Induction Chemotherapy Followed by Concurrent Chemoradiotherapy in Advanced Head and Neck Squamous Cell Carcinoma

C. BARONE[1], R. GRILLO[1], D. DONGIOVANNI[1], N. BIROCCO[1], M. RAMPINO[2], M.G. RUO REDDA[2], E. GARIBALDI[2], F. MUNOZ[2], G. PECORARI[3], A. CAVALOT[3], P. GARZINODEMO[4], L. BUFFONI[1], L. CIUFFREDA[1], U. RICARDI[2], G. CORTESINA[3], C. GIORDANO[3], M. FASOLIS[4], S. BERRONE[4], O. BERTETTO[1] and M. SCHENA[1]

[1]UOA Oncologia Medica, COES, ASO S.Giovanni Battista, Torino;
[2]SCDU di Radioterapia, [3]SCDU ORL I e II and
[4]SCDU di Chirurgia, Maxillo-Facciale Università di Torino ASO S. Giovanni Battista, Torino, Italy

Abstract. *Background: A phase II study was carried out to investigate an induction regimen with cisplatin, paclitaxel followed by radiotherapy concurrent with weekly cisplatin for locally advanced squamous cell carcinoma of the head and neck. Patients and Methods: Stage III-IV disease patients were eligible. Two cisplatin (100 mg/m^2) and paclitaxel (175 mg/m^2) courses were administered every 21 days followed by standard fractionated external beam radiotherapy (approximately 70 Gy), concomitant to weekly cisplatin (30 mg/m^2). Results: Thirty-five patients were enrolled: over 70% had unresectable disease with bulky lesions. Grade 3-4 neutropenia developed in 14% and G3 mucositis in 23%. Locoregional control was achieved in 51%. Median time to progression and overall survival were 10,7 and 17 months respectively; 2- and 3-year survival rates were 30% and 25% respectively. Conclusion: Our induction two-drug regimen followed by chemoradiotherapy with concurrent weekly cisplatin was well tolerated with low acute toxicity and good locoregional control and survival rate.*

Squamous cell cancer of the head and neck (HNSCC) comprises a heterogeneous group of carcinomas of the upper aerodigestive tract that share similar epidemiological characteristics and clinical management strategies. Standard surgery and radiotherapy for locally advanced disease is burdened by a low overall cure rate and poor functional outcome: approximately 50-60% of patients have local disease recurrence within 2 years and 20-30% develop metastatic disease (1).

These disappointing results have led to new therapeutic strategies that incorporate chemotherapy in combined modality treatments (2). Several phase III trials comparing radiotherapy alone to concomitant or alternating chemoradiotherapy (CRT) showed a statistically significantly improvement in locoregional control with the latter and an impact on overall survival (3, 4). The results of four meta-analyses confirmed that patients treated concurrently with chemotherapy and radiotherapy had a statistically significant survival benefit compared with those treated with radiotherapy alone (5-8). This benefit was more pronounced with a platinum-based regimen. Cisplatin 100 mg/m^2 for 3 cycles during the course of radiotherapy has become a standard of care, although it is associated with substantial toxicity and relatively poor compliance (9).

Induction chemotherapy (CT) has been frequently administered in advanced HNSCC, with an overall response rate often exceeding 75%; however, the use of a neoadjuvant strategy failed to demonstrate a consistent improvement in survival. Some studies showed a certain benefit and a small but significant survival advantage was reported in at least one meta-analysis (5). Moreover phase III clinical trials evaluating induction CT showed better control of distant disease in the induction CT arms (9-11) suggesting the possibility of a sequential approach in which induction CT may eradicate occult metastatic foci and that subsequent concomitant CRT may suppress locoregional disease in head and neck cancer (12, 13). Phase II trials of a neoadjuvant cisplatin-5fluorouracil induction regimen followed by CRT showed impressive overall survival (OS) and progression-free survival (PFS) but toxicity was high and only selected patients could be safely treated (14, 15).

Correspondence to: Dott. Carla Barone, Oncologia Medica c/o COES, Azienda Ospedaliera San Giovanni Battista, Via Cherasco 15, 10126 Torino, Italy. Tel: +39 0116335189, Fax: +39 0116335189, e-mail: carla.barone@hotmail.it

Key Words: Head and neck carcinoma, cisplatin, paclitaxel, chemotherapy, radiotherapy.

Recently, taxanes (paclitaxel and docetaxel) showed significant single-agent activity in HNSCC and have been investigated in combination with cisplatin and 5-fluorouracil (PF) regimens in several phase II studies in recurrent and or metastatic disease as well as in the induction setting (16-17). Phase III studies comparing PF and docetaxel, cisplatin and 5-fluorouracil (TPF) induction regimens have shown a better clinical response with a favourable toxicity profile for the latter (18, 19).

The use of anti-epidermal growth factor receptor (EGFR) antibodies concomitant to radiotherapy has been recently proposed. These agents showed an advantage in response rate, OS and PFS over radiotherapy alone in a phase III study (20) without increasing toxicity. However, the role of anti-EGFR target therapy and its optimal combination with chemo- and radiotherapy in head and neck cancer needs to be clarified.

The aim of this single center phase II study was to evaluate the feasibility and outcome of a two-drug induction regimen, with combined cisplatin and paclitaxel, followed by CRT with a cisplatin-modified schedule in a target population of patients with locally advanced HNSCC who were unresectable or poor candidates for resection.

Patients and Methods

Patient population. Patients with histologically proven SCC of the oral cavity, oropharynx, hypopharynx, nasopharynx or larynx, with advanced locoregional stage III or IV disease, ineligible for conservative surgical or exclusive radiation therapy, or with recurrence after primary surgery for stage I/II disease, ≥18 years of age, with ECOG performance status ≤1 and a life expectancy of at least 6 months were eligible for this study. Bidimensionally measurable disease was determined by physical examination and computed tomography scan and/or magnetic resonance imaging studies obtained within 28 days of enrolment. Exclusion criteria were prior chemo- or radiotherapy, metastatic disease beyond the neck by physical examination or chest x-ray; pregnancy or breast feeding; baseline serum laboratory tests within 28 days before registration showing white cell counts ≤4,000/μL, absolute neutrophil count (ANC) ≤1,500/μL, platelets ≤100,000/μL; calculated creatinine clearance ≤50 ml/min, serum bilirubin or serum glutamic oxalacetic transaminase or serum glutamic pyruvic transaminase greater than twice the institutional upper limits of normal. Other exclusion criteria were prior malignancies, except for adequately treated basal cell skin carcinoma, in situ cervical carcinoma, or other malignancy for which the patient had been disease-free >5 years. Written informed consent was obtained from all patients.

Treatment plan. During the screening phase, patients were evaluated and formally staged by the Head and Neck Cancer Tumor Board. Pre-treatment evaluation included history taking and physical examination, measurement of detectable mass, chest X-rays and computed tomography (CTI) or magnetic resonance (MRI) imaging of the head and neck, blood cell count with differential counts, liver function studies, blood urea nitrogen, creatinine, albumin, calculated creatinine clearance, nutrition evaluation and dental examination.

Chemotherapy. Cisplatin 100 mg/m^2 and paclitaxel 175 mg/m^2 were administered on day 1 every 21 days for two cycles. CRT began approximately on day 42 or when chemotherapy-related toxicity recovered. Concomitant chemotherapy consisted of intravenous infusion of cisplatin (30 mg/m^2) over 30 minutes, weekly, on irradiation days 1, 8, 15, 22, 29, 36, 42, 49, 56.

Supportive hydration was given with cisplatin; dexamethasone and 5-HT3 antagonists were given as antiemetic prophylaxis; antiH1 and antiH2 were given as anti-allergic prophylaxis with paclitaxel.

Chemotherapy dose modification was based on blood cell counts obtained on the day of treatment. The planned dose was administered if WBC>3,000/μL with ANC>1,500/μL and platelets >100,000/μL. Doses were not modified based on hematocrit or hemoglobin. If the nadir ANC count was <500/μL and/or platelet count was <50,000/μL, the cisplatin and paclitaxel dose were reduced to 80 mg/m^2 and 160 mg/m^2 respectively, during induction chemotherapy; a chemotherapy delay of one week was allowed when neutropenia or thrombocytopenia developed during concomitant chemoradiotherapy.

Cisplatin was not administered when serum creatinine was >1.6 and calculated creatinine clearance was <45 mL/min; audiometric examination was performed when clinical evidence of ototoxicity appeared; planned cisplatin dose was delivered when neurotoxicity or ototoxicity were grade 1 or less. Patients with grade 2 neuro- or ototoxicity during induction chemotherapy were taken off the study; when the same toxicity developed during concomitant treatment, chemotherapy was discontinued, radiotherapy was given alone and the patient remained in the study; switching to carboplatin (AUC 2, weekly) was considered in case of grade 2 nephrotoxicity. Patients taken off the study during induction chemotherapy were re-evaluated by the Head and Neck Cancer Tumor Board and underwent radiotherapy or surgery. The protocol plan was to continue the treatment cycle despite mucositis or dermatitis without dose reduction.

Granulocyte-stimulating factors were not allowed as prophylaxis against neutropenia and were given only in case of G4 neutropenia in patients with a high risk of infection or febrile neutropenia; erythropoietin with iron support was permitted when anemia (Hb <11 g/dl) developed and was discontinued when Hb recovered to ≥12 g/dl.

All patients underwent weekly physical examination, blood cell counts, nutrition evaluation and recording of weight changes. Nutritional support started at the beginning of the treatment with education and advice; parenteral or enteral nutrition was instituted when body weight decreased by ≥10% baseline values. Toxicity events were recorded weekly according to National Cancer Institute Common Toxicity Criteria, version 2.0 (NCI) (21)

Radiotherapy. External-beam radiation therapy was delivered to all patients (megavoltage source of 5 MV). An immobilization thermoplastic mask was used for all patients. Twenty-eight (80%) were treated with two-opposite shaped lateral fields encompassing the primary site and the upper neck; an anterior portal (with a laryngeal shield when necessary) was used to treat lower neck and supraclavicular areas in 13 patients (37%); 6-9 MeV electron beams were used to boost spinal nodes in 10 patients.

Table I. *Patient characteristics.*

	No.	%
Gender		
M/F	27/8	77/23
Age (years)	Median 60	Range 39-71
PS ECOG		
0	24	68
1	11	32
Site of disease		
Oral cavity	13	37
Oropharynx	12	34
Ipopharynx	5	14
Larynx	2	6
Rhinopharynx	2	6
Other	1	3
Stage		
III	7	20
IVA	19	54
IVB	5	14
Recurrent disease	4	11
Surgery		
Unresectable	25	71
Resectable	10	29
All patients	35	100

Treatment assessment. After two induction cycles, patients were re-evaluated with physical examination and CTI or MRI. Response was determined according to the RECIST criteria (22); briefly complete response (CR) was defined as complete disappearance of all known sites; partial response (PR) was an at least 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter and no new lesions; stable disease (SD) was defined as neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter after the start of treatment; progressive disease (PD) was when at least a 20% increase in the sum of the longest diameter of the target lesions was observed, taking as reference the smallest sum longest diameter recorded after the start of treatment or the appearance of one or more new lesions.

After induction CT, patients with resectable SD and PD were offered surgery but they could also choose to remain in the study. Those who completed the treatment underwent clinical re-evaluation during concomitant CRT usually around the fourth week of radiotherapy and at the end of treatment. Complete clinical and imaging evaluation was performed 60 days after the end of treatment, or erlier, when PD was clinically suspected. Suspicious lesions underwent biopsies. Neck dissection was not routinely performed in patients with N2-N3 disease at diagnosis, when a clinical CR was obtained.

Organ preservation was one goal of the protocol but was secondary to achieving cure. Patients who failed to achieve a CR with positive biopsy after treatment, or who developed PD after concomitant CRT underwent surgery if resectable.

Table II. *Outcome of treatment.*

Response	Induction CT (%)	Concomitant CT/RT (%)	Surgical recovery (%)
CR	3 (9)	16 (46)	6 (17)
PR	19 (54)	12 (34)	2 (6)
SD	10 (28)	0	
PD	2 (6)	7 (20)	
NE	1 (3)		
No. patients	35 (100)	35 (100)	8 (23)

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, NE: not evaluable.

Statistical analysis. The response rate is expressed as the proportion of patients who demonstrated CR and/or PR. Time to progression was measured as the time from the first day of therapy until death from disease or toxicity, appearance of new lesions, or an increase of >25% of the product of perpendicular diameters of tumor lesions. Survival was measured from the day of entry into the study until death from any cause. Overall survival and time to progression (TTP) were calculated by means of the Kaplan-Meier method with the log-rank test to determine statistical significance.

The aim of this phase II study was to evaluate feasibility and outcome of locoregional control and survival of this treatment regimen for HNSCC. The primary objective was to determine the feasibility of neoadjuvant CT followed by a CRT in patients with locally advanced HNSCC; we aimed to obtain more than 30% prolonged (>2 years) disease-free survival with organ preservation. The null hypothesis of 30% was chosen on the basis of a previous study (23) that showed a 20-40% of 3-year survival in stage III-IV laryngeal cancer treated with radiotherapy and salvage surgery. We estimated that treating at least 25 patients would ensure that the estimated standard error (SE) associated with the observed CR rate would be ≤0.01.

Results

Between January 2003 and January 2006, 35 eligible patients (27 men [77%] and 8 women [23%]; median age 60 years [range 39-71 years]) with histologically proven HNSCC were enrolled; patient characteristics are presented in Table I.

The primary site was the oral cavity in 13 patients (37%), the oropharynx in 12 (34%), hypopharynx in 5 (14%), the larynx in 2 (6%); the rinopharynx in 2 (6%) and the otomastoid in 1 (3%).

Most (66%) patients presented with a bulky stage IV disease, while 4 (11%) had recurrent disease after previous resection of T1-T2, N0 disease; the 10 patients (29%) who were potentially resectable by pharyngo-laryngectomy or glossectomy refused surgery, aiming for organ preservation instead; 25 patients (71%) had unresectable disease: 23 due to disease extension, 2 due to co-morbidity.

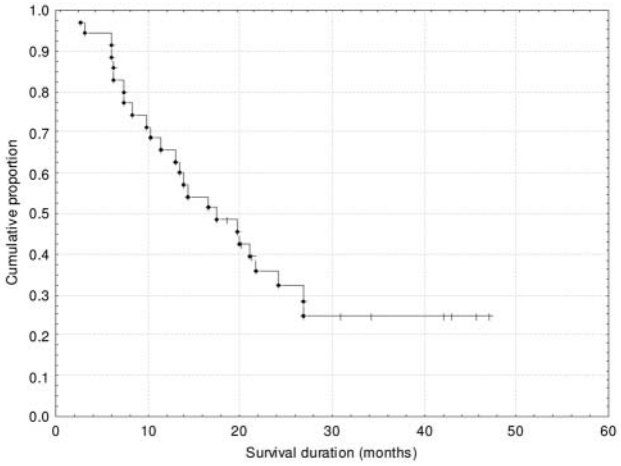

Figure 1. *Kaplan-Meier overall survival (OS) curve. Median OS was 17 months.*

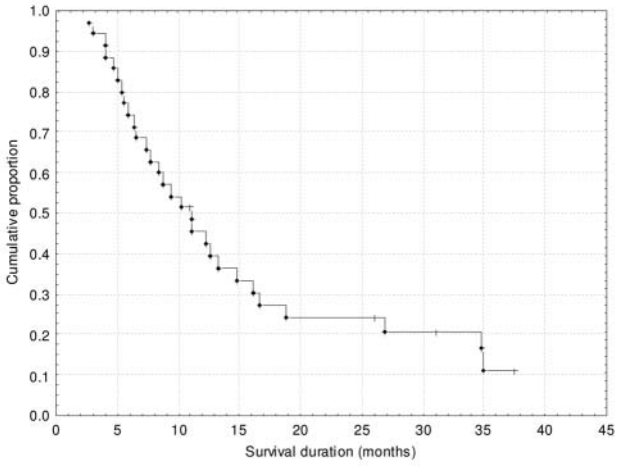

Figure 2. *Kaplan-Meier time to progression (TTP) curve. Median TTP was 10.7 months.*

Induction chemotherapy. Of a total of 35 patients, 31 (88.5%) received two cycles of induction chemotherapy; 3 (8.5%) received three cycles caused by a delay in radiotherapy availability; 1 patient (3%) received only one cycle owing to toxicity.

After induction chemotherapy, an overall response (OR) was observed in 63% of patients, 9% achieved CR and 54% PR (Table II). One patient received only one chemotherapy cycle and was not considered evaluable for response after induction chemotherapy. Dose intensity was high: 91% of the planned cisplatin dose and 95% of paclitaxel.

Concomitant chemoradiotherapy. Chemotherapy: the median duration of cisplatin chemotherapy concomitant to radiotherapy was 7 weeks (range 0-9 weeks). One patient switched to carboplatin during CRT because of G2 nephrotoxicity. The dose intensity was 82% of the planned cisplatin dose.

Radiotherapy: The average duration of radiotherapy was 63 days (range 33-96 days) with a median of 65 days. The total dose was delivered by a conventional fractionation schedule in all patients, with 1.8-2.0 Gy, 5 fractions/week and all fields treated daily. The median total dose of radiotherapy was 70 Gy (range 34-72.8 Gy). A two-dimensional treatment planning was implemented in 28 patients (80%); in 7 (20%) a three-dimensional treatment plan was used with 8 MLC-shaped fields techniques. Starting in 2006 we implemented intensity-modulated techniques (IMRT) particularly for nasopharyngeal tumors.

Outcome. After concomitant chemoradiotherapy, 16 patients achieved CR (46%) and 12 PR (34%) (Table II); 2 patients with only nodal residual disease underwent surgical neck dissection; locoregional disease control was obtained in 51% of patients.

Survival. After a median follow-up time of 36.7 months (range 3-47 months) median survival was 17 months and median TTP was 10.7 months. The 2- and 3-year OS rates were 30% and 25% respectively (Figure 1-2).

Relapse pattern. After a median follow up of 36.7 months, 28/35 patients experienced disease progression or relapse. Locoregional progression occurred in 93% of relapsing patients; distant relapse was observed in only 7%. A second tumor (non-small cell lung cancer) occurred in 3 patients; 7 patients are presently still alive and disease-free.

Surgery. Two patients underwent an ipsilateral radical neck dissection for persistent nodal disease after CT-CRT treatment. A surgical approach was also manageable in 6 patients after disease recurrence: 1 total laryngectomy, 2 total glossectomies, 2 radical neck dissections, 1 pharyngectomy.

Toxicity. Toxicity was mild during induction chemotherapy: 14% developed G3-G4 neutropenia without febrile neutropenia; asthenia, nausea and emesis were prevalent toxicity effects (Table III); 2 patients developed nephrotoxicity, G1 and G2 respectively. During concomitant treatment, stomatitis developed in all patients but was grade 3 in 23%; no grade 4 stomatitis was observed. Grade 1-2 anemia required erythropoietin (EPO) support in 4 patients.

During radiotherapy with concomitant weekly cisplatin, 10 patients (29%) experienced weight loss ≥10%. A feeding tube was necessary in 4 (11%) before the start of treatment because

Table III. *NCI toxicity.*

Adverse events	Induction CT				Concomitant CT-RT			
(35 patients)	Grade				Grade			
	1(%)	2(%)	3(%)	4(%)	1(%)	2(%)	3(%)	4(%)
Neutropenia	7 (20)	5 (14)	1 (3)	4 (11)	6 (17)	1 (3)	2 (6)	0
Thrombocytopenia	0	0	0	0	3 (9)	0	2 (6)	0
Anemia	4 (11)	0	0	0	5 (14)	0	1 (3)	0
Nausea	3 (9)	6 (17)	1 (3)	0	8 (23)	2 (6)	1 (3)	0
Emesis	2 (6)	3 (9)	1 (3)	0	2 (6)	0	0	0
Stomatitis	4 (11)	1 (3)	0	0	17 (49)	10 (28)	8 (23)	0
Diarrhoea	1 (3)	0	2 (6)	0	0	0	0	0
Costipation	0	1 (3)	0	0	5 (14)	1 (3)	0	0
Neuropathy	5 (14)	1 (3)	0	0	2 (6)	1 (3)	1	0
Nephropathy	1 (3)	1 (3)	0	0	0	0	0	0
Ototoxicity	0	0	0	0	0	0	0	0
Alopecia	1 (3)	4 (11)	3 (9)	0	0	4 (11)	4 (11)	0
Skin toxicity	0	0	0	0	0	0	0	0
Asthenia	3 (9)	6 (17)	0	0	3 (9)	1 (3)	0	0
Weight loss>10%	0	0	0	0				10 (29)

of very poor baseline nutritional status; 8 (23%) required feeding support during treatment; 6 received time-limited *i.v.* feeding; 2 were supported with a gastric tube (PEG). Five (14%) patients were hospitalized for longer than five days. Nephrotoxicity G2 was observed in 1 patient who discontinued cisplatin and switched to carboplatin. One patient discontinued radiotherapy because of tumor-skin fistula.

Major adverse events occurred in 6 patients, leading to early interruption of CT in 4:1 developed an acute pulmonary thromboembolia during CRT; 1 experienced reactivation of a previous lung tuberculosis and 2 a sudden decrease in performance status; 1 developed a severe lung fibrosis after the first induction chemotherapy cycle and was subsequently treated with radiotherapy alone; 1 had an ischemic stroke during CRT and died of complications.

Prevalent long-term toxicities were xerostomia in 12 (34%) patients, 5 (14%) of whom had difficulty in swallowing and persistent low weight.

Discussion

The increased complexity of integrated treatment is a clear improvement in the management of advanced HNSCC, offering inoperable patients or those requiring a conservative approach an additional therapy option. Chemoradiotherapy with concomitant cisplatin is currently considered the standard treatment in patients with resectable laryngeal cancer (24), but the optimal treatment strategy remains unclear for those with other primary sites or unresectable tumors. While phase II and phase III studies of induction chemotherapy followed by standard CRT showed considerable locoregional control (LRC), OS and PFS (14-19), most of them reported severe G3-G4 toxicity and toxic deaths. Our goal was to design a treatment schedule able to minimize toxicity of concurrent chemoradiotherapy, while maintaining high cisplatin dose intensity.

We evaluated a two-drug neoadjuvant treatment that included cisplatin and paclitaxel, followed by concomitant weekly cisplatin. The induction treatment was well tolerated and toxicity was low: neither febrile neutropenia nor toxic death were observed and mucositis was negligible; a good overall response (63%) was obtained after induction, comparable with the results of other studies on two-drug regimens (25). A better overall response was shown with a three-drug regimens, including cisplatin-paclitaxel/docetaxel and 5 fluorouracil, with 80% OR and 33% CR (18) but reported toxicity was consistently higher, with 45% G3-G4 neutropenia, febrile neutropenia and toxic deaths. Moreover a two-drug regimen with combined cisplatin and taxane is more convenient than a 5-fluorouracil infusion regimen which requires indwelling catheters and ambulatory pumps.

The chemoradiotherapy phase of treatment with concurrent weekly cisplatin was also well tolerated and 63% of patients completed the planned treatment. The weekly cisplatin regimen appears less toxic than that reported with the Radiation Therapy Oncology Group (RTOG) intermittent high-dose cisplatin (4). We observed less severe nausea/vomiting, renal toxicity, peripheral neuropathy and ototoxicity; G3-G4 stomatitis was also much less evident.

Our treatment obtained response and survival rates comparable with some CRT studies (25) but lower than others (14-18), with a CR of 49% (locoregional control 51%) and a 2-year survival of 30%. A possible reason for these results may lie with the study population: an unselected population with very poor prognosis. Most patients had an extralaryngeal primary site of disease; 71% were unresectable and among those potentially resectable, most were poorly resectable because of tumoral or nodal bulky disease. Moreover, 4 patients had recurrent disease after a previous surgery; we decided to keep them in the study because they were eligible for a chemoradiotherapy treatment and the primary end point was feasibility. In this setting, the expected outcome was suboptimal. Another possible explanation may be related to a slightly lower overall chemotherapy dose-intensity than that obtained in other studies in which a three-drug induction regimen followed by radiotherapy and three concomitant courses of cisplatin (100 mg/m^2) were administered. Most relapsing patients showed loco-regional disease progression (71%) and only 6% presented distant failure, confirming previous observations suggesting the possibility of a reduction in distant metastasis in patients treated with neoadjuvant systemic chemotherapy (13).

The aim of our study was to design a treatment with a good toxicity profile that could obtain an acceptable outcome in patients with poor prognosis that hardly fit an intensive chemoradiotherapy treatment. Our results show that toxicity can be reduced with a two-drug induction regimen (cisplatin and paclitaxel) followed by concomitant weekly cisplatin; the presented schedule offers a good safety profile in the treatment of locally advanced head and neck cancer and permits treatment of an unselected patient population with a grim prognosis without added severe toxicity.

References

1 Forastiere A, Koch W, Trotti A and Sidransky D: Head and neck cancer. N Engl J Med *345*: 1890-1900, 2001.

2 Stupp R, Weichselbaum RR and Vokes EE: Combined modality therapy of head and neck cancer. Semin Oncol *21(3)*: 349-358, 1994.

3 Merlano M, Vitale V, Rosso R, Benasso M, Corvò R, Cavallari M, Sanguineti G, Bacigalupo A, Badellino F and Margarino G: Treatment of advanced squamous-cell carcinoma of the head and neck with alternating chemotherapy and radiotherapy. N Eng J Med *327(16)*: 1115-1121, 1992.

4 Ang KK, Harris J, Garden AS, Trotti A, Jones CU, Carrascosa L, Cheng JD, Spences SS, Forastiere A and Weber RS: Concomitant boost radiation plus concurrent cisplatin for advanced head and neck carcinomas: radiation therapy oncology group phase II trial 99-14. J Clin Oncol *23(13)*: 3008-3015, 2005.

5 Pignon JP, Bourhis J, Domenge C and Designè L: Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individal data. MACH-NC Collaborative Group. Meta-Analyses of Chemotherapy on Head and Neck Cancer. Lancet *355(9208)*: 949-955, 2000.

6 Pignon JP, Baujat B and Bourhis J: Individual patient data meta-analyses in head and neck carcinoma: what have we learnt? Cancer/Radioterapie *9*: 31-36, 2005.

7 Bourhis J: Conventional *vs.* modified fractionated radiotherapy. Meta-analysis of radiotherapy in head and neck carcinoma: a meta-analysis based on individual patient data. Int J Rad Oncol Biol Phys *54(Suppl)*: 71-72, 2002.

8 Bourhis J: Meta-analysis of conventional versus altered fractionated radiotherapy in head and neck squamous cell carcinoma (HNSCC): final analysis. Int J Rad Oncol Biol Phys *60(Suppl)*: S190-191, 2004.

9 Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, Glisson B, Trotti A, Ridge JA, Chao C, Peters G, Lee DJ, Leaf A, Ensley J and Cooper J: Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Eng J Med *349*: 2091-2098, 2003.

10 Paccagnella A, Orlando A, Marchiori C, Zorat PL, Cavaniglia G, Sileni VC, Jirillo A,Tomio L, Fila G and Fede A: 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 *86*: 265-272, 1994.

11 Zorat PL, Paccagnella A, Cavaniglia G, Loreggian L, Gava A, Mione CA, Boldrin F, Marchiori C, Lunghi F, Fede A, Bordin A, Da Mosto MC, Sileni VC, Orlando A, Birillo A, Tomio L, Pappagallo GL and Ghi MG: Randomized phase III trial of neoadjuvant chemotherapy in head and neck cancer: 10-years follow-up. J Natl Cancer Inst *96*: 1714-1717, 2004.

12 Forastiere AA: Is there a role for induction chemotherapy in the treatment of head and neck cancer? J Natl Cancer Inst *96(22)*: 1647-1649, 2004.

13 Adelstein DJ and LeBlanc M: Does induction chemotherapy have a role in the management of locoregionally advanced squamous cell head and neck cancer? J Clin Oncol *24*: 2624-2628, 2006.

14 Psyrri A, Kwong M, DiStasio S, Lekakis L, Kassar M, Sasaki C, Wilson LD, Haffty BG, Son YH, Ross, DA, Weinberger PM, Chung GG, Zelterman D, Burtness BA and Cooper DL: Cisplatin, fluorouracil and leucovorin induction chemotherapy followed by concurrent cisplatin chemoradiotherapy for organ preservation and cure in patients with advanced head and neck cancer: long-term follow up. J Clin Oncol *22*: 3061-3069, 2004.

15 Giralt JL, Gonzalez J, del Campo JM, Maldonado J, Sanz X, Pamias J, Eraso A, Bescos S and Raspall G: Preoperative induction chemotherapy followed by concurrent chemoradiotherapy in advanced carcinoma of the oral cavity and oropharynx. Cancer *89(5)*: 939-945, 2000.

16 Tsao AS, Garden AS, Kies MS, Morrison W, Feng L, Lee JJ, Khuri F, Zinner R, Myers J, Papadimitrakopoulou V, Lewin J, Clayman GL, Ang KK and Glisson BS: Phase I/II study of docetaxel, cisplatin and concomitant boost radiation for locally advanced squamous cell cancer of the head and neck. J Clin Oncol *24(25)*: 4163-4169, 2006.

17 Hitt R, Paz-Ares L, Brandariz A, Castellano D, Pena C, Millan JM, Calvo F, Ortiz de Urbina D, Lopez E, Alvarez-Vicent JJ and Cortés-Funes H: Induction chemotherapy with paclitaxel, cisplatin and 5-fluorouracil for squamous cell carcinoma of the head and neck: long term results of a phase II trials. Ann Oncol *13*: 1665-1673, 2002.
18 Hitt R, Lopez-Pousa A, Martinez-Trufero J, Escrig V, Carles J, Rizo A, Isla D, Vega ME, Martì JL, Lobo F, Pastor P, Valenti V, Belòn J, Sanchez MA, Chaib C, Pallarés C, Anton A, Cervantes A, Paz-Ares L and Cortés-Funes H: 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 *23*: 8636-8645, 2005.
19 Calais G, Pointreau Y and Alfonsi M: Randomized phase III trial comparing induction chemotherapy using cisplatin (P) fluorouracil (F) with or without docetaxel (T) for organ preservation in hypopharynx and larynx cancer. Proc ASCO J Clin Oncol Suppl *24*: 5506 (abstr 18s), 2006.
20 Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, Jones CU, Sur R, Raben D, Jassem J, Ove R, Chies MS, Baselga J, Youssoufian H, Amellal N, Rowinsky EK and Ang KK: Radiotherapy plus cetuximab for squamous cell carcinoma of head and neck. N Eng J Med *354*: 567-578, 2006.
21 Miller AB, Hoogstroten B, Staquet M and Winkler A: Reporting results of cancer treatment. Cancer *47(1)*: 207-214, 1981.
22 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubistein L, Verweij J, VanGlabbeke M, VanOosterom AT, Cristian MC and Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst *92(3)*: 205-215, 2000.
23 Vermund H, Boysen M, Brandenburg JH, Evensen J, Jacobsen AB, Kaalhus O, Tausjo J, Thorud E, Wiley AL and Winther F: Primary irradiation, surgery or combined therapy in squamous cell carcinoma of the larynx: a comparison of treatment results from two centers. Acta Oncol *29*: 489-503, 1990.
24 Pfister DG, Laurie SA, Weinstein GS, Mendenhall WM, Adelstein DJ, Ang KK, Clayman GL, Fisher SG, Forastiere AA, Harrison LB, Lefebvrie JL, Leupold N, List MA, O'Malley BO, Patel S, Posner MR, Schwartz MA and Wolf GT: American Society of Clinical Oncology practice guideline for the use of larynx-preservation strategies in the treatment of laryngeal cancer. J Clin Oncol *24(22)*: 1-10, 2006.
25 Cmelak AJ, Murphy BA and Burkey BA: Induction chemotherapy (IC) followed by concurrent chemoradiation (CCR) for organ preservation (OP) in locally advanced squamous head and neck cancer (SHNC): results of a phase II trial. Proc ASCO J Clin Oncol *Suppl 22*: 501 (abstr 2016), 2003.

Received October 29, 2007
Revised January 15, 2008
Accepted February 12, 2008