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Functional organ preservation in patients with locoregionally advanced head and neck squamous cell carcinoma treated by platinum-based multidrug induction chemotherapy and concurrent chemoradiotherapy

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Background: The objective of this study was to evaluate the feasibility, safety, and efficacy in terms of functional organ preservation of multidrug induction chemotherapy and concurrent chemoradiotherapy (IC–CCRT) protocol in patients with locoregionally advanced head and neck squamous cell carcinoma (LA-HNSCC).

Patients and methods: Patients with previously untreated, inoperable, histologically proven nonmetastatic stage III or IV HNSCC were eligible. Following one cycle of IC, two cycles of cisplatinum and 5-fluorouracil CCRT with conventional fractionated radiotherapy up to a dose of 66–70 Gy were administrated.

Results: Between January 2000 and July 2007, a total of 139 patients were candidates to receive IC–CCRT for LA-HNSCC. Overall, 83% of the patients completed the treatment. Three-year overall survival estimate was 68% [95% confidence interval (CI) 57% to 79%]. Three-year progression-free survival (PFS) estimate was 62% (95% CI 50% to 74%). Three-year functional PFS was 57% (95% CI 44% to 69%). There were no cases of treatment-related deaths. The most frequent severe acute toxicity was pharyngeal mucositis.

Conclusions: Cisplatinum-based multidrug IC–CCRT can result in functional organ preservation and curative treatment in most patients with LA-HNSCC. The toxicity profile and patients' compliance to treatment confirmed the safety and tolerability of this approach.

Key words: chemotherapy, combined modality therapy, functional outcome, head and neck cancer, radiotherapy

introduction

The focus of treatment of locoregionally advanced head and neck squamous cell carcinoma (LA-HNSCC) has recently shifted away from surgical approach toward nonsurgical organ preservation strategies. Nowadays, concurrent chemoradiotherapy (CCRT) has been increasingly integrated into first-line therapy of LA-HNSCC. The benefit of the addition of concurrent chemotherapy to radiotherapy (RT) in patients with HNSCC was recently confirmed in an updated meta-analysis by Pignon et al. [1] showing an absolute benefit in overall survival (OS) of 6.5% at 5 years.

In 1986, several of the co-authors of the present article were involved in a multicenter randomized trial comparing induction chemotherapy (IC) with cisplatinum and 5-fluorouracil (FU) followed by locoregional treatment with locoregional treatment alone in patients with LA-HNSCC [2, 3]. The results of that trial showed a significant improvement in locoregional control and OS by the addition of IC only among patients who were considered ineligible for resection. Moreover, a statistically significant reduction in distant failure was observed in both operable and inoperable cases.

Taking into account these results and the increasing evidence of a benefit in both survival and organ preservation rates with strategies employing simultaneous administration of cytotoxic chemotherapy and RT [4], we explored the efficacy, feasibility of functional organ preservation, and safety of multidrug IC–CCRT in patients with LA-HNSCC. A single induction cycle of chemotherapy was planned both to avoid delay in definitive treatment due to a long-course IC and to deliver cytotoxic chemotherapy during the 4 weeks needed to plan and start RT. In contrast, definitive chemoradiation treatment was limited to two cycles of concurrent chemotherapy in an attempt to reduce the toxic effects and treatment interruptions. Finally, patients

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received three cycles of full-dose cisplatinum (100 mg/m^2) and 5-FU (1000 mg/m^2 per day for 5 days) with potential systemic effect on distant micrometastases [5].

In this article, we report data on efficacy and safety of a regimen of multidrug IC–CCRT in prospective case series at a single institution.

patients and methods

criteria for inclusion

Patients who satisfied the following criteria were eligible: (i) previously untreated, histologically proven nonmetastatic stage III or IV squamous cell carcinoma of the oral cavity, oropharynx, larynx, or hypopharynx; (ii) age ≤80 years; (iii) Karnofsky performance status ≥60%; (iv) no history of head and neck cancer; (v) acceptable medical and laboratory status in order to tolerate chemotherapy; and (vi) informed consent. Tumors were considered inoperable after evaluation by a multidisciplinary team of physicians consisting of head and neck surgeons, radiation oncologists, and medical oncologists. Criteria for inoperability were as follows: (i) technical unresectability and (ii) physician decision based on low surgical curability including T3–4 stages, N2–3 stages, and patients for organ-sparing approach.

Patients with extensive invasion of bone and/or cartilage with organ destruction were not considered candidates for organ preservation.

The institutional review board approved the protocol of this study.

pretreatment evaluation

All patients were assessed by complete blood cell count with differential, serum electrolytes, liver function tests, electrocardiogram, fiberoptic endoscopy of the upper respiratory tract, tracheobronchoscopy, and esophagoscopy. Baseline imaging included chest X-ray, head and neck contrast-enhanced computed tomography, and/or magnetic resonance imaging. Computed tomography scans of the chest and abdomen, and in few cases, a positron emission tomography scan, were carried out as clinically indicated on the basis of abnormal screening test results or symptoms. Staging was carried out according to the International Union Against Cancer 1997 tumor–node–metastasis classification.

treatment

Induction cisplatinum (100 mg/m^2) was administered on day 1; 5-FU (1000 mg/m^2 per day) was administered as a 24-h continuous infusion for 5 days. Definitive RT started 3 weeks after IC, regardless of response to IC. Patients underwent computed tomography scan-based simulation for treatment planning. Three-dimensional conformal RT with multileaf collimator was carried out using 4- to 6-MV photons from a linear accelerator with conventional fractionation (2 Gy per fraction, once a day, five times a week). The dose was prescribed to the 95% isodose according to the International Commission on Radiation Units and Measurements recommendations. The planning target volume 1 (PTV1) included the gross tumor volume (including primary tumor and involved lymph nodes as detected on physical and radiographic examination) plus a 1.0- to 1.5-cm expansion. The PTV2 included PTV1 plus uninvolved lymph nodes at high risk of harboring microscopic metastatic disease. The prescribed dose to PTV2 was 50 Gy in N0 patients and 60 Gy in N+ patients, whereas the final dose to PTV1 was 66–70 Gy. The maximal dose to the spinal cord was 46 Gy. Bilateral electron fields (6–9 MeV) were used to treat lymph nodes in level IIb and V to boost the dose to 50 Gy in N0 patients and 60 Gy in N+ patients in the case where the dose distribution was not optimal. Concurrently with RT, patients were administered two cycles of chemotherapy using cisplatinum (100 mg/m^2) on day 1 and 5-FU (1000 mg/m^2 per day) as a continuous infusion for 5 days during the first and fourth week of the RT course. Adequate antiemetic regimen including a 5-HT$_3$ antagonist given before and after cisplatinum administration along with a program of forced diuresis was administrated at each cycle.

Patients received nutritional assessment before the beginning, during, and after the end of treatment. Toxicity was monitored on a weekly basis and graded according to the National Cancer Institute—Common Toxicity Criteria (NCI–CTC). During concurrent chemoradiation, locoregional toxicity was grade according to the Radiation Therapy Oncology Group (RTOG) toxicity criteria.

Between 4 and 8 weeks after completing treatment, patients were assessed by all members of the multidisciplinary team to evaluate the response to chemoradiotherapy. A complete response required total resolution of all clinical and radiological measurable lesions. A biopsy was carried out only on clinical suspicion of residual disease. A neck dissection was recommended for patients with node metastasis >3 cm regardless of the response to therapy and planned for patients who had suspected persistent neck disease 8–12 weeks after completing treatment. Salvage surgery was considered for histologically proven persistent or recurrent tumor in the primary site.

follow-up

The routine follow-up program consisted of locoregional examination at 2-month intervals during the first year, 3-month intervals in the second year, 4-month intervals between the third and fifth year, and every 6 months thereafter. A computed tomography and/or magnetic resonance imaging of the primary tumor and the neck was carried out 8–12 weeks after treatment to assess tumor response. A chest radiograph was carried out annually.

quality-of-life assessment

A cross-sectional evaluation of quality of life (QoL) was carried out using the European Organisation for Research and Treatment of Cancer (EORTC) QoL Questionnaire-Core 30 (QLQ-C30) and the EORTC QoL Questionnaire-Head and Neck 35 (QLQ-H&N35).

statistical analysis

Patients' characteristics were summarized by descriptive measurements (median, range, and proportion). Analyses of efficacy and safety were conducted in the intention-to-treat population. Time-to-event data were described using Kaplan–Meier actuarial curves. Complete response to therapy was defined as clinical and radiological disappearance of all measurable and evaluable disease within the treatment field at 8–12 weeks after therapy. The presence of viable tumor cells after a planned post-treatment dissection was considered as persistent disease in the neck. Locoregional control (persistent disease or locoregional recurrence considered as an event), distant failure (metastasis to any site beyond the primary tumor and regional lymph nodes considered as an event), OS (death of any cause considered as an event), and progression-free survival (PFS; recurrence or progression and death considered as an event) were measured from the date of enrollment. In evaluation of functional PFS (FPFS), radical surgery, permanent percutaneous endoscopic gastrostomy (PEG), permanent tracheotomy, recurrence, progression, and death were considered as events. Crude organ preservation rate was estimated as the rate of patients undergoing CCRT who avoided local recurrence, radical surgery, permanent tracheotomy, and/or permanent PEG. The log-rank test was used for stratified analysis, to assess differences among time-to-event curves by different covariates including age (≤65 versus >65 years), T category (T2–3 versus T4), N category (N0–1 versus N2–3), tumor site (oropharynx versus others), and pretreatment hemoglobin level (<13 g/dl versus ≥13 g/dl). Multivariate Cox regression analysis was carried out using the forward stepwise data selection method to assess the prognostic effect of continuous pretreatment hemoglobin level and other parameters found predictive on univariate analysis on OS, PFS, and FPFS. Tests were two-tailed, and levels of statistical significance have been calculated at the 5% level of probability. Statistical analyses were conducted using the SPSS/PC

statistical program (version 17.0 for Windows; SPSS Inc., Chicago, IL) and the confidence interval (CI) analysis program CIA.

results

demographics

Between January 2000 and July 2007, a total of 139 patients were candidates to receive cisplatinum-based CCRT for LA-HNSCC. The cut-off date for the analysis of efficacy was 31 July 2009; thus, the minimum potential follow-up guaranteed for any patient was 24 months. Table 1 shows demographics and tumor characteristics in the intention-to-treat population. Median age was 61 years (range, 39–77 years). The majority of patients were male (85%) and the oropharynx was the primary site of disease in 55% of cases.

exposure to treatment protocol

Overall, 115 patients (83%) completed the study treatment per protocol receiving ≥66 Gy and ≥80% of the planned cisplatinum and 5-FU doses. The most common reasons for discontinuation of treatment were progressive disease and adverse events (Table 2). All patients completed the induction cycle of chemotherapy. One hundred thirty-seven started concurrent chemotherapy. A median total dose of 66 Gy (range, 52–70 Gy) was administered. Thirteen patients received a dose of RT <66 Gy. Nine patients received only one cycle of concurrent chemotherapy. Sixteen (12%) and 18 (13%) patients received <80% of the planned cisplatinum and 5-FU doses, respectively. Seventeen patients (12%) completed planned treatment with minor dose variations of chemotherapy. Treatment breaks during chemoradiation were infrequent, with all therapies delivered in a mean of 54 days (range, 44–82 days).

toxic effects

Severe acute toxic effects of treatment are showed in Table 3. There were no cases of treatment-related deaths. The most frequent severe acute toxicity associated with coadministration of chemotherapy and RT was pharyngeal mucositis. Mucositis grade ≥3 occurred in 57 patients (41%). Six patients developed grade 4 mucositis requiring hospital admission and treatment interruption longer than 3 days. Seventy-nine patients received feeding tubes, which was a prophylactic measure in most of the cases. Enteral nutrition was usually administered by nasogastric tube; PEG tube was used when enteral nutrition was indicated at pretreatment assessment or in the first week of RT. Severe neutropenia was the most significant toxicity associated with chemotherapy (39%). Overall, 89 patients (64%) developed severe toxic effects, with grade 4 toxicity accounting for 25%. The rate of grade ≥3 late toxic effects was 25.2%. The sites most commonly affected were salivary glands, larynx, pharynx,

Table 1. Patients' characteristics (n = 139)

Characteristics	n	%
Age (years)		
Median	61	
Range	39–77	
Gender		
Male	118	84.9
Female	21	15.1
Site of primitive tumor		
Oral cavity	14	10.1
Oropharynx	76	54.7
Hypopharynx	26	18.7
Larynx	23	16.5
Stage of primary tumor		
T2	29	20.8
T3	51	36.7
T4	59	42.2
Nodal stage		
N0	33	23.7
N1	31	22.3
N2a	16	11.6
N2b	23	16.5
N2c	22	15.8
N3	14	10.1
Overall stage		
III	46	33.1
IV	93	66.9

Table 2. Exposure to treatment and reasons for discontinuation

	n	%
Induction chemotherapy	139	100
Chemoradiotherapy	137	98.6
Completion of treatment per protocol	115	82.7
Discontinuation of treatment	24	17.3
Reason for discontinuation		
Progressive disease	10	7.2
Treatment toxicity	8	5.7
Death from cancer	1	0.7
Other	5	3.6

Table 3. Severe toxic effects during induction chemotherapy–concurrent chemoradiotherapy (n = 139)

Toxicity	Grade 3 (n)	Grade 4 (n)	Grade 5 (n)	Grade 3–5	
				n	%
Mucous membrane	51	6	0	57	41.0
Skin	22	1	0	23	16.5
Nausea or vomiting	27	0	0	23	19.4
Pharynx/esophagus	43	5	0	48	34.5
Larynx	21	0	0	21	15.1
Neutropenia	39	15	0	54	38.8
Febrile neutropenia	6	0	0	3	4.3
Anemia	8	0	0	8	5.7
Renal	3	1	0	4	2.8
Neurological	8	0	0	8	5.7
Other	3	0	0	3	2.2
Overall maximal severity	64	25	0	89	64.0

esophagus, and skin. Eight patients required a permanent tracheotomy and seven patients a permanent PEG. Four patients with critical airway narrowing requiring permanent tracheotomy had their feeding tubes removed within 3 months; five patients required only permanent feeding tube due to pharyngoesophageal stricture.

effectiveness

Follow-up time in survivors ranged from 24 to 112 months, with a median of 41 months.

Forty-six patients developed locoregional failure. The 3-year actuarial rates of local and locoregional control were 76% (95% CI 67% to 85%) and 68% (95% CI 59% to 78%), respectively.

There were 10 patients who developed distant metastases. The rate of freedom from distant metastases was 94% (95% CI 88% to 99%) at 3 years.

In all, 52 of 139 patients died. Of these 52 patients, 38 died of disease, 5 died of second primary tumors, and 9 died due to other unrelated causes. Three-year OS estimate was 68% (95% CI 57% to 79%). Figure 1 shows the Kaplan–Meier curve for OS. Sixty-one patients experienced recurrence or progression. Three-year PFS estimate was 62% (95% CI 50% to 74%). Figure 2 shows the Kaplan–Meier curve for PFS. Second primary tumors were detected in 24 patients. The actuarial rate of developing second primary tumors at 3 years was 14% (95% CI 6% to 22%).

Salvage radical surgery was carried out in 18 patients. Preservation of a functional upper aerodigestive tract with intact voice and maintenance of normal deglutition was achieved in 65% of patients. Actuarial 3-year FPFS was 57% (95% CI 44% to 69%).

long-term QoL assessment

We carried out a cross-sectional QoL assessment. Of the 87 patients alive at July 2009, 74 filled out the questionnaires. Calculated scores for QLQ-C30 and QLQ-H&N35 module are

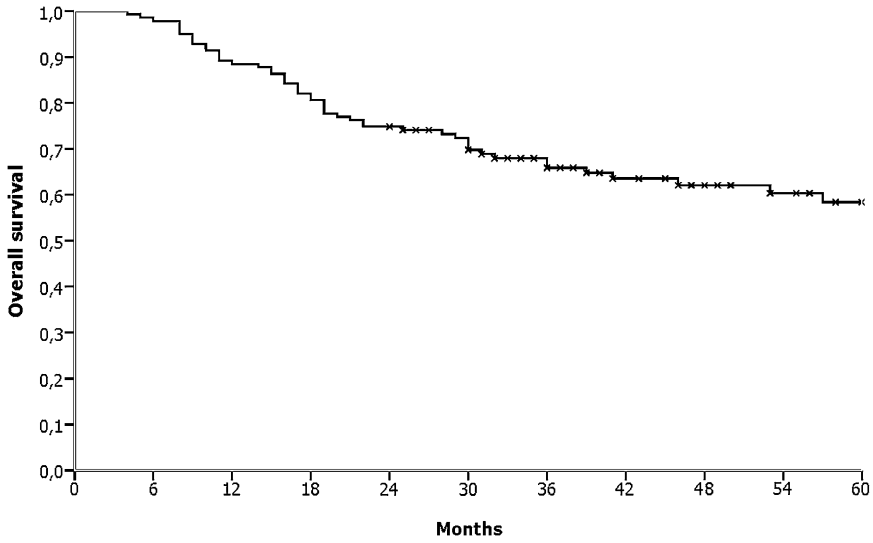

Figure 1. Kaplan–Meier estimates of overall survival.

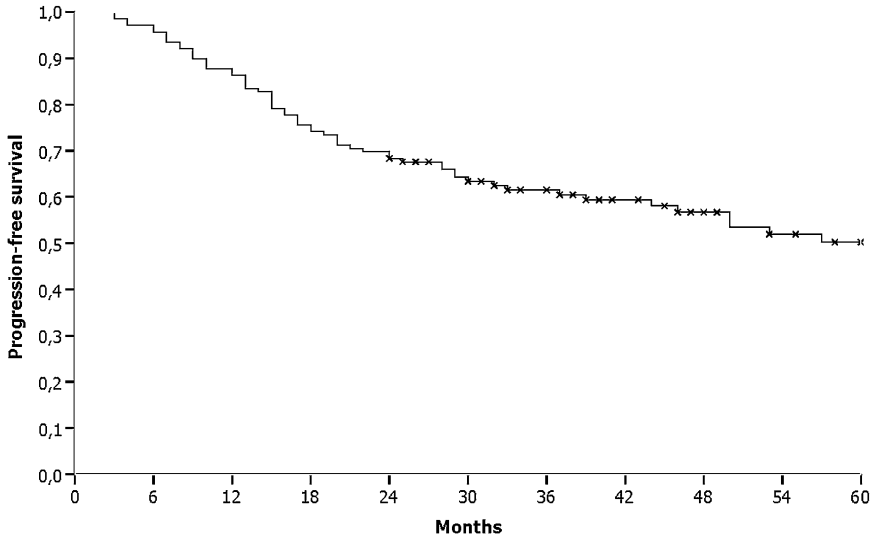

Figure 2. Kaplan–Meier estimates of progression-free survival.

shown in Table 4. Mean global health status was calculated as 82. The lowest functional scores were found for 'emotional functioning' and 'physical functioning'. Considering both the QLQ-C30 and QLQ-H&N35 questionnaires, the highest symptom scores were found for 'dry mouth' and 'sticky saliva'. Overall, 70%, 59%, and 30% of patients reported some degree of swallowing, speech, and breathing problems, respectively.

Table 4. Results from the EORT quality-of-life (QoL) questionnaires[a]

	Mean (95% CI)
EORT QLQ-C30	
Physical functioning	89.6 (85.6–93.6)
Role functioning	91.0 (86.9–95.2)
Social functioning	92.3 (87.9–96.8)
Emotional functioning	83.7 (79.8–87.5)
Cognitive functioning	93.6 (90.7–96.5)
Global QoL	81.5 (77.5–85.6)
Fatigue	15.1 (11.2–19.1)
Nausea and vomiting	1.6 (0.0–3.2)
Pain	5.0 (2.6–7.3)
Dyspnea	11.3 (7.0–15.5)
Sleep disturbance	7.2 (2.7–11.7)
Appetite loss	14.4 (9.4–19.4)
Diarrhea	4.9 (2.2–7.7)
Constipation	15.3 (10.3–20.3)
Financial impact	16.2 (10.5–22.0)
EORT QLQ-H&N35	
Pain	7.1 (4.4–9.3)
Swallowing	14.7 (10.8–18.6)
Senses	17.6 (12.5–22.7)
Speech	15.4 (10.7–20.1)
Social eating	13.3 (8.8–17.8)
Social contact	6.3 (2.6–10.0)
Sexuality	21.8 (14.5–29.2)
Teeth	38.3 (30.2–46.3)
Open mouth	19.4 (13.0–25.8)
Dry mouth	50.9 (43.4–58.4)
Sticky saliva	44.6 (37.0–52.2)
Coughing	22.1 (16.4–27.7)
Felt ill	1.5 (0.5–3.5)
Painkillers	13.5 (5.5–21.5)
Nutritional supplements	17.6 (8.7–26.4)
Feeding tube	6.8 (0.9–12.6)
Weight loss	10.8 (3.6–18.0)
Weight gain	31.1 (20.3–41.9)

[a]The EORTC QLQ-C30 incorporates 30 items and consists of five functional scales (physical, role, cognitive, emotional, and social functioning), three symptom scales (fatigue, pain, and nausea/vomiting), a global QoL scale, and six single items (dyspnea, insomnia, appetite, constipation, diarrhea, and financial impact). All scales pertaining to the EORTC QLQ-C30 range from 0 to 100. A high score for a functional or global QoL scale represents a relatively high/healthy level of functioning or global QoL, whereas a high score for a symptom scale indicates a higher level of symptoms or problems. The head and neck-specific questionnaire EORTC QLQ-H&N35 consists of seven multiple-item scales and six symptom items with a total of 35 questions that assess pain, swallowing, senses (taste and smell), speech, social eating, social contact, sexuality, teeth problems, trismus, dry mouth, sticky saliva, cough, and feeling ill. A high score for a symptom scale indicates a higher level of symptoms or problems. CI, confidence interval; EORT QLQ-C30, European Organization for Research and Treatment of Cancer QoL Questionnaire-Core 30; EORTC QLQ-H&N35, European Organization for Research and Treatment of Cancer Quality QoL Questionnaire-Head and Neck 35.

univariate analysis for time-to-event outcomes

A univariate analysis of OS, PFS, and FPFS related to different variables was carried out. Patients with T4 disease had a worse OS (log-rank test, $P = 0.006$), PFS (log-rank test, $P = 0.048$), and FPFS (log-rank test, $P = 0.002$). Patients with N2–3 disease had a worse OS (log-rank test, $P = 0.014$), PFS (log-rank test, $P = 0.003$), and FPFS (log-rank test, $P = 0.010$). Patients with pretreatment low hemoglobin level (<13 g/dl) had a worse OS (log-rank test, $P = 0.000$), PFS (log-rank test, $P = 0.002$), and FPFS (log-rank test, $P = 0.003$). Patients with oropharyngeal cancer showed a trend toward a better OS (log-rank test, $P = 0.076$), PFS (log-rank test, $P = 0.075$), and FPFS (log-rank test, $P = 0.058$). All other analyses yielded nonsignificant results.

multivariate Cox regression model for time-to-event outcomes

After deleting the nonsignificant variables in multivariate regression model, continuous pretreatment hemoglobin level was the strongest predictor of OS ($P = 0.000$), PFS ($P = 0.001$), and FPFS ($P = 0.005$). N category (N0–1 versus N2–3) was also predictor of OS ($P = 0.040$), PFS ($P = 0.011$), and FPFS ($P = 0.043$). T category (T2–3 versus T4) was predictor of only FPFS ($P = 0.039$). In patients with the same N category, the hazard of death associated with each 1 g/dl increase in pretreatment hemoglobin level decreased by 28% (Table 5).

discussion

The aim of the present investigation was to evaluate the feasibility, safety, and efficacy in terms of functional organ preservation of a multidrug IC–CCRT protocol in patients with LA-HNSCC. Following one cycle of IC, two cycles of multidrug concurrent chemotherapy with RT up to a dose of 66–70 Gy were given to PTV1. This treatment regimen was chosen in an attempt to both deliver systemically active doses of chemotherapy and enhance locoregional control of disease by concurrent administration of chemotherapy and RT.

To limit toxicity, conventional fractionated RT was used. In that regard, the hypothesis that concurrent chemotherapy with hyperfractionated accelerated RT would improve PFS as compared with concurrent chemotherapy with conventional RT was not confirmed as yet [6, 7].

Some authors have suggested that one course of IC is able to identify patients who are highly likely to be successfully treated with CCRT [8]. Because, according to the study protocol, patients started CCRT regardless of the response to the induction cycle, an accurate assessment of the response after IC was not carried out in our series.

At the time our study was begun, results from phase III trials comparing docetaxel plus cisplatinum and 5-FU (TPF) with the classical regimen of cisplatinum plus 5-FU as IC were not available [9, 10]. These trials have demonstrated that, when compared with the control arm, the three-drug IC followed by

Table 5. Multivariate Cox regression analysis for overall survival

	Regression coefficient	Wald statistic	Significance of Wald statistic	Hazard ratio (95% confidence interval)
Pretreatment hemoglobin (continuous variable)	−0.331	14.317	0.000	0.72 (0.60–0.85)
N category (N2–3 versus N0–1)	0.629	4.213	0.040	1.87 (1.03–3.42)

radiation or concurrent chemoradiation improve survival. Now, several investigators consider TPF regimen an emerging standard when systemically active doses of chemotherapy are appropriate (e.g. patients with bulky nodal disease or with hypopharyngeal neoplasms) [11, 12].

A total of 83% of the patients completed the study treatment per protocol. No treatment-related death occurred in this series. The rate of patient compliance with chemoradiotherapy regimens is reported to be 66%–94%, with a lower rate in patients receiving multidrug chemotherapy [4, 9, 10, 13, 14]. The reported rate of early toxic death in patients undergoing intensive multidrug chemoradiotherapy regimens is up to 10% [10, 14–17].

Even if 64% of patients experienced severe acute toxic effects, grade 4 toxicity was limited (25%); most toxic effects were transient and the full-course RT schedule could be delivered in the majority of patients without significant treatment interruptions. Fifty-seven patients (41%) developed grade >2 mucositis. When compared with reports by other investigators, the rate of severe mucositis in the present series seems low. Severe mucositis is reported to affect ∼43% of patients receiving CCRT for HNSCC and considered the most debilitating adverse event of chemoradiotherapy in these patients [18]. Moreover, in patients undergoing multiagent CCRT, the acute toxicity, particularly radiation-induced mucositis, is reported to be formidable [13, 19–21]. Lavertu et al. [21] reported a 88% rate of grade 3/4 mucositis/dysphagia in a series of 105 patients with HNSCC receiving 5-FU 1000 mg/m^2 per day and cisplatinum 20 mg/m^2 per day, both given as continuous infusions during 4 days beginning on days 1 and 22 of concurrent RT course. The regimen was given without interruption or dosage modification regardless of the severity of the adverse effects. Thus, several investigators have abandoned 5-FU as a concurrent agent as it strongly enhances radiation-induced mucositis [13]. In contrast, in a retrospective survey, Nakamura et al. [22] reported a 32% rate of grade 3/4 mucositis in patients with oropharyngeal carcinoma receiving two courses of chemotherapy consisting of continuous infusion of 5-FU 700 mg/m^2 per 24 h for 5 days (days 1–5) and cisplatinum 50 mg/m^2 per 24 h for 2 days (days 6–7) during weeks 1 and 3 or 4 of conventionally fractionated RT; interruption or dosage modification was considered for patients developing severe adverse events. In a phase II randomized multicentric trial by Paccagnella et al. [14], the arm A, receiving two cycles of cisplatinum 20 mg/m^2, days 1–4, plus 5-FU 800 mg/m^2 per day, 96-h continuous infusion, during weeks 1 and 6 of conventionally fractionated RT, experienced a rate of grade 3/4 mucositis/stomatitis of 36.7%. The reason for this disparity in rates of severe mucositis prevalence may be multifactorial. Interruption and dosage modifications, modality of cisplatinum and 5-FU infusion, numbers of cycles of concurrent chemotherapy, timing and dosage of chemotherapy, and intensive nutritional support may likely impact the rate of severe mucositis. Furthermore, use of different scoring systems (e.g. NCI–CTC versus RTOG system) may influence the reported rates of severe toxicity. Particularly, RTOG system for 'mucous membrane' is assessed by the physician based on the macroscopical features of the mucosal inflammation. In contrast, NCI–CTC for grading of 'stomatitis' also considers the ability of the patient to eat. Based on the RTOG system, when 'mucous membrane' and 'pharynx and esophagus' categories are combined, the rate of patients with grade 3/4 mucositis/dysphagia raised to 58.9% in the present series. Although enteral feeding tube placement was a prophylactic measure in most cases, many patients have feeding tubes in place for >1 month after completion of treatment. However, only seven patients required a permanent PEG. Long-term use of feeding tube ranged between 8% and 18% in the literature [23]. Noteworthy, on the basis of QoL questionnaire findings, 70% and 59% of patients reported some degree of eating and speech problems. This high rate of late functional problems is probably attributable to the more sensitivity of QoL questionnaires when compared with toxicity scales [24]. Furthermore, EORTC QoL questionnaires also assess social aspects of eating and speech problems.

Thus, we consider two cycles of cisplatinum and 5-FU chemotherapy concurrent with conventionally fractionated RT after one cycle of IC an acceptable treatment with an overall moderate toxicity profile.

The 3-year OS of 68% and the 3-year PFS of 62% support the curative potential of our treatment schedule. In the study by Adelstein et al. [19], patients were treated with radiation plus concurrent administration of cisplatinum and 5-FU during weeks 1 and 4 of RT. Taking into account the limitations imposed by different follow-up periods, the 3-year distant metastasis rate in on-study population was higher compared with the present study (18% versus 6%). However, the 3-year OS was similar to the 3-year OS reported in the present series. In the study by Posner et al. [9], the experimental arm receiving TPF IC followed by chemoradiotherapy with weekly carboplatin yielded an OS at 3 years of 62%, with a distant metastases rate of 5%. Hitt et al. [15] reported a 2-year OS rate of 66.5% among 189 patients with LA-HNSCC randomly assigned to receive IC with paclitaxel, cisplatinum, and 5-FU followed by CCRT with cisplatinum. The randomized phase II trial by Paccagnella et al. [14] reported a 2-year OS of 61% in

sequential arm. In a phase II trial using induction carboplatin and paclitaxel followed by concurrent carboplatin, paclitaxel, FU, and hydroxyurea and twice daily RT in stage III/IV head and neck cancer patients, Salama et al. [25] reported 68% and 62% OS at 3 and 5 years, respectively, with distant control rate of 89% at 3 years and 87% at 5 years.

Moreover, the 3-year FPFS was 57% in the present series. This rate, including exclusively patients who were alive without locoregional recurrence and with a functionally preserved upper aerodigestive tract, demonstrates the efficacy in terms of functional organ preservation of our approach. Indirect comparison suggests that the present sequential regimen may be a valid alternative in patients in whom systemically active doses of chemotherapy seem appropriate. Among the advantages of our regimen are good compliance and reduced duration of treatment.

According to other studies [26, 27], sticky saliva and dry mouth were the most troublesome long-term adverse effects of chemoradiotherapy. The use of amifostine has been suggested to decrease the incidence of xerostomia in patients undergoing head and neck irradiation. However, recent guidelines [28] and data from our personal experience [29] do not support the routine use of amifostine in patients undergoing RT with platinum-based chemotherapy.

Anemia is common in patients being treated for HNSCC. Our results show the same degree of significance as those previously published by Agarwala et al. [30], who found that low baseline hemoglobin levels were strongly associated with PFS and OS after chemoradiotherapy. Moreover, we found pretreatment hemoglobin level as the strongest independent predictor of FPFS. Intensive chemoradiotherapy may not offer an outcome benefit over RT alone in patients with significant anemia. In the design of future clinical trials, stratifying patients according to their hemoglobin levels should be considered.

Interestingly, age was not found to affect outcome. Other studies found similar results [31]. This result shows that a selection of elderly patients to be submitted to combined modality therapy based on age is probably obsolete. The management of HNSCC must be based not only on tumor characteristics but also on the physiological, rather than the chronological, age of the patient [32].

A trend toward a better outcome was observed in patients with oropharyngeal carcinoma. Although, in our geographic area, tobacco- and alcohol-related oropharyngeal cancer remains dominant [33], the outcome of this population might be positively affected by human papillomavirus (HPV)-related carcinomas. However, the effect of HPV status is not estimable because it was not systematically evaluated in the present series. Treatment of HPV-related oropharyngeal carcinoma is a pressing issue, as although there is no evidence from randomized, controlled trials to support a de-escalation of treatment intensity in HPV-positive oropharyngeal carcinomas, some investigators argue that intensive concomitant chemoradiation regimens may represent an overtreatment in these cases [34].

Even though this study cannot claim to demonstrate a superiority of this treatment regimen over cisplatinum monochemotherapy or other sequential schedules, the results from the present case series are overall encouraging.

However, the study suffered significant limitations. The definition of organ preservation we used is still restrictive and a more qualitative evaluation of the function of upper aerodigestive tract should be advisable.

Although randomized phase III trials comparing intensity-modulated radiotherapy (IMRT) and three-dimensional conformal RT in HNSCC are still ongoing, a series of cohort data have suggested that IMRT provides a more favorable outcome compared with conventional irradiation techniques with regard to both locoregional control and toxicity profiles. Therefore, IMRT had become the standard treatment of cancers of the oropharynx in several institutions [35, 36].

The obvious main limitation of this study is its lack of a randomized, controlled design. Until peer-reviewed data from large randomized trials evaluating TPF IC followed by chemoradiation versus chemoradiation alone became available, CCRT with cisplatinum 100 mg/m^2 on days 1, 22, and 43 should be still considered the standard of care in nonsurgical treatment of LA-HNSCC. Therefore, phase III randomized trials comparing the present treatment with the current standard of care should be advisable to assess the appropriate role of our regimen in LA-HNSCC.

Finally, although to date there are no evidence-based data to conclude that HPV-related tumors should be treated differently, the present sequential chemoradiation regimen may represent an overtreatment in patients with HPV-positive oropharyngeal carcinomas without a history of smoking and alcohol abuse [37]. For the future, stratification by HPV status or trials selectively dedicated to patients with HPV-positive HNSCC may provide the opportunity to define a more patient-specific strategy.

conclusions

Cisplatinum-based multidrug IC–CCRT can result in functional organ preservation and curative treatment in most patients with LA-HNSCC. The low rate of distant metastasis suggests a potentially systemic effect of our treatment schedule. The toxicity profile and patients' compliance to treatment confirmed the safety and tolerability of this approach. Finally, baseline hemoglobin level is confirmed as among the most consistent predictors of outcomes in patients treated by combined modality therapy for HNSCC.

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disclosure

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references

1. Pignon JP, le Maître A, Maillard E et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009; 92: 4–14.
2. Zorat PL, Paccagnella A, Cavaniglia G et al. Randomized phase III trial of neoadjuvant chemotherapy in head and neck cancer: 10-year follow-up. J Natl Cancer Inst 2004; 96: 1714–1717.
3. Paccagnella A, Orlando A, Marchiori C et al. Phase III trial of initial chemotherapy in stage III or IV head and neck cancers: a study by the Gruppo di Studio sui Tumori della Testa e del Collo. J Natl Cancer Inst 1994; 86: 265–272.
4. Forastiere AA, Goepfert H, Maor M et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003; 349: 2091–2098.
5. Lefebvre JL, Chevalier D, Luboinski B et al. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. J Natl Cancer Inst 1996; 88: 890–899.
6. Bourhis J, Sire C, Lapeyre M et al. Accelerated versus conventional radiotherapy with concomitant chemotherapy in locally advanced head and neck carcinomas: results of a phase III randomized trial. Int J Radiat Oncol Biol Phys 2008; 72: S31–S32.
7. Budach V, Stuschke M, Budach W et al. Hyperfractionated accelerated chemoradiation with concurrent fluorouracil–mitomycin is more effective than dose-escalated hyperfractionated accelerated radiation therapy alone in locally advanced head and neck cancer: final results of the radiotherapy cooperative clinical trials group of the German Cancer Society 95–06 prospective randomized trial. J Clin Oncol 2005; 23: 1125–1135.
8. Urba S, Wolf G, Eisbruch A et al. Single-cycle induction chemotherapy selects patients with advanced laryngeal cancer for combined chemoradiation: a new treatment paradigm. J Clin Oncol 2006; 24: 593–598.
9. Posner MR, Hershock DM, Blajman CR et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007; 357: 1705–1715.
10. Vermorken JB, Remenar E, van Herpen C et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 2007; 357: 1695–1704.
11. Specenier PM, Vermorken JB. Current concepts for the management of head and neck cancer: chemotherapy. Oral Oncol 2009; 45: 409–415.
12. Fury MG, Shah JP. Induction chemotherapy in the management of head and neck cancer. J Surg Oncol 2010; 101: 292–298.
13. Adelstein DJ, Li Y, Adams GL et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 2003; 21: 92–98.
14. Paccagnella A, Ghi MG, Loreggian L et al. Concomitant chemoradiotherapy versus induction docetaxel, cisplatin and 5 fluorouracil (TPF) followed by concomitant chemoradiotherapy in locally advanced head and neck cancer: a phase II randomized study. Ann Oncol 2010; 21: 1515–1522.
15. Hitt R, López-Pousa A, Martínez-Trufero J et al. Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. J Clin Oncol 2005; 23: 8636–8645.
16. Pointreau Y, Garaud P, Chapet S et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. J Natl Cancer Inst 2009; 101: 498–506.
17. Argiris A, Brockstein BE, Haraf DJ et al. Competing causes of death and second primary tumors in patients with locoregionally advanced head and neck cancer treated with chemoradiotherapy. Clin Cancer Res 2004; 10: 1956–1962.
18. Trotti A, Bellm LA, Epstein JB et al. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. Radiother Oncol 2003; 66: 253–262.
19. Adelstein DJ, Saxton JP, Rybicki LA et al. Multiagent concurrent chemoradiotherapy for locoregionally advanced squamous cell head and neck cancer: mature results from a single institution. J Clin Oncol 2006; 24: 1064–1071.
20. Adelstein DJ, Saxton JP, Lavertu P et al. A phase III randomized trial comparing concurrent chemotherapy and radiotherapy with radiotherapy alone in resectable stage III and IV squamous cell head and neck cancer: preliminary results. Head Neck 1997; 19: 567–575.
21. Lavertu P, Adelstein DJ, Saxton JP et al. Aggressive concurrent chemoradiotherapy for squamous cell head and neck cancer: an 8-year single-institution experience. Arch Otolaryngol Head Neck Surg 1999; 125: 142–148.
22. Nakamura T, Kodaira T, Tachibana H et al. Clinical outcome of oropharyngeal carcinoma treated with platinum-based chemoradiotherapy. Oral Oncol 2009; 45: 830–834.
23. Rieger JM, Zalmanowitz JG, Wolfaardt JF. Functional outcomes after organ preservation treatment in head and neck cancer: a critical review of the literature. Int J Oral Maxillofac Surg 2006; 35: 581–587.
24. Frowen JJ, Perry AR. Swallowing outcomes after radiotherapy for head and neck cancer: a systematic review. Head Neck 2006; 28: 932–944.
25. Salama JK, Stenson KM, Kistner EO et al. Induction chemotherapy and concurrent chemoradiotherapy for locoregionally advanced head and neck cancer: a multi-institutional phase II trial investigating three radiotherapy dose levels. Ann Oncol 2008; 19: 1787–1794.
26. Fung K, Lyden TH, Lee J et al. Voice and swallowing outcomes of an organ-preservation trial for advanced laryngeal cancer. Int J Radiat Oncol Biol Phys 2005; 63: 1395–1399.
27. Sasse AD, Clark LG, Sasse EC et al. Amifostine reduces side effects and improves complete response rate during radiotherapy: results of a meta-analysis. Int J Radiat Oncol Biol Phys 2006; 64: 784–791.
28. Hensley ML, Hagerty KL, Kewalramani T et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. J Clin Oncol 2009; 27: 127–145.
29. Pavanato G, Polico C, Ferrarese A et al. Amifostine in the prevention of xerostomia of irradiated head & neck tumors: preliminary results of a multicentric outcome study. Proc Am Soc Clin Oncol 2003; 22: 543 (Abstr 2184).
30. Agarwala SS, Cano E, Heron DE et al. Long-term outcomes with concurrent carboplatin, paclitaxel and radiation therapy for locally advanced, inoperable head and neck cancer. Ann Oncol 2007; 18: 1224–1229.
31. Denis F, Garaud P, Bardet E et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol 2004; 22: 69–76.
32. Bernardi D, Barzan L, Franchin G et al. Treatment of head and neck cancer in elderly patients: state of the art and guidelines. Crit Rev Oncol Hematol 2005; 53: 71–80.
33. Boscolo-Rizzo P, Da Mosto MC, Fuson R et al. HPV-16 E6 L83V variant in squamous cell carcinomas of the upper aerodigestive tract. J Cancer Res Clin Oncol 2009; 135: 559–566.
34. Forastiere AA. Chemotherapy in the treatment of locally advanced head and neck cancer. J Surg Oncol 2008; 97: 701–707.
35. Daly ME, Le QT, Maxim PG et al. Intensity-modulated radiotherapy in the treatment of oropharyngeal cancer: clinical outcomes and patterns of failure. Int J Radiat Oncol Biol Phys 2010; 76: 1339–1346.
36. de Arruda FF, Puri DR, Zhung J et al. Intensity-modulated radiation therapy for the treatment of oropharyngeal carcinoma: the Memorial Sloan-Kettering Cancer Center experience. Int J Radiat Oncol Biol Phys 2006; 64: 363–373.
37. Ang KK, Harris J, Wheeler R et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010; 363: 24–35.