Eur Arch Otorhinolaryngol (2017) 274:3757–3765
DOI 10.1007/s00405-017-4687-4

HEAD AND NECK

The impact of cumulative dose of cisplatin on outcome of patients with head and neck squamous cell carcinoma

A. Al-Mamgani[1] · M. de Ridder[1,2] · A. Navran[1] · W. M. Klop[3] · J. P. de Boer[4] · M. E. Tesselaar[4]

Received: 24 April 2017 / Accepted: 21 July 2017 / Published online: 28 July 2017

Abstract Despite the wide use of cisplatin-based concomitant chemoradiotherapy (CCRT) for head and neck squamous cell carcinoma (HNSCC), data on the optimal regimen and cumulative dose are scarce and frequently conflicting. We aimed to evaluate the compliance and the impact of the cumulative dose of cisplatin on overall survival (OS), disease-free survival (DFS), loco-regional control (LRC), and distant-metastasis-free survival (DMFS) in a retrospective study. Between 2008 and 2015, 279 patients with HNSCC scheduled for CCRT (three courses of 3-week 100 mg/m^2 cisplatin) were identified. Of the whole group, 14% did not receive any cisplatin and 26% received daily cisplatin. In patients planned for three courses ($n = 167$), 56% received 3, 20% received 2, and 24% received one course. After median follow-up of 31.6 months, the actuarial OS, DFS, LRC, and DMFS rates at 3 years for patients received cumulative dose of ≥200 mg/m^2 were significantly better compared to those received <200 mg/m^2; 74 vs. 51% for OS, 73 vs. 49% for DFS, 80 vs. 58% for LRC ($p < 0.001$), and 85 vs. 76% for DMFS ($p = 0.034$). At multivariate analysis, the cumulative cisplatin dose (≥200 vs. <200 mg/m^2) was significantly predictive for OS (HR 2.05; 95% CI 1.35–3.13, $p = <0.001$). Borderline GFR (60–70 mL/min) at baseline predicts compliance for ≥two courses ($p = 0.003$). In conclusion, considerable proportion of patients did not receive all pre-planned courses of cisplatin. Patients receiving cumulative cisplatin dose ≥200 mg/m^2 had significantly better outcome than those receiving <200 mg/m^2 and cumulative dose <200 mg/m^2 might even be detrimental. These findings increased the bulk of slowly growing evidence on the optimal cumulative dose of cisplatin. Baseline GFR might predict compliance.

Keywords Cisplatin · Dose reduction · Head and neck cancer · Squamous cell carcinoma · Radiotherapy · Chemoradiotherapy

Introduction

Over 500,000 new cases with head and neck squamous cell carcinoma (HNSCC) are diagnosed worldwide annually, the majority of them with locally-advanced disease [1]. Chemoradiotherapy (CRT) is nowadays the standard of care for locally-advanced HNSCC (LA-HNSCC). The meta-analysis of chemotherapy in head and neck cancer (MACH-NC) included a total of 16,485 patients in 87 randomized trials conducted between 1965 and 2000, showed an overall survival (OS) benefit of 4.5% at 5 years; hazard ratio (HR) for death = 0.88, $p < 0.0001$ by the addition of chemotherapy to radiotherapy (RT), compared to RT alone. The meta-analysis also showed a more profound benefit of concomitant as compared to induction chemotherapy (50 trials; 9615 patients), with an absolute

✉ A. Al-Mamgani
a.almamgani@nki.nl

1 Department of Radiation Oncology, Netherlands Cancer Institute/Antoni van Leeuwenhoek, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands

2 Department of Radiation Oncology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

3 Department of Head and Neck Surgery, Netherlands Cancer Institute/Antoni van Leeuwenhoek, Amsterdam, The Netherlands

4 Department of Medical Oncology, Netherlands Cancer Institute/Antoni van Leeuwenhoek, Amsterdam, The Netherlands

OS benefit of 6.5% at 5 years in case of concomitant chemotherapy (HR for death 0.81, $p < 0.0001$). There was also a decreasing benefit from the addition of chemotherapy with increasing age ($p = 0.003$, test for trend) [2]. Regarding the type of chemotherapy, the same meta-analysis showed that OS benefit did not differ significantly between poly- and monochemotherapy. However, inferior results were seen using single-agent chemotherapy drugs other than cisplatin and, therefore, should not be recommended for the daily clinical practice.

The rationale for the addition of cisplatin to the RT is its radiosensitizing effect and the fact that radiation- and cisplatin-related toxicities are mostly not overlapping. Most institutions use the 3-week regimen, preferably giving a cumulative dose of 300 mg/m^2 during the course of RT. However, considerable proportion of these patients did not receive a second or third course of cisplatin [3] because of cisplatin-related toxicity such as renal insufficiency, severe gastro-intestinal symptoms, ototoxicity, and hematological toxicity.

Despite the wide use of cisplatin, data on the optimal regimen and cumulative dose are scarce and frequently conflicting. The recently published systemic review by Strojan et al. [4] supports the idea that the cumulative dose of cisplatin for HNSCC is quite important. However, no solid conclusions were drawn with regard to the optimal dose and schedule, as the currently available data are mainly collected from retrospective studies and provide, therefore, a low level of evidence. We performed a retrospective analysis on patients treated by four different dose levels of cumulative cisplatin (300, 200, 150, and 100 mg/m^2) and patients who did not receive any type of cisplatin at all (as control group). Therefore, we believe that the findings of the current study would increase the bulk of the slowly growing evidence about the cut-off cumulative dose level of concurrent cisplatin as monotherapy in combination with RT in LA-HNSCC.

Patients and methods

Between January 2008 and December 2015, 279 consecutive patients with histologically proven primary squamous cell carcinoma of the oropharynx, hypopharynx, and larynx scheduled for concomitant chemoradiotherapy (CCRT) according to the institutional guidelines were identified. All patients were treated in one tertiary referral institution with curative intentions.

Pre-treatment evaluations consisted of complete history and physical examination, including examination under general anesthesia. All patients had a chest X-ray, ultrasound with fine needle aspiration cytology (FNAC) when indicated, and head and neck MRI or CT scan. P16 and P53 staining was performed on the tissue blocks obtained during examination under general anesthesia. An 18-FDG-PET was performed in all stage III/stage IV patients, and all patients were discussed at the weekly multidisciplinary head and neck tumor board. Tumor classification was done according to the seventh edition of the American Joint Commission on Cancer. Based on the joint recommendations of the multidisciplinary board, patients were scheduled for RT with or without chemotherapy. Patients will subsequently be evaluated by the medical oncologist whether they are fit enough to be planned for three courses of 3-week high dose of cisplatin. Based on our institutional guidelines, chemotherapy will be added to radiotherapy concomitantly in all patients with T3, T4, N2c, N3 disease, or any node-positive disease with extra-capsular extension, with one exception; bulky T3 laryngeal cancer will receive CRT, and patients with non-bulky T3 laryngeal cancer will be treated with RT alone. Furthermore, all patients with node-positive disease hypopharyngeal cancer, irrespective of T classification, will receive CCRT in our institution. None of these patients received induction chemotherapy.

Radiotherapy

Patients were immobilized in supine treatment position in a custom-made head-and-neck mask. For planning, contrast-enhanced CT-scan simulation was performed in all patients. The planning treatment volume (PTV) included a margin of 5 mm beyond the clinical target volume (CTV) of the primary tumor and the involved neck to account for different geometric uncertainties. All patients were treated with intensity-modulated radiotherapy (IMRT) or volumetric modulate arc therapy (VMAT). The radiation treatment consisted of 46 Gy of elective irradiation to both sides of the neck (levels II–IV in case of node-negative neck and levels I–V in case of cervical lymph node metastases), followed by a boost of 24 Gy in 12 fractions to the primary tumor and the involved nodes in case of node-positive disease, to a total dose 70 Gy.

Chemotherapy

Patients were scheduled for a 3-week intravenous high-dose cisplatin (100 mg/m^2 on days 1, 22, and 43 of radiotherapy) CCRT regimen as a hospital admission. Before and after each cisplatin infusion, patients received at least 3.5 L of saline with 60 mmol/L of KCl and 30 mmol/L of MgSO4, as well as antiemetics (aprepitant). Patients who could not receive the third course of cisplatin no further chemotherapy were given, whereas those who could not receive the second and third courses were treated by combining the RT with weekly carboplatin (AUC = 3), as from the fourth week of CCRT. Low-dose daily cisplatin was given in a daily dose of 6 mg/m^2 for 5 weeks (weeks 1–5 of RT) (cumulative dose of 150 mg/m^2). The reason

why patients did not receive any type of cisplatin schemes or received low-dose daily cisplatin or only two or one course of 100 mg/m^2 is illustrated in Fig. 1. The following baseline patient's demographics were tested for the correlation with compliance for ≥two courses of cisplatin: WHO status, serum creatinine level, glomerular filtration rate (GFR), hemoglobin level, smoking status, diabetes mellitus, and hypertension.

Follow-up

During CCRT, patients were seen twice weekly at the outpatient clinic to monitor the acute radiation- and cisplatin-related toxicities. After completion of treatment, patients were seen every 2 weeks until the acute radiation-induced toxicity had subsided. At 10–12 weeks after treatment, response evaluation was done by means of MRI or CT scan and ultrasound, with FNAC when indicated. In patients with residual disease after the (chemo)radiation, the possibility of salvage surgery will be evaluated by the head and neck surgeon. The type of surgery will depend on the site and extent of the residual disease. After the response evaluation, patients were seen at least 3 months for the first year, 4 months for the second year and 6 months thereafter. At each visit, history and clinical examination (including flexible endoscopy) were performed. In case of any doubt about the presence of recurrent disease, examination under general anesthesia will be done.

Statistical analysis

The recurrence and survival analyses were performed using the Kaplan–Meier method. Univariate testing was done by Chi square, Kruskal–Wallis or Fisher's exact test. Variables included in the univariate analysis are: age, gender, smoking, T site, T classification, N classification, AJCC stage, P16 status, ACE-27 score, extra-capsular extension, and dose of cisplatin. Multivariate survival analyses including age, gender, AJCC stage, P16 status, and dose of cisplatin was performed using the Cox regression analysis. All tests were two-sided, and P-values <0.05 were considered statistically significant. Statistical programs used were SPSS (version 22.0, IBM Chicago, IL) and STATA data analysis and statistical software (version 10.0, StataCorp LP, TX, 1996).

Results

Patient's demographics are shown in Table 1. The median follow-up of all patients is 31.6 months (range 2.1–106.3) and for those still alive at the time of the analysis ($n = 161$) is 50.8 months (range 13.1–106.3).

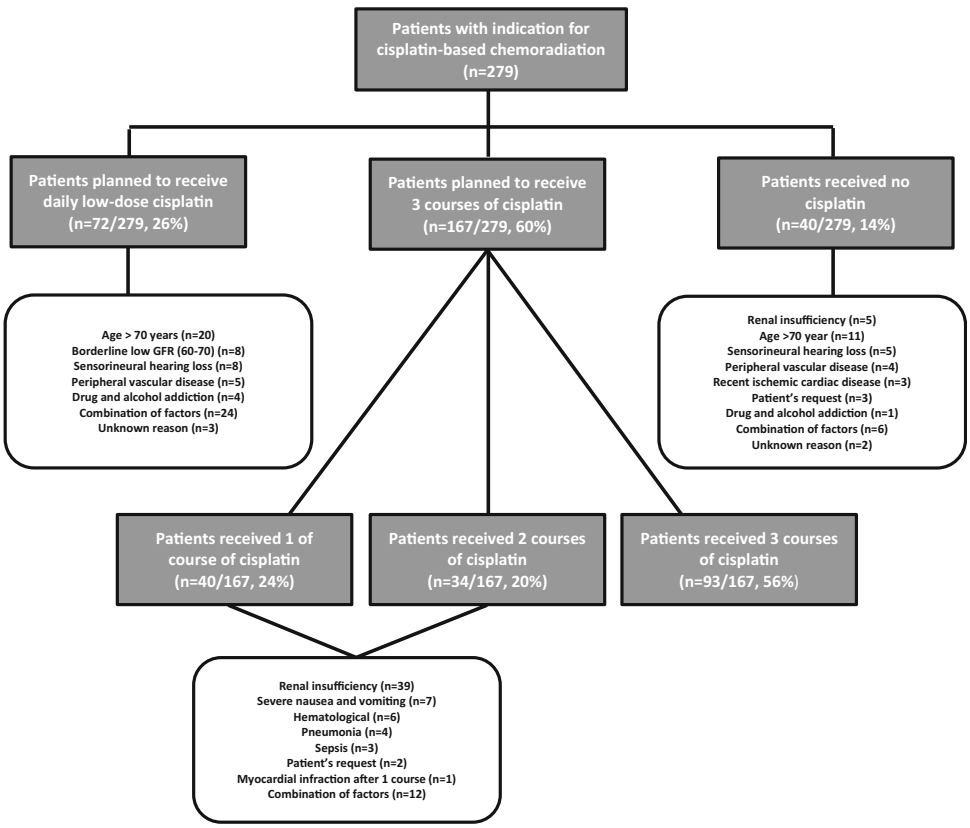

Fig. 1 Flow chart illustrating the number of patients received different schemes and dose levels of cisplatin and those who did not received any type of cisplatin and the reason why patients did not received any type of cisplatin schemes, received daily cisplatin or only two or one course of 100 mg/m^2 instead of the intended three courses of 3-week cisplatin with a total intended cumulative dose of 300 mg/m^2

Table 1 Patient's characteristics ($n = 279$)

	Number	%
Age (years)		
Median	62	
Range	37–83	
Gender		
Male	202	72.4
Female	77	27.6
Smoking		
Yes	213	76.3
No, stopped	29	10.4
Never	37	13.3
Tumor site		
Oropharynx	150	53.8
Hypopharynx	83	29.7
Larynx	46	16.5
T classification		
T1	28	10
T2	70	25.1
T3	96	34.4
T4	85	30.5
N classification		
N0	36	12.9
N1	31	11.1
N2a	12	4.3
N2b	115	41.2
N2c	70	25.1
N3	15	5.4
AJCC stage		
Stage II	11	3.9
Stage III	100	35.8
Stage IV	168	60.2
Extra-capsular extension		
Yes	81	29
No	198	71
P16 status in OPC	$n = 150$	
Positive	56	37.4
Negative	77	51.3
Unknown	17	11.3
Chemotherapy (scheme)	$n = 279$	
No cisplatin	40	14.3
Cisplatin 3 courses	93	33.3
Cisplatin 2 courses	34	12.3
Cisplatin 1 course	40	14.3
Cisplatin daily	72	25.8
Cisplatin (dose)	$n = 239$	
Cisplatin $\geq$ 200 mg/m^2	127	53.1
Cisplatin $<$ 200 mg/m^2	112	46.9

AJCC American Joint Committee on Cancer, *OPC* oropharyngeal cancer

Of the whole study population ($n = 279$), 40 patients (14%) did not receive any cisplatin whereas 72 patients (26%) received daily cisplatin. All other patients ($n = 167$) were scheduled for the three courses of 3-week cisplatin with a total intended cumulative dose of 300 mg/m^2.

Feasibility of 3-week cisplatin

Of patients who were planned for three courses of cisplatin ($n = 167$), only 93 patients (56%) received the intended three courses, 34 patients (20%) received two courses, and 40 patients (24%) received only one course of cisplatin. All patients who received one course of cisplatin received carboplatin AUC = 3 as from the fourth week of CCRT. From the tested variables, only borderline GFR (60–70 mL/min) at baseline was significantly predictive for the compliance for two or three courses. Significantly more patients with borderline GFR (60–70 mL/min) at baseline could not receive the second and the third courses as compared to those with baseline GFR > 70 mL/min (24 vs. 6%, respectively, $p = 0.003$). The correlation between compliance and other baseline characteristics were statistically not significant: WHO status ($p = 0.601$), serum creatinine level ($p = 0.335$), hemoglobin level ($p = 0.201$), smoking status ($p = 374$), diabetes mellitus ($p = 0.958$) and hypertension (0.773). Grade 3 toxicity was the most important reason why patients did not receive the second or the third course of cisplatin. The reported grade 3 toxicities in patients received 3-week intravenous high-dose cisplatin are renal insufficiency in 52%, sever nausea and vomiting in 9%, hematological in 8% and pneumonia and sepsis in 9% of patients.

Outcome

Table 2 shows the outcome of patients received different dose schemes and dose levels of cisplatin. The actuarial OS rates at 3 years were not significantly different between patients who received three or two courses (74 and 72%, respectively, $p = 0.531$). The same is true for DFS, LRC, and DMFS. The actuarial OS rates at 3 years for patients received $\geq$200 mg/m^2 (three or two courses) was significantly better as compared to those received $<$200 mg/m^2, regardless of the scheme used (74 vs. 51%, $p < 0.001$) (Table 2; Fig. 2). The actuarial rates of DFS, LRC, and DMFS at 3 years for patients received at least 200 mg/m^2 were significantly better as compared to those who received $<$200 mg/m^2 (one course of cisplatin or daily cisplatin); 73 vs. 49% for DFS, 80 vs. 58% for LRC (all $p < 0.001$), and 85 vs. 76% for DMFS ($p = 0.034$). Furthermore, no OS benefit was observed in patients who received $<$200 mg/

Table 2 Actuarial incidence of different outcome measures at 3 years, comparing different dose schemes of cisplatin

	OS (%)	*p* value	DFS (%)	*p* value	LRC (%)	*p* value	DMFS (%)	*p* value
3-Cycles cisplatin (300 mg/m^2)	74	0.531	75	0.254	83	0.104	87	0.293
2-Cycles cisplatin (200 mg/m^2)	72		66		72		79	
3-Cycles cisplatin (300 mg/m^2)	74	**0.014**	75	**0.004**	83	**0.019**	87	0.245
1-Cycles cisplatin (100 mg/m^2)	54		45		59		80	
3-Cycles cisplatin (300 mg/m^2)	74	**0.001**	75	**<0.001**	83	**<0.001**	87	**0.013**
Daily cisplatin (150 mg/m^2)	50		49		57		73	
Cisplatin ≥ 200	74	**<0.001**	73	**<0.001**	80	**<0.001**	85	**0.034**
Cisplatin < 200	51		49		58		76	
Cisplatin < 200	51	0.507	49	0.406	58	0.605	76	0.445
No chemotherapy	56		58		65		81	

Bold values indicates significant *p* values

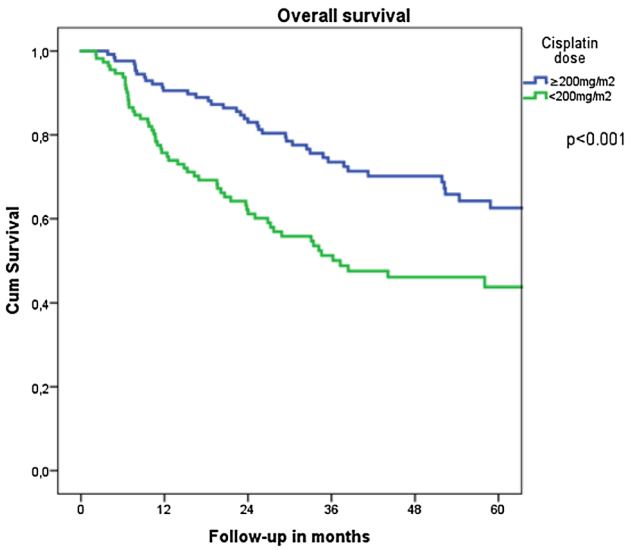

Fig. 2 Actuarial rates of overall survival at 3 years for patients received ≥200 mg/m^2 as compared to those who received <200 mg/m^2

m^2, as compared to those who did not receive any type of cisplatin (51 vs. 56%, $p = 0.507$) (Table 2; Fig. 3).

Cancer-specific survival was also significantly related to the dose of cisplatin. The actuarial cancer-specific survival at 3 years for patients received ≥200 mg/m^2, compared to those received <200 mg/m^2 were 78 and 65%, respectively ($p = 0.009$).

Table 3 shows the results of univariate and multivariate analyses using different variables to predict OS in these patients. In the multivariate analysis, the cumulative dose of cisplatin (≥200 vs. < 200 mg/m^2) was, beside P16 status, and AJCC stage, significantly predictive for OS (HR 1.79; 95% CI 1.17–2.73, $p = 0.007$). When the analysis was repeated without P16-positive patients, the dose of cisplatin retained the significant correlation with OS (HR 1.65; 95% CI 1.09–2.51, $p = 0.019$), beside the AJCC stage (HR 2.22; 95% CI 1.33–3.71, $p = 0.002$), and extracapsular extension (HR 1.73; 95% CI 1.10–2.73, $p = 0.019$).

Discussion

Despite the fact that cisplatin is the most commonly used radiosensitizer in combination with RT for LA-HNSCC for long time, data on the optimal dose and regimen are scarce and frequently conflicting [2]. However, there is slowly growing evidence that a cumulative dose level around 200 mg/m^2 might be sufficient to achieve reasonable outcome and weighted out against detrimental side effect [4]. In the current study, 2 dose levels (1 with cumulative dose <200 mg/m^2 and 1 with cumulative dose of 200 mg/m^2 or more) were evaluated and compared to a control group which was treated with RT alone. Our results are in line with the findings of recently published systemic review by Strojan et al. [4] and support the idea that a cumulative cisplatin dose of at least 200 mg/m^2 might be sufficient to achieve reasonable oncologic outcome. Furthermore, our study clearly shows that lowering the cumulative dose of cisplatin below 200 mg/m^2 may be detrimental and should not be recommended in the daily clinical practice. We found that the OS, DFS, LRC, cancer-specific survival, and DMFS of patients received only RT or a cumulative dose <200 mg/m^2, independent of the given regimen (low-dose daily cisplatin or one course of cisplatin) were significantly worse as compared to those receiving ≥200 mg/m^2 (two or three courses) (Table 2). However, the conclusion with regard to the impact of the cisplatin dose on OS should be interpreted with caution since patients received low-dose daily cisplatin or no chemotherapy might have lower OS rates at baseline because of the competing risk of death

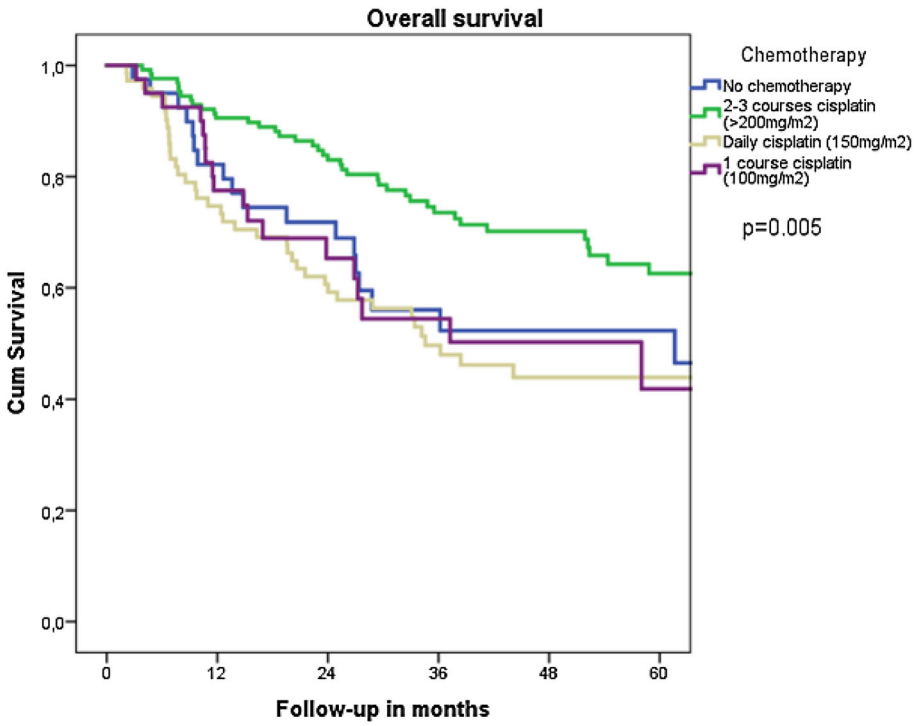

Fig. 3 Actuarial rates of overall survival at 3 years for patients received two or three courses of cisplatin as compared to those who received one course cisplatin, daily cisplatin, or no cisplatin at all

from their comorbidity. However, the impact of cumulative dose of cisplatin was very obvious for other end points not directly influenced by comorbidity, such as cancer-specific survival, LRC, and DMFS. The comorbidity score was not significantly predictive for OS in the univariate analysis. This is probably because the impact of cancer-related death on the whole survival was stronger than the risk of death from intercurrent disease, since cause-specific survival was significantly better in patients received $\geq$200 mg/m^2.

HPV-positive oropharyngeal cancer patients have better outcome, compared to the HPV-negative group.

Ang et al. [5], showed that the 3-year OS of HPV-positive oropharyngeal cancer was significantly better, compared to HPV-negative patients (82.4, vs. 57.1%; $p < 0.001$). These patients might be candidates for treatment de-intensification and lower dose of cisplatin might be sufficient to cure these patients. To exclude the possible confounding effect of better outcome of this group, we repeated the analysis without the P16-positive patients. Nevertheless, the dose of cisplatin retained the significant correlation with OS (HR 1.65; 95% CI 1.09–2.51, $p = 0.019$), beside the AJCC stage, and extra-capsular extension.

In our study, 72 patients were treated by daily cisplatin (cumulative dose 150 mg/m^2). The outcomes of these patients are in line with results from the only negative randomized study included in the MACH-NC, the study of the intergroup trial of the Eastern Cooperative Oncology Group [6], where RT in combination with weekly cisplatin dosed at 20 mg/m^2 (cumulative dose of 140 mg/m^2) was compared to RT alone. The addition of a cumulative dose of 140 mg/m2 cisplatin to RT did not significantly improve outcome, compared to 70 Gy of RT alone.

The randomized Swiss trial [7], comparing RT alone with RT in combination with two cycles of concomitant cisplatin (20 mg/m^2 on 5 days of weeks 1 and 5, rather than 100 mg/m^2 given in a single administration), reported 51 and 46% LRC and OS rates, respectively, in the CRT arm. Compared to other CRT trials, the use of this cisplatin regimen seems to reduce cisplatin-related toxicity without jeopardizing the oncologic outcome. These findings are consistent with the notion that the cisplatin radiosensitization is more dependent on the cumulative dose than on the scheme.

Our conclusions with regard to the optimal dose level are also in line with the results of the literature-based meta-analysis published by Ghi et al. [8] in an abstract mentioned in the systemic review of Strojan et al. [4]. The survival outcome of patients treated with high cumulative cisplatin dose (300 mg/m^2) was similar to those treated with cumulative cisplatin dose <300 mg/m^2. However, there was significant difference in HR for death between intermediate cumulative cisplatin dose (200–225 mg/m^2) and low cumulative cisplatin dose (<150 mg/m^2) (HR for death 0.68 and 1.04, respectively).

Since the prognosis of patients scheduled for 3-week cisplatin will depend on the ability to receive at least two courses ($\geq$200 mg/m^2), careful selection of patients

Table 3 Univariate and multivariate analyses for overall survival of the whole group and the whole group without P16-positive patients

Variables	Univariate analysis for whole group			Multivariate analysis for whole group		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	1.78	1.12–2.84	**0.015**	0.88	0.47–1.62	0.875
Gender	0.52	0.32–0.83	**0.007**	0.63	0.37–1.05	0.626
Smoking	0.63	0.40–1.02	0.059			
T site	1.98	1.37–2.87	**<0.001**[a]			
T classification	1.14	0.78–1.68	0.448			
N classification	1.96	0.99–3.87	0.053			
AJCC stage	2.53	1.67–3.84	**<0.001**	2.17	1.34–3.50	**0.002**
ACE-27	0.85	0.59–1.23	0.392			
P16 status	0.13	0.05–0.31	**<0.001**	0.18	0.07–0.44	**<0.001**
Extra-capsular extension	1.19	0.80–1.78	0.379			
Dose of cisplatin	2.02	1.35-3.01	**<0.001**	1.79	1.17–2.73	**0.007**
Variables	Univariate analysis without P16+ patients			Multivariate analysis without P16+ patients		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	1.46	0.90–2.39	0.123			
Gender	0.58	0.36–0.95	**0.032**	0.61	0.36–1.03	0.064
Smoking	1.95	0.72–5.32	0.191			
T site	1.02	0.69–1.51	0.927			
T classification	1.03	0.69–1.54	0.874			
N classification	2.09	1.05–4.13	**0.035**	1.56	0.70–3.47	0.275
AJCC stage	1.79	1.16–2.79	**0.009**	2.22	1.33–3.71	**0.002**
ACE-27	0.78	0.53–1.14	0.775			
Extra-capsular extension	1.79	1.18–2.72	**0.006**	1.73	1.10–2.73	**0.019**
Dose of cisplatin	1.68	1.11–2.55	**0.014**	1.65	1.09–2.51	**0.019**

Bold values indicates significant *p* values

HR hazard ratio, *95% CI* 95% confidence interval, *T site* tumor site, *T classification* tumor stage according to the TNM classification, *N classification* nodal stage according to the TNM classification, *AJCC* American Joint Committee on Cancer, *ACE-27* adult comorbidity evaluation score

[a] T site was not included in the multivariate analysis because of strong impact of the P-16 status on this variable

regarding their expected compliance is of utmost importance. Although no validated tools to date are available to identify patients at risk of low compliance, we investigated different baseline patient's demographics with regard to the compliance for two or three courses. The only possible predictive factor for reduced compliance is the baseline GFR. Significantly, more patients with borderline GFR (60–70 mL/min) at baseline could not receive the second and the third courses as compared to those with baseline GFR > 70 mL/min (24 vs. 6%, respectively, $p = 0.003$). The explanation might be that patients who are not able to receive two or three courses might have a latent renal insufficiency, expressed by the borderline GFR (60–70 mL/min), who subsequently decompensate after the first course of cisplatin and will not be timely recovered enough to receive the second and the third course of cisplatin. Therefore, caution is needed before 3-week cisplatin will be scheduled in patients with borderline GFR, especially in combination with other comorbidities were silent renal insufficiency might be elicited, such as diabetes, hypertension, or heavy smoking as indirect indicators of microvascular disease. Furthermore, there is slowly growing evidence that sarcopenia in cancer patients might be cisplatin dose-limiting factor. Sacropenic cancer patients seem to have increased incidence of chemotherapy-related toxicity and a shorter time to tumor progression [9, 10]. By identifying these patients at risk of low cisplatin compliance, other alternative treatment options might be considered instead of 3-week cisplatin. Several studies have shown that renal toxicity might be reduced and compliance might be improved by modulating the cisplatin scheme. Although different retrospective studies comparing the compliance of weekly with 3 weeks showed conflicting results [11–15], some of studies showed that nephrotoxicity

and mucositis were significantly higher with 3-week cisplatin, compared to the weekly scheme [9, 10]. The randomized trial conducted by the Swiss group [7] showed that two cycles of cisplatin were well tolerated and associated with reduced renal toxicity without jeopardizing oncologic outcomes.

Another strategy for reducing chemotherapy-related toxicity is the replacement of cisplatin with cetuximab. Bonner et al. [16] confirmed in randomized trial that the addition of cetuximab to primary RT in patients with locally-advanced HNSCC significantly improves median survival and OS at 5 years as compared to RT alone. This is meanwhile the standard of care in many institutions in patients who are unfit for cisplatin. The only randomized trial conducted [17] to compare the outcome of RT with concomitant cisplatin vs. concomitant cetuximab was, unfortunately, discontinued early due to slow accrual. However, the published results on the treated patients showed lowered compliance by the addition of cetuximab to RT and increased acute toxicity while the outcomes of both arms were comparable. The study raised the importance of appropriate selection of patients for treatment with cetuximab. The RTOG-0522 trial randomly assigned patients with locally-advanced HNSCC to receive radiation and cisplatin without (arm A) or with (arm B) cetuximab. Cisplatin radiation combined with cetuximab, versus cisplatin-radiation alone, resulted in more frequent interruptions in radiation therapy and more grade 3–4 radiation-related toxicity without improvement of OS, DFS, LRC, or DMFS [18].

Another promising approach to improve outcome is decreasing radioresistance by the concomitant use of new radiosensitizers, for example, drugs inhibiting DNA repair, such as poly ADP ribose polymerase (PARP) inhibitors [19]. Currently, a phase I trial is ongoing at our institution to investigate the safety and tolerability of RT with concurrent olaparib in stage II–III laryngeal and stage II–III HPV-negative oropharyngeal cancer. Another study on novel radiosensitizers in HNSCC is the TRYHARD study [20]. In this placebo-controlled randomized phase II study, the addition of lapatinib (a dual tyrosine-kinase inhibitor) to platinum-based CRT in HPV-negative locally-advanced HNSCC is evaluated.

Different studies are nowadays conducted to investigate the benefit of adding immunotherapy to RT in patients with recurrent or metastatic HNSCC. Ferris et al. [21] published the results of the randomized trial comparing the efficacy of nivolumab (human IgG4 anti-PD-1 monoclonal antibody) among patients with recurrent and metastatic HNSCC who had disease progression after platinum-based chemotherapy, compared to standard, single-agent systemic therapy (methotrexate, docetaxel, or cetuximab). The treatment with nivolumab resulted in significantly longer survival, compared to treatment with the standard therapy. This treatment option might also be promising for the primary treatment of HNSCC, especially when low cisplatin compliance is expected, such in case of sacropenic HNSCC or patients with borderline GFR at baseline. Several ongoing prospective studies are investigating this approach at the primary setting by combining the radiation treatment with anti-PD-1 or anti-PDL-1 (programmed death-ligand 1). At our institution, in patients unfit for cisplatin-based chemoradiotherapy, the RT will be given in combination with weekly cetuximab and 2-week avelumab (anti-PDL-1) (programmed death-ligand 1) followed by adjuvant 2-week avelumab for 6 months. The results of these studies need to be awaited.

Conclusions

Of all patients scheduled for three courses of cisplatin, 24% received only one course of cisplatin. The outcome of patients received $\geq$200 mg/m^2 was significantly better compared to patients received <200 mg/m^2, regardless of the cisplatin regimen. Patients receiving a cumulative dose <200 mg/m^2 (one course or daily cisplatin) have comparable outcome to those who did not receive any chemotherapy at all. The findings of the current study increased the bulk of the slowly growing evidence about the cut-off dose level of concurrent cisplatin as monotherapy in LA-HNSCC of around 200 mg/m^2 and support the idea that a cumulative dose of cisplatin <200 mg/m^2 might be detrimental and should not be recommended.

Although no validated tools are available to date to identify patients with poor compliance, caution is needed before 3-week cisplatin will be scheduled in patients with borderline GFR (60–70 mL/min), especially in combination with other comorbidities which might elicit latent renal insufficiency, such as diabetes, hypertension, heavy smoking, and atherosclerotic disease. However, this tool should be validated in prospective clinical studies.

Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

Funding None of the authors have received any funding.

Ethical approval This article does not contain any experimental study with human participants performed by any of the authors. For this type of work, formal consent is not required due to its retrospective nature.

References

1. Parkin DM, Ferlay J, Curado MP, Bray F, Edwards B, Shin HR, et al (2014) Cancer incidence in five continents volume I to X.

IARC Cancer Base No. 12. IARC Press (http://gco.iarc.fr). Also at http://seer.cancer.gov/statfacts/html/oralcav.html. Accessed 1 Feb 2017
2. Pignon JP, Le Maitre A, Maillard E, Bourhis J (2009) Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 92:4–14
3. Hoek J, Bloemendal KM, van der Velden LA, van Diessen JN, van Werkhoven E, Klop WM et al (2016) Nephrotoxicity as a dose-limiting factor in a high-dose cisplatin-based chemoradiotherapy regimen for head and neck carcinomas. Cancers (Basel) 8:21
4. Strojan P, Vermorken JB, Beitler JJ, Saba NF, Haigentz M Jr, Bossi P et al (2016) Cumulative cisplatin dose in concurrent chemoradiotherapy for head and neck cancer: a systematic review. Head Neck 38:2151–2158
5. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF et al (2010) Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 363:24–35
6. Quon H, Leong T, Haselow R, Leipzig B, Cooper J, Forastiere A (2011) Phase III study of radiation therapy with or without cisplatinum in patients with unresectable squamous or undifferentiated carcinoma of the head and neck: an intergroup trial of the Eastern Cooperative Oncology Group (E2382). Int J Radiat Oncol Biol Phys 81:719–725
7. Huguenin P, Beer KT, Allal A, Rufibach K, Friedli C, Davis JB et al (2004) Concomitant cisplatin significantly improves loco-regional control in advanced head and neck cancers treated with hyperfactionated radiotherapy. J Clin Oncol 22:4665–4673
8. Ghi MG, Paccagnella A, Floriani I, Garavaglia D (2011) Concomitant chemoradiation in locally advanced head and neck squamous cell carcinoma: a literature-based meta-analysis on the platinum concomitant chemotherapy. J Clin Oncol 29(suppl):5534
9. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L et al (2008) Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol 9:629–635
10. Prado CM, Baracos VE, McCargar LJ, Reiman T, Mourtzakis M, Tonkin K et al (2009) Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clin Cancer Res 15:2920–2926
11. Espeli V, Zucca E, Ghielmini M, Giannini O, Salatino A, Martucci F et al (2012) Weekly and 3-weekly cisplatin concurrent with intensity-modulated radiotherapy in locally advanced head and neck squamous cell cancer. Oral Oncol 48:266–271
12. Geeta SN, Padmanabhan TK, Samuel J, Pavithran K, Iyer S, Kuriakose MA (2006) Comparison of acute toxicities of two chemotherapy schedules for head and neck cancers. J Cancer Res Ther 2:100e4
13. Uygun K, Bilici A, Karagol H, Caloglu M, Cicin I, Aksu G et al (2009) The comparison of weekly and three weekly cisplatin chemotherapy concurrent with radiotherapy in patients with previously untreated inoperable non-metastatic squamous cell carcinoma of the head and neck. Cancer Chemother Pharmacol 64:601–605
14. Tsan DL, Lin CY, Kang CJ, Huang SF, Fan KH, Liao CT et al (2012) The comparison between weekly and three-weekly cisplatin delivered concurrently with radiotherapy for patients with postoperative high-risk squamous cell carcinoma of the oral cavity. Radiat Oncol 7:215
15. Rades D, Kronemann S, Meyners T, Bohlen G, Tribius S, Kazic N et al (2011) Comparison of four cisplatin-based radiochemotherapy regimens for nonmetastatic stage III/IV squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 80:1037–1044
16. Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK et al (2010) Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol 11:21–28
17. Magrini SM, Buglione M, Corvò R, Pirtoli L, Paiar F, Ponticelli P et al (2016) Cetuximab and radiotherapy versus cisplatin and radiotherapy for locally advanced head and neck cancer: a randomized phase II trial. J Clin Oncol 34:427–435
18. Ang KK, Zhang Q, Rosenthal DI, Nguyen-Tan PF, Sherman EJ, Weber RS et al (2014) Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. J Clin Oncol 32:2940–2950
19. Verhagen CV, de Haan R, Hageman F, Oostendorp TP, Carli AL, O'Connor MJ et al (2015) Extent of radiosensitization by the PARP inhibitor olaparib depends on its dose, the radiation dose and the integrity of the homologous recombination pathway of tumor cells. Radiother Oncol J Eur Soc Ther Radiol Oncol 116:358–365
20. Harrington K, Berrier A, Robinson M, Remenar E, Housset M, de Mendoza FH et al (2013) Randomised Phase II study of oral lapatinib combined with chemoradiotherapy in patients with advanced squamous cell carcinoma of the head and neck: rationale for future randomized trials in human papilloma virus-negative disease. Eur J Cancer 49:1609–1618
21. Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L et al (2016) Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med 375:1856–1867