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ORIGINAL ARTICLE

Weekly cisplatin with radiotherapy for locally advanced head and neck squamous cell carcinoma

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Summary

Purpose: *Although commonly used for the treatment of locally advanced head and neck squamous cell carcinoma (HNSCC) concomitant radio-chemotherapy (RT-CT) with weekly cisplatin has not been definitely studied. We conducted a single centre retrospective study with the aim to evaluate efficacy and acute toxicity of definitive concomitant RT-CT with 40 mg/m² weekly cisplatin in patients with locally advanced HNSCC with a particular emphasis on RT modality (conventional or accelerated) and dose of cisplatin delivered.*

Methods: *One hundred and twelve consecutive patients were included. They were given cisplatin 40 mg/m²/week concomitantly with conventionally fractionated (CFRT) (N=33) or accelerated (ART) (N=79) RT.*

Results: *RT was delivered according to the treatment plan in 104 patients and full dose was given to 107 patients. A median cumulative cisplatin dose of 240 mg/m² was administered to patients treated with CFRT and of 200 mg/m² to those treated with ART. Overall complete response rate was 81.3%. With a median follow up of 38.4 months, median overall survival (OS) was 75 months, not influenced by RT type or cisplatin dose received. The most clinically significant grade 3 or 4 acute toxicities were stomatitis (35.7%), neutropenia (25%), anemia (12.5%) and acute kidney injury (5.4%).*

Conclusions: *Our study shows that a median cumulative dose of 200 mg/m² cisplatin can be safely administered using a weekly regimen to patients treated with concomitant RT (CFRT or ART). Efficacy results and toxicity compare favorably with those described with triweekly cisplatin RT-CT, suggesting that a randomized comparison should be undertaken.*

Key words: *chemotherapy, head and neck cancer, radio-chemotherapy, radiotherapy, squamous cell carcinoma, weekly cisplatin*

Introduction

RT-CT is a commonly accepted standard treatment in locally advanced HNSCC. The updated MACH-NC (Meta-Analysis of Chemotherapy in Head and Neck Cancer) has shown that the addition of chemotherapy administered concomitantly with RT provides a 6.5% absolute OS benefit as compared to RT alone [1]. A number of platinum-based chemotherapy regimens has been used but cisplatin monotherapy at 100 mg/m² given on days 1, 22 and 43 has been used in most randomized trials although this regimen is toxic and the third dose is omitted in up to 40% of the cases [2-5]. Weekly administration of 40 mg/m² cisplatin with conventional [6-9] or with altered fractionation [10-13] definitive RT has been reported and is common practice for large groups such as DAHANCA (Danish Head and Neck Cancer). It might allow an increased cisplatin dose intensity with a possibly reduced toxicity. Because it also allows outpatient treatment administration with

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good tolerance, this regimen is routinely used in our institution.

This retrospective study aimed at evaluating the efficacy and acute toxicity of concomitant RT-CT with 40 mg/m^2 weekly cisplatin in an unselected set of consecutive patients with locally advanced HNSCC with particular emphasis on RT modality (conventional or accelerated) and dose of cisplatin administered.

Methods

Patients

All patients with locally advanced HNSCC treated with RT-CT at the University Hospital of Liege between February 2007 and April 2015 were retrospectively reviewed. Only patients with locally advanced non-metastatic HNSCC (American Joint Committee on Cancer (AJCC) Stage III and IV) who were planned for definitive concurrent cisplatin-based RT-CT were included. Nasopharyngeal carcinomas and patients treated with neoadjuvant or adjuvant chemotherapy were excluded. A total of 116 patients fulfilled these criteria but 4 patients were excluded because of insufficient or missing follow-up data, leaving a total of 112 patients available for analysis.

This study was approved by the Ethics Committee of the University Hospital of Liège.

Data collection

Data concerning disease site, clinical stage (AJCC staging, 2010), RT and treatment details were collected. Tumors from the oropharynx were assessed for human-papilloma virus (HPV) status using p16INK4A immunohistochemistry expression on primary tumor sample [14]. Toxicity was recorded according to Common Terminology Criteria of Adverse Events (CTCAE v.4.02). Follow up data were collected until October 2015.

Radiotherapy

From February 2007 until May 2010, definitive RT was delivered using a 3D conformal technique. Patients were treated with CFRT and received 70 Gy in 35 fractions of 2 Gy/day over 7 weeks with sequential boost. From May 2010, ART was delivered using an intensity-modulated radiation therapy (IMRT) technique with concomitant boost to reach a total dose of 70 Gy in 30 fractions of 2.33 Gy/day over 6 weeks.

Chemotherapy

Weekly 40 mg/m^2 cisplatin for 6 or 7 weeks depending on the RT type was given starting on day 1 of RT. The intended maximum total cisplatin dose to be administered was 280 mg/m^2 for patients treated with CFRT and 240 mg/m^2 for patients treated with ART. Intravenous hydration was given before (1.5 litre 0.9 % saline over 4 hours) and after (1 litre 0.9% saline over 3 hours) cisplatin perfusion. 5HT3 antagonists and dexamethasone were given as antiemetic prophylaxis. Minimum requirements for cisplatin administration were creatinine clearance ≥ 60 ml/min, neutrophils ≥ 1 500/mm^3, platelet count ≥ 100 000/mm^3. Chemotherapy was administered or held without dose reduction or carboplatin shift. The regimen was administered on an outpatient basis and patients were evaluated weekly during the treatment period.

Response assessment and follow-up

At baseline, all patients underwent a routine staging procedure consisting of clinical examination, chest X-ray or CT scan, head and neck CT or MRI scan, tumor biopsy, 18F-FDG PET-scan and routine laboratory tests. Response to therapy was assessed by physical examination, fiberoptic nasolaryngoscopy and imaging of the head and neck 6 to 8 weeks (CT scan) and, if required, 10 to 12 weeks (18F-FDG PET-scan) after completion of therapy.

Complete response (CR) was defined as clinical and radiological disappearance of all lesions. In case of suspected residual neck disease, salvage surgery with complete lymph node dissection was performed. If no evidence of residual disease was observed (i.e. pathological complete response (pCR), patients were considered in CR after RT-CT. Partial response (PR) was defined by at least 50% decrease in the sum of the lesion diameters. Progressive disease (PD) was defined by an increase of at least 20% in the sum of diameters of lesions, or when a new lesion appeared. Patients not meeting the CR, PR or PD criteria were considered as having stable disease (SD).

Statistics

Survival analyses were done using the Kaplan-Meier method and all estimates were calculated from the date of diagnosis till the defined event if any or until the last follow-up or death. Progression-free survival (PFS) was defined as the time from diagnosis until tumor relapse/progression or death from any cause. OS was defined as the time from diagnosis until death due to any cause.

Disease-free survival (DFS) and locoregional relapse free survival (LRRFS) were calculated in patients in CR after RT-CT. DFS was defined as the time from diagnosis until tumor relapse or death from any cause. LRRFS was defined as the time between diagnosis and local or regional relapse. The log-rank (Mantel-Cox) test and the computed hazard ratio (HR) were used to compare the curves. Median follow up was computed by the reverse Kaplan-Meier method. P values <0.05 were considered significant.

Statistical analyses were performed using GraphPad Prism for Windows (GraphPad Software Inc, v5, 2007).

Results

Patient characteristics

One hundred twelve consecutive patients who were treated with RT-CT for locally advanced HNSCC between February 2007 and April 2015 at the University Hospital of Liege were enrolled in the study. Patient characteristics are summarized in Table 1.

Treatment delivered

All patients received definitive RT-CT either with CFRT (N=33) or ART (N=79). RT was delivered according to the treatment plan in 104 patients (92.9%). It was delayed in 4 patients due to social reasons, and in 4 patients due to adverse events (hematologic toxicity, infection, weight loss and gastric perforation due to ulcer). Full dose RT was achieved in 107 patients (95.5%) and median overall treatment times were 50 days (range 45-59) for CFRT and 43 days (range 39-69) for ART.

Detailed cisplatin treatment administered is described in Table 2. Thirty-four patients (30.3%) managed to complete the full treatment planned (6 or 7 cycles, depending on the RT modality). Median total dose of cisplatin was 200 mg/m^2 (range 40-280) for the whole population, 240 mg/m^2 (range 120-280) for patients treated with CFRT and 200 mg/m^2 (range 40-240) for patients treated with ART. Globally, 66% of the patients received ≥ 200 mg/m^2 of cisplatin. Reasons leading to cancel a dose of cisplatin were renal function deterioration, neutropenia, thrombocytopenia or clinical function deterioration due to severe stomatitis.

Response evaluation (Figure 1)

Among 33 patients treated with CFRT and CT, 18 were considered as CR at first evaluation while 15 were suspected to harbor residual neck disease. Of them, 3 were unfit for salvage treatment but 12 underwent salvage surgery and no residual disease (pCR) was found in 9 of them who were therefore considered as CR after RT-CT. Three patients had residual disease completely removed.

Among 79 patients treated with ART and CT, 43 were in CR at first evaluation while 36 were not. Six patients were unfit for salvage treatment. Thirty patients underwent neck dissection and 21 had no residual tumor identified (pCR). Seven patients had residual disease completely removed with clear margins while margins were involved in the remaining 2 patients.

Table 1. Patient and disease characteristics (N=112)

Characteristics	*N*	*%*
Age (years)		
Median	58	
Range	43 - 71	
Sex		
Male	83	74.1
Female	29	25.9
Primary site		
Oropharynx	67	59.8
Hypopharynx	30	26.8
Larynx	11	9.8
Unknown	4	3.6
T stage		
T1	26	23.2
T2	40	35.7
T3	23	20.5
T4	18	16.1
Tx	5	4.5
N stage		
N0	3	2.7
N1	25	22.3
N2	78	69.6
N3	6	5.4
Clinical stage (2010 AJCC staging)		
III	26	23.2
IVA	79	70.5
IVB	7	6.3
Addiction		
Smoking ≥ 20 pack-year	103	92
Alcohol consumption	80	71.4
Co-addiction	79	70.5
No addiction	8	7.1
Oropharynx HPV status		
Positive	38	56.7
Negative	29	43.3

HPV: human papillomavirus

Overall CR rate was 81.3% and was not influenced by the type of RT (81.8 vs 81%, p=0.92, CFRT vs ART, respectively).

Survival analysis

With a median follow up of 38.4 months (range 4.5-94.6) for all patients, median OS was 75 months and 2-year OS was 71.5 % (95%CI: 61.5-79.3) for the entire patient population. No difference in OS was observed between patients who

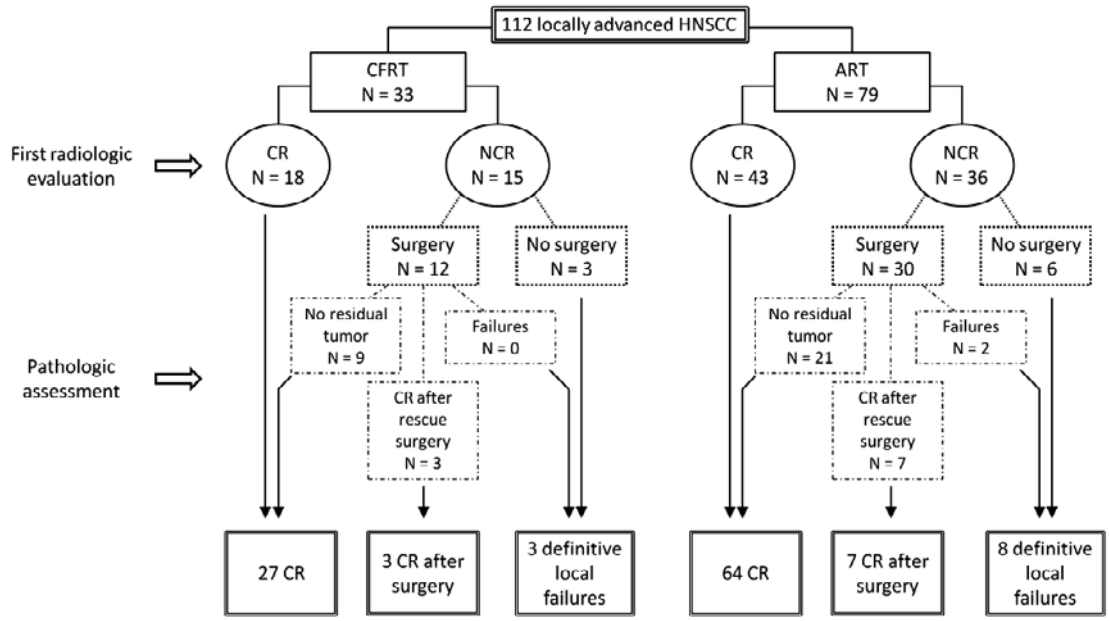

Figure 1. Response evaluation. ART: accelerated radiotherapy, CFRT: conventionally fractionated radiotherapy, CR : complete response, HNSCC : head and neck squamous cell carcinoma, NCR : non complete response

Table 2. Chemotherapy characteristics according to radiotherapy modality

Characteristics	*CFRT 35 fractions (N = 33)*		*ART 30 fractions (N = 79)*	
	N	%	*N*	%
Number of cisplatin cycles (mg/m^2)				
1 (40)	-	-	3	3.8
2 (80)	-	-	3	3.8
3 (120)	2	6.1	8	10.1
4 (160)	5	15.1	17	21.5
5 (200)	9	27.3	24	30.4
6 (240)	7	21.2	24	30.4
7 (280)	10	30.3	-	-
Cisplatin, total dosing (mg/m^2)				
< 200	7	21.2	31	39.2
≥ 200	26	78.8	48	60.8

had received ≥200 mg/m^2 or <200 mg/m^2 cisplatin (88.6 vs 75.1 months respectively, p=0.54; (Figure 2). Similarly, OS was not affected by RT type (72.8 months vs not reached (NR), p=0.2, CFRT vs ART, respectively).

The median PFS was 75 months and 2-year PFS was 67% (95%CI:56.8-75.3). Similarly, neither total chemotherapy dose nor RT modality resulted in modified PFS.

Among the 67 patients with oropharyngeal cancer, a better survival was noted for those with HPV-positive tumors (median OS : NR vs 24.7 months, p=0.0016; median PFS : NR vs 19.2 months, p=0.0005; HPV-positive vs HPV-negative respectively) (Figure 3). Two and 3-year OS were 89.1% and 89.1% for HPV-positive patients and 54.2% and 49.7% for HPV-negative patients.

Among 91 patients in CR, 2 experienced local relapse, 6 distant relapse and 2 both locoregional and distant relapse. Median DFS was 88.6 months and 2-year DFS 76.2% (95%CI:65.1-84.2). Median LRRFS was NR and 2-year LRRFS was 95.4% (95% CI: 86.4-98.5).

Among 10 patients with totally resected persistent neck disease at salvage surgery and never considered in CR, 6 were alive and free of disease

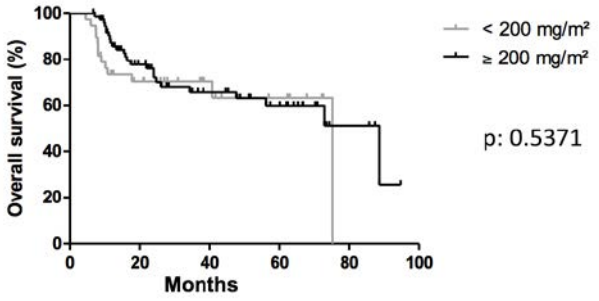

Figure 2. Overall survival of patients by total dose of cisplatin received (< 200 vs ≥ 200 mg/m^2).

Table 3. Acute treatment-related toxicities (according to CTCAE v.4.02 if applicable)

	Toxicity grade		
Acute toxicity	*3* *N (%)*	*4* *N (%)*	*All (grade 3 and 4)* *N (%)*
Anemia	14 (12.5)	-	14 (12.5)
Neutropenia	21 (18.7)	7 (6.3)	28 (25)
Thrombocytopenia	6 (5.4)	-	6 (5.4)
Acute kidney injury	5 (4.5)	1 (0.9)	6 (5.4)
Nausea / vomiting	8 (7.1)	-	8 (7.1)
Mucositis	38 (33.9)	2 (1.8)	40 (35.7)
Skin toxicity	2 (1.8)	-	2 (1.8)
Infection	10 (8.9)	-	10 (8.9)
Osteoradionecrosis	4 (3.6)	-	4 (3.6)
Tube feeding			53 (47.3)
Tube feeding before start of treatment			4 (3.6)
Total parenteral nutrition			6 (5.4)

at follow-up ranging from 22.2 to 87.4 months; the remaining 4 patients died at follow up ranging from 7.9 to 72.8 months from unknown cause (N=1), metastasis (N=1) or secondary cancer (N=2).

Acute toxicity

The main acute grade 3 and grade 4 toxicities are described in Table 3. Forty patients (35.7%) suffered grade 3 or grade 4 acute stomatitis and 60 (53.6%) experienced at least grade 2 acute stomatitis. Tube feeding (TF) or total parenteral nutrition (TPN) was needed in 56.3% of the patients, regardless of RT fractionation. Six patients (5.4%) remained TF-dependant 6 months after the end of RTCT.

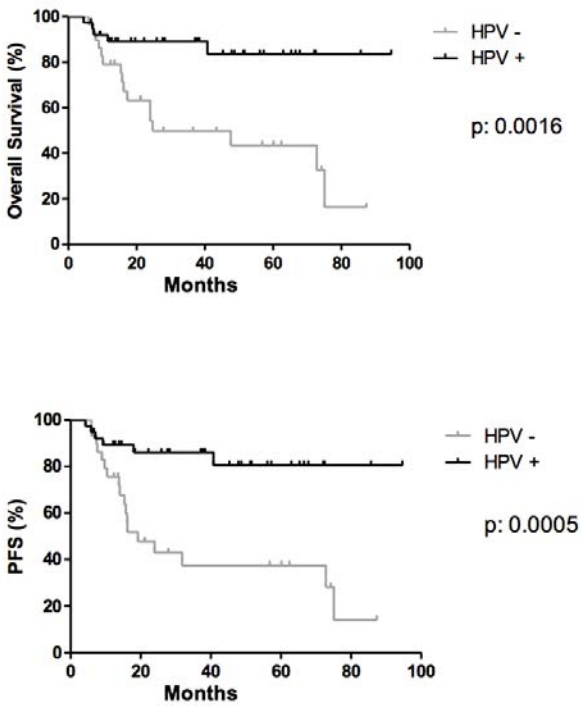

Figure 3. Overall survival and progression free survival (PFS) according to HPV status for 67 patients with oropharyngeal cancer.

Grade 2 acute renal toxicity was noted in 42 (37.5%) patients and could be overcome with increased hydration. Respectively, 5 patients and 1 patient experienced grade 3 or grade 4 renal toxicity but no patient required dialysis therapy.

Anemia was the most common haematological toxicity with grade 2 in 49 patients and grade 3 in 14 patients. Neutropenia was not uncommon leading to infectious complications in 10 patients and contributing with thrombocytopenia, acute renal toxicity and severe stomatitis to CT holding in 67 patients. However, some of them had CT held because of multiple reasons and another 11 patients because of other unlisted causes.

Twelve cases (10.7%) of osteoradionecrosis of the jaw, 8 grade 2 and 4 grade 3, were reported irrespective of RT modality. No patient was pretreated with bone targeting agent.

During the course of treatment and the 8 following weeks 64% of the patients required hospitalization for reasons such as dysphagia, pain control, neutropenic fever, dehydration with acute renal injury or because their social situation prevented them from living alone at home.

Table 4. Relevant studies using weekly or 3-weekly cisplatin-based RT-CT

Study	*Study design*	*N*	*Cisplatin regimen mg/m²*	*Median follow up (months) (*: for surviving patients only)*	*Median OS (months)*	*CR rate %*	*2-year OS %*
The present study	Retrospective Monocentric study	112	40 - qw	38.37	75	81.25	71.50
Adelstein et al. [2]	Prospective, phase III Randomized trial Multicentric study	87	100 - q3w	41	19.1	40.20	37 (3 yr)
Ang et al. [23]	Prospective, phase II Multicentric study	76	100 - q3w	26.4*	NR	83	71.60
Beckmann et al. [13]	Prospective, phase I-II Monocentric study	37	40 - qw	24	36	73	67
Driessen et al. [12]	Retrospective Monocentric study	106	40 - qw	34	-	-	61 (3 yr)
Espeli et al. [30]	Retrospective Monocentric study	40	40 - qw	20.4	22.8	-	51
		54	100 - q3w	38.4	51.6	-	78
Fayette et al. [34]	Retrospective Monocentric study	165	40 - qw	73 (for the entire study population)	-	-	59.6 (3 yr)
		97	100 - q3w		-	-	71.3 (3 yr)
Forastiere et al. [5]	Prospective, phase III Randomized trial	172	100 - q3w	45.6*	-	-	74
Gupta et al. [24]	Retrospective Monocentric study	264	30 - qw	17	-	-	-
Ho et al. [18]	Retrospective Monocentric study	24	33 - 40 - qw	26	-	87.5	-
		27	80 - 100 - q3w	49	-	74.1	-
Homma et al. [6]	Retrospective Monocentric study	53	40 - qw	29	-	80.6 – 88.7 (primary neck disease)	93.7
Kang et al. [36]	Retrospective Monocentric study	35	30 - qw	10.7	42.7	71.4	51.2 (3 yr)
Krstevska et al. [37]	Retrospective Monocentric study	65	30 - qw	14	15	72.3	49.7
Maguire et al. [38]	Prospective, Phase II Multicentric study	39	33 - qw	37.5	NR	79.5	80 (3 yr)
Nuyts et al. [22]	Retrospective Monocentric study	90	100 - q3w	24	-	88.9	74
Otty et al. [15]	Retrospective Monocentric study	62	40 - qw	20.1	-	88.7	64.5 (3 yr)
Rutten et al. [10]	Retrospective Monocentric study	77	40 - qw	-	-	-	66
Sharma et al. [19]	Prospective, Phase II Monocentric study Randomized trial	77	40 - qw	22	NR	80.5	62 (3 yr)
Steinmann et al. [39]	Retrospective Monocentric study	103	40 - qw	19	-	66	-
Uygun et al. [40]	Retrospective Monocentric study	20	40 - qw	12.5	-	40	-
		30	100 - q3w	12	-	50	-

NR: not reached

Discussion

A cumulative cisplatin dose ≥200 mg/m² could be administered to 66% of our patient population which is in line with results published by others using weekly schedules [8,15,16] or 3-weekly schedules and accelerated RT with concomitant boost [17]. Driessen et al. reported that 89.6% of their patients received at least 200mg/m² cisplatin, probably thanks to reduced nephrotoxicity [12]. Given the longer duration of RT when CFRT was used, median cisplatin total dose was higher for these patients than when ART was used. However, with a median dose of 200 mg/m² our patients received a similar or higher median dose than those in other series [6] and a higher dose than reported by Ho et al. (180 mg/m²) for patients treated with a 3-weekly schedule [18]. This difference was reported in RTOG 0129 randomized study comparing CFRT and ART with 3-weekly concomitant cisplatin where an impressive 298 mg/m² median cisplatin dose was administered with CFRT while patients treated in the ART arm received a median dose of 200 mg/m² [17], similar to ours.

Response rates (RR) after definitive RT-CT vary widely in the literature but the overall 81.3% CR rate observed in our cohort is in line with other series using various cisplatin regimens [6,15,18,19] or RT schedules [11] and compares favorably with the 40% reported in a large randomized trial [2]. A similar response rate was also reported when cetuximab was added to RT [20]. We did not observe a lower CR rate in patients who received less than 200 mg/m² cisplatin. This absence of dose-response relationship may be due to the low number of patients in this group (N=38), most of them (N=22) having received 160 mg/m², but it must be stressed that no formal dose/response relationship has been clearly demonstrated in the literature. Similarly, no difference in RR was seen between CFRT and ART groups in contrast with a report in the absence of concomitant chemotherapy where ART yielded better locoregional control [21].

Two-year OS ranging from 66 to 93.7% has been reported for patients treated with weekly cisplatin-based RT-CT [6,10,13] while whose treated with triweekly cisplatin ranged between 71.6 and 74% [5,22,23]. With 71.5% our unselected patient population compares favorably with other reports using weekly or triweekly cisplatin.

No difference in OS according to cisplatin dose could be observed in our patients. The same was true for PFS. This contrasts the reports by Otty et al. who found inferior 3 year-OS (52.6 vs 75.2%) for patients who received less than 5 weekly cycles as compared to those who received 5 or more cycles [15] and Gupta et al. who reported improved DFS for patients receiving ≥180 mg/m² [24]. We postulate that the high median dose received by our patients and therefore the low number of patients receiving less than 200 mg/m² is responsible for this observation. It is noticeable that no clear relationship between the dose of cisplatin administered and OS has been shown in the context of concurrent RT-CT. In one data set included in the MACH-NC meta-analysis [25], no positive impact of cisplatin at 140 mg/m² was seen on OS, suggesting a minimum threshold of 140 mg/m² to impact survival. This is supported by the results from RTOG 0129 where patients receiving only 1 cycle of triweekly cisplatin had a poorer OS as compared with those who received 2 or 3, while no difference was noted between those who received 2 or 3 [17]. As this threshold is close to the minimal total cisplatin dose received by all patients in our study this could also explain the absence of dose/survival relationship in our series.

In line with the results from GORTEC 99.02 study reported by Bourhis et al. [26] and from RTOG 0129 study by Ang et al. [17], no significant improvement in OS and PFS was obtained with ART in the context of concomitant CT.

Expression of p16, a surrogate marker for HPV positivity, has been shown to be a strong prognostic variable in oropharyngeal SCC [27] and HPV positivity is associated with improved survival in oropharyngeal cancer [17]. We also reported improved OS and PFS for patients with HPV-positive cancer of the oropharynx receiving definitive RT-CT. Ongoing clinical trials are expected to identify less intensive treatments for HPV-positive patients, at least for those with low risk features [28].

RT-CT for head and neck cancer leads to severe acute and late toxicities [29]. No toxic death occurred in our cohort as opposed to the 4-5% death rate reported with 3-weekly schedule in phase 3 studies [2,5]. We observed a somewhat similar all-grades renal acute toxicity (38%) as others [30] while Ho et al. reported no grade 3 renal injury neither after weekly nor 3-weekly cisplatin possibly because of an increased hydration pre- and post-chemotherapy [18]. In randomized phase 3 trials with 3-weekly cisplatin at 100 mg/m², a 4 to 8% grade 3-5 acute renal toxicity was reported [2,5,17], while we observed only 5% grade 3 in an

unselected patient population.

Although treatment was scheduled to be administered on an outpatient basis, 64% of the patients were admitted during or within 8 weeks following the end of treatment, a somewhat higher rate as compared with the 55% reported in a similar population [12], probably because of our higher incidence of acute renal toxicity (5.4 vs 0%), requiring prolonged intravenous hydration.

Despite the OS improvement obtained with the addition of cetuximab to RT as compared to RT alone [31] and with hyperfractionated as compared to conventional RT [32], concurrent cisplatin-based RT-CT remains the best therapeutic option for locally advanced head and neck cancer [1]. In patients with nasopharyngeal carcinoma, a recently published phase 2 randomized study found better quality of life and non-inferior efficacy with weekly vs triweekly cisplatin [33]. In the absence of large randomized studies comparing weekly and 3-weekly cisplatin schedules clinicians are left with scarce data to choose the best option for their individual patients with HNSCC.

Table 4 summarizes relevant studies describing outcomes of patients treated either with weekly or 3-weekly cisplatin-based RT-CT. Studies performed in the adjuvant setting or exclusively for nasopharyngeal carcinoma were not taken into account. For instance, Espeli et al. reported increased median OS (1.9 vs 4.3 years) but not PFS with 3-weekly cisplatin vs weekly cisplatin in a population of patients treated with definitive or postoperative RT-CT but weekly cisplatin was administered to older patients deemed unfit for triweekly CT [30]. Similarly a recent comparative retrospective single-centre study failed to demonstrate improved OS or PFS with triweekly cisplatin once adjusted for unbalancement between their 2 groups of patients in the definitive or adjuvant setting, a large minority (38.3%) being treated with neo-adjuvant CT [34]. Although comparison of studies is uneasy and needs caution due to the numerous biases such as patient clinical stage, HPV status, age, performance status, tobacco habits, that can affect the results, our series, one of the biggest retrospective single-centre studies confirms the favorable results published by other authors and brings data suggesting that weekly cisplatin is not inferior to 3-weekly cisplatin.

Other authors reported on comparative toxicity between weekly and 3-weekly CT and although some did report similar toxicity [18] most authors found weekly regimen less toxic including reduced nephrotoxicity [30,34,35], reduced mucositis [34] and fewer unplanned hospitalization [34,35]. However, late toxicity may be significant, particularly with ART [10].

Due to its retrospective design and the limited sample size this study does not allow to draw definitive conclusions. However, our data show that weekly cisplatin and concomitant RT can be delivered easily in an outpatient basis to a large number of unselected patients in daily practice. Although no difference in OS according to cisplatin dose could be shown probably because of a high median dose administered, the OS and CR rate observed compare favorably with those reported with triweekly or other weekly cisplatin RT-CT regimens. The threshold of cisplatin needed to improve survival as compared to RT alone remains to be determined. Only prospective randomized trials properly stratified and comparing RT with weekly cisplatin, weekly cetuximab and 3-weekly cisplatin would allow the identification of the best regimen.

Conflict of interests

The authors declare no confict of interests.

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