused over 1 h, before radiotherapy, diluted in normal saline 500 ml. Supportive pre- and post-hydration with 500 ml normal saline solution and mannitol 18% 250 ml in 30 min intravenously were also given. Prophylactic anti-emetic therapy consisted of granisetron 3 mg and dexamethasone 8 mg intravenously before chemotherapy.
Chemotherapy dose modification was based on blood cell counts obtained on the treatment day. The planned total dose was given if the white cell count > 3000/μl with absolute neutrophyl count > 1500/μl and platelets >100 000/μl. Doses were not modified based on haematocrit or haemoglobin. A 1 week chemotherapy delay was allowed when neutropenia or thrombocytopenia developed during concomitant chemoradiation. Cisplatin was not given when serum creatinine was >1.6 mg/dl and calculated creatinine clearance was <45 ml/min; an audiometric examination was carried out when clinical evidence of ototoxicity appeared. Chemotherapy was discontinued if grade 2 neuro- or ototoxicity occurred, with EBRT alone continuing; a therapeutic switch to carboplatin (AUC 2, weekly) was considered in the case of grade 2 nephrotoxicity. The treatment cycle was to continue without dose reduction despite mucositis or dermatitis. Granulocyte-stimulating factors were given only in case of grade 4 neutropenia in patients with a high-risk of infection or febrile neutropenia; erythropoietin with iron support was permitted when anaemia (haemoglobin<10 g/dl) developed and was discontinued when haemoglobin recovered to >12 g/dl.

Toxicity Evaluation

All patients underwent baseline and weekly assessments with a physical examination, full blood tests, nutrition evaluation and weight modification recording. Toxicity events were scored on a weekly basis according to National Cancer Institute Common Toxicity Criteria version 2.0 [11]. Nutritional support started at the beginning of the treatment with education and advice; enteral feeding was instituted when body weight decreased by >10% compared with baseline values. Late radiation toxicity was scored using the RTOG/EORTC Late Radiation Morbidity Scoring Scheme [12].

Statistical Analysis

The primary end points of our study were toxicity of the combined treatment, defined as grade 3–4 mucositis, and compliance with the proposed schedule; secondary end points were locoregional control, DFS and overall survival. Locoregional control was defined as the absence of recurrence above the clavicles. DSF was defined as absence of recurrence at any site or death. All deaths were considered an event in overall survival. Univariate analysis, based on survival curves, was generated using the Kaplan–Meier method, and a Log-rank test was used to test for differences. A multivariate Cox regression analysis was applied to compute the hazard ratio (with 95% confidence

interval), which correlated expression levels of the variables with overall survival, locoregional control and DFS. The time to locoregional failure, DFS and overall survival was measured from the date of radiotherapy end to the date of subsequent event. In multivariate analysis, Cox proportional hazards regression models were applied to compare the variables with traditional factors. The model for overall survival, DFS and locoregional control included age, gender, tumour characteristics (size, grade, vascular invasion, perineural extension), lymph node status (number, size and extracapsular invasion), surgical margins. Computations were carried out with the STATA statistical package, release 10.0 (STATA Corp, College Station, TX, USA) [13]. All *P* values were two-sided, and $P < 0.05$ was considered statistically significant.

Sample Size Determination

A single-stage design, according to the method of Fleming [14], was selected, based on the following assumptions: (1) we defined the toxicity of the combined treatment as severe (grade 3–4) mucositis; (2) the experimental treatment under study in this trial would be considered with inacceptable toxicity, if the non-toxicity was lower than 50%; (3) or acceptable if the treatment non-toxicity rate exceeded 70%; (4) the α error (one-sided type I error) was set at 2.5%; (5) the β error was 20% (type II error; power 80%).
On the basis of a sample size of 54 patients, non-toxicity in more than 33 patients (62%) fulfils the criteria for non-toxicity defined above.

RESULTS

During the observation period, 54 consecutive patients were enrolled (49 primary lesions and five recurrences). The baseline characteristics of the study cohort are outlined in Table 1. Most patients were men (80%) with a median age of almost 60 years (range 24–70 years). Primary lesions were mainly located within the oral cavity (33%), oropharynx (33%) and larynx (26%), whereas only 7% of the patients were affected with hypopharynx cancer. Interestingly, 40 of 54 patients (80%) had stage IV disease at diagnosis, with another eight patients having stage III HNSCC (16%). The primary and nodal staging are described in Table 2. Concerning high-risk features, 36 patients (67%) presented with ECE and 20 patients had positive to close (<5 mm) surgical excision margins; adjunctively, 25 patients (47%) had poorly differentiated tumours (World Health Organization grade 3), eight patients (15%) had multiple involved nodes, nine (17%) had perineural invasion, seven (13%) had lymphovascular space invasion and finally three patients (6%) had a primary lesion size >4 cm. Two risk factors were associated in 21 patients (38%), whereas three factors were shared in seven cases (12%).

Table 1.

Characteristics of the study cohort

	Number	**%**
Gender		
Male	43	80
Female	11	20
Age		
Median	59.7	
Range	24–70	

	Number	%
Performance status (ECOG)		
0	26	48
1	28	52
Site		
Oropharynx	18	33
Oralcavity	18	33
Larynx	14	26
Hypopharynx	4	8
Stage		
I	1	2
III	8	16
IV	40	82
Grading		
1	5	9
2	23	43
3	26	48

ECOG, Eastern Cooperative Oncology Group.

Table 2.

Primary and nodal staging

	N0	N1	N2	Total
T1	1	2	11	14
T2	1	1	9	11
T3	1	4	11	16
T4	2	5	6	13
Total	5	12	37	54

Radiotherapy and chemotherapy characteristics are presented in Table 3.

Table 3.

Radiotherapy and chemotherapyschedules

Radiotherapy
Three-dimensionalconformalradiotherapy planning

X-rays 5 MV
1.8 Gy/day (5 days/week)
Median dose 66.60 Gy (average 65 Gy; range 54–68.40 Gy)
Lower neck region average dose 50 Gy/25 fractions (range 44–56 Gy)
Median overall treatment time 54 days (mean 53 days)
Median interruption gap 3 days (range 1–12 days)
Full course external beam radiotherapy accomplished 93% (50/54)

Chemotherapy
Cisplatin (30 mg/m^2 of body surface area)
Once a week for 7–8 weeks
Reduction in chemotherapy dose intensity 10/54 (18.5%)

Whole combined treatment completed 81.5% (44/54)

As far as radiation is concerned, the median overall treatment time was 54 days (mean: 53; range 40–69 days), with a median interruption gap of 3 days (range 1–12 days). No delay occurred in 15 patients (28%); 16 (29%) patients had a radiotherapy gap longer than 3 days. The whole combined treatment was completed in 44 of 54 patients (81.5%); of the remaining 10 cases, six (11%) experienced a reduction in chemotherapy dose intensity, with a delay of 1 or 2 weeks due to haematological toxicity (five cases) and infection (one case). Only four patients (7%) did not receive full-course EBRT and the radiotherapy interruption was due to severe mucositis; in these four patients chemotherapy was also not completed.
After a median follow-up time of 23 months (range 8–64 months), 5 year overall survival and DFS Kaplan–Meier estimates were, respectively, 63% (confidence interval 38–80.7%) and 62% (confidence interval 37.2–78%) (Fig. 1 and Fig. 2). The locoregional control rate was 82% (confidence interval 61.6–92.3%) (Figure 3). Nine patients (18%), all with stage IV disease at diagnosis, developed metastatic spread, with lung (eight cases) and liver and bone (one case) involvement. Simultaneous distant and locoregional failure was observed in only one case. Five patients developed a second malignancy during the observational time (four lung and one oesophageal cancers). On univariate analysis, a trend towards a statistically significant difference was observed for locoregional control only for ECE (100% vs 75% at 48 months; $P = 0.07$), whereas Eastern Cooperative Oncology Group performance status, T stage, Union InternationaleContre le Cancer stage, positive surgical margins, three or more lymph nodes involved, vascular invasion, perineural invasion did not affect this clinical end point. A trend towards a statistically significant difference in terms of DFS could be outlined for three or more involved nodes, whereas ECE did statistically relate to DFS. On multivariate analysis, ECE was confirmed as an independent prognostic factor for DFS ($P = 0.045$; hazard ratio 7.98; 95% confidence interval 1.04–60.8); no predictive factors could be found for both overall survival or locoregional control on multivariate analysis.

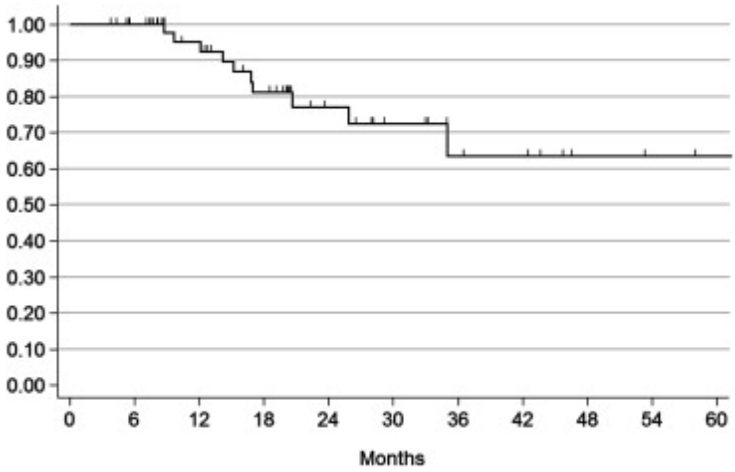

Fig. 1.

Overall survival.

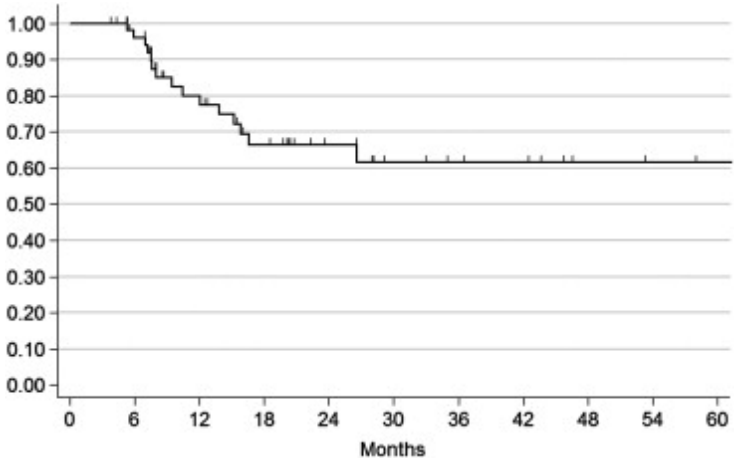

Fig. 2.

Disease-free survival.

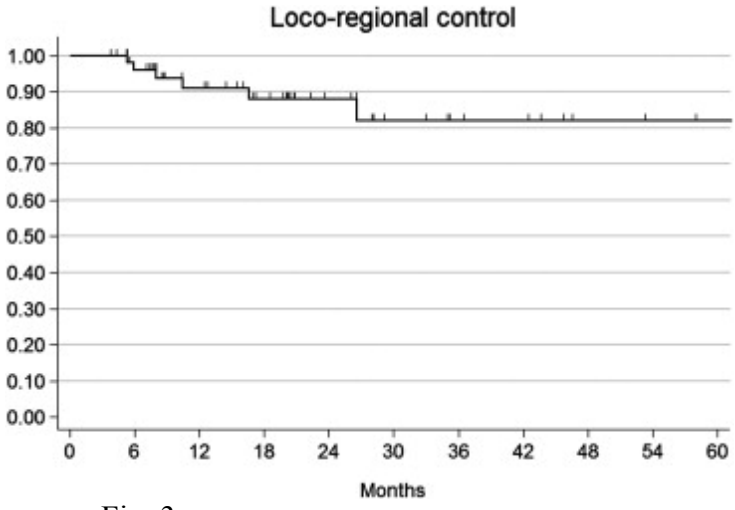

Fig. 3.

Local control.

Toxicity

Acute and late toxicities are outlined in Table 4.

Table 4.

Toxicity

Acute toxicity	**Number**	**%**
Weightloss>10%	1	1
Haematological neutropenia (grade 3–4)	5	9
Nothaematological (grade 3–4)		
Mucositis	19	35.2
skinreactions	7	13

Late toxicity	**Grade 1–2 (%)**	**Grade 3–4 (%)**
Xerostomia	21 (40)	1 (2)
Shouldersyndrome	_	11 (21)
Dysphagia	12 (23)	6 (12)
Necklymphaticimpairment	11 (21)	_
Neckfibrosis	9 (17)	1 (2)
Trismus	2 (4)	_

Our analysis showed a severe mucositis rate of 35.2% (confidence interval 22.5–49.2%). Thus, 65% of patients did not experience severe toxicity, which fulfilled the minimum criteria of 62% required for this treatment to achieve the predefined statistical requirements for success. Severe neutropenia developed in 10% of patients, whereas 15% had grade 3–4 systemic toxicity (nausea 7%, vomiting 4%, diarrhoea 2%, constipation 2%). Our analysis showed a severe mucositis rate of 35.2%. We also observed grade 3 cutaneous reactions in 13% of patients, which could have been related more to radiotherapy than to the combined schedule. A 5–10% weight loss was observed in 10 cases (19%), whereas only one patient (1%) had >10%. Seven patients needed a feeding tube during treatment (13%); a percutaneous endoscopic gastrostomy was placed in 14 cases (26%; in seven patients it was already present at the beginning of EBRT); total parenteral nutrition was carried out in six patients (11%); these three nutritional modalities often took place in the same patients at different treatment times. However, no fatal complications occurred and 81.5% of patients completed the planned combined modality approach.

The total late toxicity rate was 16%, with a grade 3–4 dysphagia rate of 12%. In 21%, shoulder syndrome developed as a surgical complication. We had a very low rate of xerostomia (grade 3–4: 2%), despite 66% of patients having oral cavity or oropharynx primaries, as we often used a three-dimensional conformal radiotherapy technique with oblique fields excluding the controlateral parotid gland and part of the minor salivary glands. Moreover, we carried out only a subjective evaluation of xerostomia without an objective control of salivary flow and our follow-up period was not long (median 19 months); we could therefore have under-evaluated this toxicity. Finally, we underline that seven patients (13%) were given amiphostine in order to reduce salivary gland injury.

DISCUSSION

Various therapeutic strategies have been proposed in an attempt to improve outcome results for high-risk resectable locally advanced HNSCC [15]. Because surgery alone might achieve cure in only about one-third of patients, the addition of adjuvant radiation therapy may lead to a detectable

locoregional failure risk reduction (above the clavicles), with an extrapolated absolute survival benefit of 10% [2]. In this way, locoregional control, distant metastasis and 5 year survival rates were 30, 25 and 40%, respectively [3]. The prognosis of stage III and IV HNSCC remained dismal; in fact, in a meta-analysis of 10 000 advanced HNSCC patients, Pignon*et al.*[16] underlined that the 5 year overall survival rate with exclusive adjuvant radiation therapy did not exceed 32%. As a matter of fact, a substantial part of this ineffectiveness might be due to a high probability of developing systemic disease (either directly in the shape of a previously present microscopic spread or indirectly 'following' an eventual prior locoregional failure). Hence, the role of the combination of chemotherapy and radiation in an adjuvant setting began to be explored. In recent years two large-scale multicentre prospective randomised (EORTC 22931 and RTOG 9501) trials yielded a new standard of care in the adjuvant setting of high-risk locally advanced HNSCC, with the association of EBRT and concurrent 100 mg/m^2 cisplatin given on days 1, 22 and 43 [7] and [8]. Both trials showed a statistically significant advantage in terms of locoregional control and DFS if compared with exclusive adjuvant radiation; the European trial also showed a significant improvement in overall survival. The alternative perspective on this issue is that the two studies also reported a high and eventually detrimental increase in the rate of severe acute effects; four toxic deaths (2%) occurred in the RTOG study [7]. The use of this regimen as an adjuvant approach found evidence in a meta-analytic context reported by Winquist*et al*. [17] in 2007. Anyway, further investigations explored the use of alternative chemotherapy regimens able to minimise treatment-related adverse effects.

One strategy is the administration of reduced dose cisplatin (75 mg/m^2) on days 1, 22 and 43, as reported by Franchin*et al.*[18]. The investigators obtained robust results in terms of locoregional control, DFS and overall survival, simultaneously being able to diminish haematological and upper gastrointestinal toxicity; unfortunately, severe mucositis frequently occurred (65%), resulting in a general low compliance towards chemotherapy (only half of the patients received all the three planned cisplatin cycles).

Another tested option was the use of carboplatin instead of cisplatin. Two randomised trials explored this issue, using either 100 or 50 mg/m^2 concomitant with EBRT. Both studies failed to show any advantage in terms of locoregional control, DFS and overall survival if compared with radiation alone. However, recorded toxicities were generally mild [19] and [20]. In this sense, another confirmatory report is the one by Airoldi*et al.*[21], who reported a low toxicity profile with carboplatin (30 mg/m^2 on days 1–5 of weeks 1, 3 and 5) concurrent with EBRT in an elderly cohort; up to 80% of the patients received all the three planned chemotherapy cycles. Another frequently explored option is the weekly administration of cisplatin concomitant with radiation (in which all cycles are given with EBRT). The French study published by Bachaud*et al.* in 1996 [10] tested 50 mg/m^2 cisplatin given on a weekly basis (7–9 weeks) concurrent with EBRT (within a randomisation with radiation only) achieving 5 year overall survival and 5 year local recurrence-free survival rates of 36 and 70%, respectively. Acute toxicity was not reported. Severe late effects (severe fibrosis, hypopharyngeal stenosis, mandibular radionecrosis) occurred in 22% of the patients belonging to the combined modality treatment arm [10] and [22].

In 2004, Porcedd*et al.*[23] reported the results of a study carried out on 47 high-risk HNSCC patients given adjuvant cisplatin (40 mg/m^2 for 6 weeks). The estimated 2 year overall survival and DFS rates were 71 and 64%, respectively. Acceptable toxicity was recorded (40% confluent mucositis; 17% severe haematological toxicity; 9% febrile neutropenia).

The chemotherapeutic regimen used in our study was chosen in order to minimise acute and late treatment-related side-effects; the slight reduction in dose intensity was believed not to, supposedly, affect effectiveness. In our experience, severe acute toxicity (grade 3–4) was relevant but manageable at the same time, with 35.2% mucositis and 10% neutropenia; these data are at least comparable (someone would say even lower) than those reported by Bachaud*et al*[10] and Porcedd*et al.*[23]. Moreover, if the comparison is made with the high-dose cisplatin toxicity profile, the difference looks more evident, as 77% severe acute effects were observed in the study

by Cooper *et al*. [7] and 41% severe acute mucositis, 16% severe acute granulocytopenia, 23% severe nausea and vomiting were recorded in the study by Bernier *et al*. [8]. In our sample size determination, we defined toxicity of the combined treatment schedule as severe (grade 3–4) mucositis. On the basis of a sample size of 54 patients, toxicity in less than 21 patients (38%) is representative of a successful treatment; we observed grade3–4 mucositis in 35.2% of patients, fulfilling that requirement for a successful treatment.

Another important issue is the 10% deviation from the planned total EBRT dose and the increase in treatment gaps (overall treatment time > 7 weeks) with the every 3 weeks high-dose regimen [7] and [8]. In our series, the median interruption gap was 3 days (range 1–12 days). Even when no delay occurred in 15 patients (28%), 23 (43%) patients had a radiotherapy gap not longer than 3 days. Moreover, we want to stress that major treatment gaps were found in those patients who were not able to complete radiotherapy treatment.

In our report, late effects were mild if compared with either the randomised trials or with the other weekly cisplatin studies. This comprehensive permissive toxicity profile allowed even generally 'unfit' patients to be treated. No apparent detrimental effect has been observed concerning local control or survival due to the reduction in cisplatin dose intensity. In fact, we observed an encouraging rate of locoregional control (82%) consistent with the data reported by the two large randomised trials (82% for the EORTC study; 81% for the RTOG study). In adjunct, estimated 5 year overall survival and DFS rates were 63 and 62%, respectively; a comparison with the EORTC (53 and 47%) and RTOG (50 and 40%) trials is not amenable as the sample sizes and follow-up differ strongly. The achievement of such a result seems remarkable to us, especially taking into account the cohort characteristics, which might be summarised as 'unfavourable' (stage IV disease in 82% of patients; ECE in 67% of patients; two or more risk factors associated in half of the cases). Moreover, in our series, the incidence of distant relapses was 17%; this finding overlaps with literature data, as the distant metastasis rate in both the EORTC and the RTOG trials was close to 20%. This is consistent with the fact that weekly low-dose cisplatin might be as effective (or in the reverse as ineffective) as 3 weeks of high-dose cisplatin in preventing HNSCC from systemic spread.

This study has all the restrictions of a single site phase II trial: only 54 patients were enrolled in over 4 years, heterogeneous tumours sites and, like most trials, a preponderance of oropharyngeal cancers and heterogeneous surgery. However, this experience contributes to the on-going debate around the use of concomitant chemotherapy in the adjuvant setting, particularly in 'unfit' patients.

Finally, our results suggest that a weekly infusion of 30 mg/m^2 cisplatin concurrent with radiation is a safe and tolerable treatment option in the postoperative setting for high-risk locally advanced HNSCC. A longer follow-up and more robust sample size is needed to strengthen our findings. Of course, controlled randomised trials are needed to confirm our preliminary results.

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