Cumulative cisplatin dose in concurrent chemoradiotherapy for head and neck cancer: A systematic review

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Accepted 25 February 2015
Published online 14 July 2015 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/hed.24026

ABSTRACT: *Background.* The optimal cumulative dose and timing of cisplatin administration in various concurrent chemoradiotherapy protocols for nonmetastatic head and neck squamous cell carcinoma (HNSCC) has not been determined.

Methods. The absolute survival benefit at 5 years of concurrent chemoradiotherapy protocols versus radiotherapy alone observed in prospective randomized trials reporting on the use of cisplatin monochemotherapy for nonnasopharyngeal HNSCC was extracted. In the case of nonrandomized studies, the outcome results at 2 years were compared between groups of patients receiving different cumulative cisplatin doses.

Results. Eleven randomized trials and 7 nonrandomized studies were identified. In 6 definitive radiotherapy phase III trials, a statistically significant association ($p = .027$) between cumulative cisplatin dose, independent of the schedule, and overall survival benefit was observed for higher doses.

Conclusion. Results support the conclusion that the cumulative dose of cisplatin in concurrent chemoradiation protocols for HNSCC has a significant positive correlation with survival. © 2015 Wiley Periodicals, Inc. *Head Neck* **38**: E2151–E2158, 2016

KEY WORDS: cisplatin, concurrent chemoradiotherapy, outcome, cumulative dose, radiotherapy

INTRODUCTION

Concurrent chemoradiotherapy is the standard treatment for locally and/or regionally advanced (stage III–IV) head and neck squamous cell carcinoma (HNSCC), either in a definitive nonsurgical setting or when used after surgery in patients with high-risk features in the pathology specimen.[1] According to the meta-analysis of chemotherapy in head and neck cancer (MACH-NC), which analyzed 16,485 randomized patients from 87 phase III trials performed between 1965 and 2000, there was an overall survival benefit of 4.5% at 5 years (hazard ratio [HR] = 0.88) when chemotherapy was added to radiation therapy versus radiotherapy alone. The observed survival benefit, however, was limited to those patients undergoing concomitant chemotherapy (50 trials; 9615 patients), with a benefit of 6.5% at 5 years (HR = 0.81).[2,3]

The survival benefit of adding chemotherapy concurrently to radiation did not differ significantly between groups of trials with postoperative radiation or definitive radiation with conventional or altered fractionation, nor was there a differences between using monochemotherapy and combination chemotherapy in that respect. However, in the monochemotherapy group of trials, the platinum-based regimens were found to be significantly more effective than other types of monochemotherapy. The only statistically significant result in the subgroup analysis was a decreasing effect of chemotherapy on survival with increasing age.[3]

In HNSCC, cisplatin is currently the most widely used cytotoxic agent when combined with radiation. According to the Longitudinal Oncology Registry of Head and Neck Carcinoma report for the years 2005 to 2010, 70% of

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This article was written by members and invitees of the International Head and Neck Scientific Group (www.IHNSG.com).

patients with HNSCC in the United States received a combination of a cisplatin-based regimen and radiotherapy; in 49% of patients, single-agent cisplatin was used.[4] The rationale for adding cisplatin to radiation therapy is based on its radiosensitizing properties and a toxicity profile not overlapping with radiotherapy.

The National Comprehensive Cancer Network currently prefers high-dose single-agent cisplatin as a radiosensitizer for this disease.[5] In the majority of prospective randomized trials, cisplatin 100 mg/m^2 given every 3 weeks to reach the targeted cumulative dose of 300 mg/m^2 was used. The importance of a third planned cisplatin dose of 100 mg/m^2 was questioned by Ang,[6] who reviewed the compliance levels within a 3-week regimen in several published phase III randomized trials. A substantial fraction of patients from these trials received fewer than 3 cisplatin doses, and a cumulative dose of 200 mg/m^2 was suggested to be sufficient to yield a beneficial antitumor effect.[6] Furthermore, the only negative trial combining single-agent cisplatin and radiotherapy in MACH-NC used a cumulative dose of 140 mg/m^2, suggesting that lowering the cumulative dose of cisplatin below 200 mg/m^2 may be detrimental.[3,7,8] These observations agree with the results of a literature-based meta-analysis of platinum-based concomitant chemotherapy in HNSCC reported by Ghi et al.[9] They found a comparable reduction in the risk of death between high-dose cisplatin (300 mg/m^2) and cumulative cisplatin dose $<$300 mg/m^2 plus 5-fluorouracil when compared to radiotherapy alone. However, there was a marked difference in HRs for death between cisplatin at an intermediate cumulative dose (200–225 mg/m^2; HR = 0.68) and at low cumulative dose ($<$150 mg/m^2; HR = 1.04) in both cases without 5-fluorouracil.[9]

Despite its routine use, the optimal dose and timing of cisplatin administration in various chemoradiotherapy protocols has not been elucidated. The purpose of the present review was to evaluate evidence on the dose-response relationship for cisplatin when used concurrently with radiotherapy for the treatment of HNSCC. Because there are insufficient studies addressing this question, an indirect approach was chosen. The relevant literature on the use of cisplatin monochemotherapy in concurrent chemoradiotherapy protocols for HNSCC was reviewed to compare the survival results after radiotherapy alone and concurrent cisplatin-based chemoradiotherapy using the different cisplatin schedules used in the literature. Using the radiation alone arms as a baseline, the therapeutic advantages of the varied schedules of cisplatin were calculated in order to quantify the value of differing dose intensities of concurrent cisplatin.

MATERIALS AND METHODS

Review of the literature

The clinical use of cisplatin was approved by the U.S. Food and Drug Administration in 1978. Therefore, the PubMed databases were searched from 1978 to 2014, and the lists of references in the relevant articles were further evaluated. The following search terms were used: cisplatin, radiotherapy, and head and neck cancer. The results were then manually filtered by using the following criteria: (1) nonnasopharyngeal head and neck primary tumors of squamous cell histology; (2) treatment with curative intent, postoperative or definitive; (3) cisplatin used as monotherapy concurrently with radiotherapy; (4) numerical or graphical (Kaplan–Meier plots) presentation of results on disease control and survival; and (5) reports of randomized trials and nonrandomized studies published in the English language. Nonrandomized studies were considered only if different dose levels of cisplatin were compared for disease control and survival. For all studies, the additional criterion was that the same radiotherapy regimen was used in both treatment arms/groups. In the case of multiple reports of the same trial/study, the last one, reporting on the most mature results, was used for data extraction.

Data extraction

If available, data on locoregional control, event-free survival, distant metastasis-free survival, and/or overall survival (OS) were extracted from the selected publications. Although there were some differences in the endpoint definition of event-free survival across the trials/studies, the different outcomes were grouped together. The absolute benefit of concurrent chemoradiotherapy protocols versus radiotherapy alone observed in prospective randomized trials was determined as the absolute difference in survival rates between the 2 treatment groups at the 5-year timepoint. Absolute differences were always calculated as chemoradiotherapy minus radiotherapy-alone arm/group. In the case of nonrandomized studies, the outcome results at 2 years were compared between groups of patients receiving different cisplatin doses. Two types of data were used for this analysis: numerical data as reported in the text or presented in the tables, and graphical data in the form of Kaplan–Meier plots. From articles with only a graphical presentation of the results, the data points of a given curve were captured using UNSCAN-IT version 6.0 Graph Digitizing Software (Silk Scientific, Orem, UT).

Statistical analysis

If not explicitly reported, the cisplatin dose intensity used in the selected studies was calculated as the mean dose administered per patient. The mean dose was calculated using the data on drug compliance described in the relevant article. In cases where no information was available on the dose intensity or compliance of cisplatin, a planned dose of the drug was used for comparison. The analysis was performed separately for randomized and nonrandomized studies, which were further categorized by type of treatment (ie, postoperative and definitive). In order to determine the trend in the dose-response relationship of cisplatin when added concurrently to radiotherapy in prospective randomized trials, a linear regression analysis was carried out. The SPSS/PC statistical package version 18.0 (SPSS, Chicago, IL) was used for this purpose.

RESULTS

Search results

The PubMed search identified 3415 articles. Those indicating the use of single-agent cisplatin concurrently

with radiotherapy were reviewed as full-text articles. The selected articles were classified into 1 of 2 major groups (ie, randomized studies and nonrandomized studies), and further categorized based on whether definitive or postoperative (chemo)radiotherapy was used. After screening against the inclusion criteria, 22 articles were found eligible for further analysis.[7,8,10–31] Of these, 17 were reports on 11 different phase II/III randomized trials, and 7 were nonrandomized studies.

Evidence from prospective randomized trials

Details of 11 randomized trials reported in 17 articles are summarized in Table 1.[7,8,10–24] Definitive and postoperative treatments were used in 8 and 3 trials (reported in 12 and 5 articles), respectively. Four studies were 3-arm trials (with only 2 arms being reviewed for the purpose of this analysis).[12,13,15–17,21] In 2 trials, the number of patients recruited was <100,[10,11,21] and a phase III clinical testing was carried out in all studies but one.[7,8,10–23] Early termination of accrual was reported in 3 of these trials,[10–12,15] and in another 3 trials, there were some imbalances in the selection of patients, contributing to a bias, mainly against the combined-therapy arm.[7,8,21,24]

In the majority of trials, conventional fractionation of radiotherapy was used, whereas 2 fractions per day were used in 2 trials.[14,18,19] Concurrently with radiation, cisplatin was administered daily, weekly, or at 3-week intervals. After reports on drug compliance, the mean cumulative dose of cisplatin administered was calculated for 7 trials,[10,11,14,16–20,22–24] whereas only a median cumulative cisplatin dose could be estimated for 1 trial.[21] Only 3 trials lacked drug compliance data.[7,8,12,15]

In all but 1 study, the follow-up time was longer than 3 years (range = 1.8–10.8 years; median = 5 years). Considering 4 survival endpoints, the results on locoregional control were reported in 6 trials, on event-free survival in 8 trials, on distant metastasis-free survival in 7 trials, and on OS in all evaluated trials. The survival advantage expressed as the difference in survival rates between the chemoradiotherapy arm and the radiotherapy-only arm at 5 years are shown in Table 2. When all trials were considered for linear regression testing, no significant relationship was found between the cumulative cisplatin dose and the survival advantage for any of the studied endpoints. In the next step, the analysis was limited to definitive radiotherapy trials in which different tumor sites were treated, thus excluding the RTOG 9111 larynx preservation trial.[16,17] Furthermore, the Intergroup 1392 trial was also excluded because of 2 major biases, as underpowered (premature termination), and without information on the actually administered cisplatin dose.[15] In 6 definitive radiotherapy trials analyzed, a statistically significant association between cumulative cisplatin dose and improved OS was noted for higher doses ($p = .027$). As shown in Figure 1, the relationship is linear with the following model parameters: slope = 0.221 (95% confidence interval [CI] = 0.040–0.401) and $r^2 = 0.742$.

Evidence from nonrandomized studies

In 7 studies, the outcome results after concurrent chemoradiotherapy using different doses of single-agent cisplatin were compared and reported accordingly (Table 3).[25–31] There were 1 prospective and 6 retrospective studies reporting on 48 to 264 patients (median = 94). In 6 studies, chemoradiotherapy was used as definitive treatment, although in 3 of these, a small number were treated postoperatively.[28–30] In 1 study, all patients had postoperative chemoradiotherapy.[31] Only conventionally fractionated radiotherapy was used, and cisplatin was administered on a daily, weekly, or every 3-week basis to reach the planned doses ranging from 160 mg/m^2 to 300 mg/m^2. The median follow-up time was 2.2 years (range = 1.3–5 years). In individual studies, the outcomes of patients treated with different dose levels of cisplatin were compared. When reviewing the outcome results across the selected studies for statistical significance, no pattern in the dose-effect relationship could be determined for cisplatin.

DISCUSSION

Although cisplatin is the most frequently used cytotoxic agent to enhance the effect of radiation in head and neck cancer, there are only limited data in the literature describing the importance of its cumulative dose. Reviewing the relevant literature, only 11 randomized trials were found in which radiotherapy was compared with concurrent chemoradiotherapy using single-agent cisplatin and the same radiotherapy regimen in both arms of the trial. After limiting the analysis to definitive chemoradiotherapy trials, a significant positive correlation was found between increased OS and higher cumulative cisplatin dose. Information on the efficacy of different cisplatin doses obtained from the nonrandomized studies was inconclusive.

The dose-effect relationship for cisplatin was suggested by the MACH-NC, in which only the Intergroup 2382 trial with the lowest cumulative cisplatin dose (140 mg/m^2) of all cisplatin-alone trials showed no survival advantage in the combined-treatment arm compared to the radiotherapy-alone arm.[3] Important information was also provided by Ang[6] who observed that due to the significant toxicity of the cisplatin-radiotherapy combination, which resulted in the omission of a third planned cisplatin dose of 100 mg/m^2 in a substantial number of patients, there might be no added benefit beyond the cumulative cisplatin dose of 200 mg/m^2. Moreover, in the RTOG 0129, a phase III randomized trial comparing 2 concurrent cisplatin-based chemoradiotherapy regimens, 31% of patients in the standard fractionated radiotherapy arm received fewer than 3 prescribed cycles of cisplatin at 100 mg/m^2.[32] With respect to the number of cisplatin cycles administered concurrently with standard fractionated radiotherapy, a nonsignificant increased risk of death was observed when the patients receiving 2 cycles of cisplatin were compared to those who received 3 cycles (HR = 1.17; 95% CI = 0.78–1.76); a more pronounced increase in risk of death was recorded when only 1 cycle of cisplatin was compared to 3 cycles (HR = 1.52; 95% CI = 0.80–2.90).[33] The results of meta-analysis, which was published only in abstract form, confirmed these observations, although the argument is confounded by the inclusion of trials using 5-fluorouracil in combination with cisplatin or carboplatin.[9] A similar observation

TABLE 1. Cumulative cisplatin dose in prospective randomized phase II/III clinical trials.

Trial no./name	TH type	Inclusion period	Patients analyzed/ randomized	Sites/stage	Treatment arms	Cumulative CP dose, mean, mg/m^2	Median follow-up, y	Survival difference at 5 y			
								LRC	EFS	DMFS	OS
Intergroup 2382[7,8]	D	1982–1987	308/371	OC, OP, HP, L, NP, other* III, IV	A1: RT A2: RT+CP 20 mg/m^2/wk RT: 70 Gy, 1.8–2 Gy/d	140†	5.2	N.R.	+4%	N.R.	0%
Toulouse[10,11]	PO	1984–1988	83/88	OC, OP, HP, L, CUP III, IV	A1: pRT A2: pRT + CP 50 mg/wk (7–9 wk) pRT: 54–74 Gy, 1.7–2 Gy/d	196‡	≥5	+15%	+22%	+9%	+23%
Kragujevac [12,13]	D	1988–1990	106/106	OC, OP, HP, L, NP III, IV	A1: RT A2: RT + CP 6 mg/m^2/d RT: 70 Gy, 1.8–2 Gy/d	210–235†	4.5.	N.R.	N.R.	+18%	+17%
Kragujevac[13,14]	D	1991–1993	130/130	OC, OP, HP, L, NP III, IV	A1: RT A2: RT + CP 6 mg/m^2/d RT: 77 Gy, 1.1 Gy/bid	210	6.6	+14%	+21%	+29%	+21%
Intergroup 1392 [15]	D	1992–1999	182/199	OC, OP, HP, L III, IV	A1: RT A2: RT+CP 100 mg/m^2/3 wk RT: 70 Gy, 2 Gy/d	300†	3.4	N.R.	N.R.	N.R.	+12%
RTOG 9111[16,17]	D	1992–2000	346/367	L III, IV	A1: RT A2: RT + CP 100 mg/m^2/3 wk RT: 70 Gy, 2 Gy/d	263	10.8	+16.5%	+10%	+8.4%	+1.3%
SAKK 1094 [18,19]	D	1994–2000	223/224	OC, OP, HP, L II–IV	A1: RT A2: RT + CP 20 mg/m^2/d 1–5, wk 1 and 5 (or 6) RT: 74.4 Gy, 1.2 Gy/bid	179|	9.5	+14%	+3%	+21%	+13%
EORTC 22931[20]	PO	1994–2000	334/334	OC, OP, HP, L I–IV	A1: pRT A2: pRT + CP 100 mg/m^2/3 wk pRT: 66 Gy, 2 Gy/d	233	5	+13%	+11%	+4%	+13%
HeCOG 9405[21]	D	1995–1999	86/88	OC, OP, HP, L III, IV	A1: RT A2: RT + CP 100 mg/m^2/3 wk RT: 70 Gy, 1.8 Gy/d	270§	5	N.R.	+34%	N.R.	+40%
RTOG 9501[22,23]	PO	1995–2000	416/459	OC, OP, HP, L I–IV	A1: pRT A2: pRT + CP 100 mg/m^2/3 wk pRT: 66 Gy, 2 Gy/d	244	9.4	+10%	N.R.	+1%	+9%
New Delhi[24]	D	2003–2005	153/176	OC, NP II–IV	A1: RT A2: RT + CP 40 mg/m^2/wk RT: 70 Gy, 2 Gy/d	269|	1.8	N.R.	+5%¶	N.R.	+20%¶

Abbreviations: TH, treatment; CP, cisplatin; LRC, locoregional control; EFS, event-free survival; DMFS, distant metastasis-free survival; OS, overall survival; D, definitive; OC, oral cavity; OP, oropharynx; HP, hypopharynx; L, larynx; NP, nasopharynx; A1, arm 1; RT, radiotherapy; N.R., not reported; A2, arm 2; PO, postoperative; CUP, cancer of unknown primary; pRT, postoperative radiotherapy; EORTC, European Organization for Research and Treatment of Cancer.

* Nasal cavity and paranasal sinuses, unknown (6 patients).

† Planned cumulative dose.

‡ Absolute cisplatin dose was recalculated to an average body surface area of 1.7 m^2.

§ Median cumulative dose.

| In cases with dose reduction, 50% of a planned dose was considered.

¶ At 3 years.

TABLE 2. Differences in survival rates at 5 years reported in prospective randomized phase II/III clinical trials.

Parameter	No. of studies	Survival difference (% at 5 y)	
		Range	Median
All trials ($N = 11$)			
LRC	6	+10 to +16.5	+14
EFS	8	+3 to +34	+10.5
DMFS	7	+1 to +29	+9
OS	11	0 to +40	+13
Definitive RT* ($N = 7$)			
LRC	2	+14 to +14	N.A.
EFS	5	+3 to +34	+5
DMFS	3	+18 to +29	+21
OS	7	0 to +40	+17
Postoperative RT ($N = 3$)			
LRC	3	+10 to +15	+13
EFS	2	+11 to +22	N.A.
DMFS	3	+1 to +9	+4
OS	3	+9 to +23	+13

Abbreviations: LRC, locoregional control; EFS, event-free survival; DMFS, distant metastasis-free survival; OS, overall survival; RT, radiotherapy; N.A., not applicable.
* RTOG 9111 larynx preservation trial excluded.

was reported from the analyses of the NPC 9901 and NPC 9902 nasopharyngeal trials, in which no benefit was observed when adding a third cycle of cisplatin at 100 mg/m^2.[34] A significant association between >5 concurrent weekly cycles of cisplatin at 40 mg/m^2 (ie, with a total dose higher than 200 mg/m^2) and better survival, but not for other cutoff values, such as >4 cycles or >6 cycles, was reported by Loong et al[35] in the subgroup analysis of 141 patients with stage II to III nasopharyngeal carcinoma.

In the present study, a significant improvement in OS was noted with increasing cumulative cisplatin doses when the analysis was limited to the 6 studies using chemoradiotherapy as a definitive treatment.[7,8,12–14,18,19,21,24] A 2.2% (95% CI = 0.4% to 4%) absolute benefit in OS between the combined-treatment arm and the radiotherapy-only arm was observed for every 10 mg increase in the cumulative cisplatin dose. In the range of doses of cisplatin used in these 6 studies (140 mg/m^2 to 270 mg/m^2), the model was statistically significant ($p = .027$). Two definitive chemoradiotherapy trials were excluded from this analysis: the RTOG 9111 larynx preservation trial, because of the option of salvage surgery for those who failed chemoradiotherapy, and the prematurely terminated Intergroup 1392 trial, because of the lack of information on the actual dose of cisplatin administered.[15–17]

With regard to other survival endpoints, no association between the magnitude of the survival benefit and cumulative cisplatin dose was noted (event-free survival) or could not be tested because of a small number of available data points (locoregional control, distant metastasis-free survival). Thus, based on our analysis, it was not possible to conclude whether the observed effect of cumulative cisplatin dose on the OS benefit was associated with improved locoregional control and/or distant metastasis-free survival. However, it is of critical importance to identify the source of the causal relationship between cumulative cisplatin dose and improvement in OS, because improved compliance to higher cumulative drug doses could merely reflect the patient's better health and general well-being.[35] Information extracted from the nonrandomized studies was also inconclusive: whereas Gupta et al[26] reported a significant improvement in the local control and locoregional control with a higher number of weekly cycles of cisplatin at 30 mg/m^2, the intensity of the same chemotherapy regimen did not influence the outcome, including distant metastasis-free survival, in the study of Newlin et al.[36] Furthermore, Granata et al[37] found a significant benefit in 2-year event-free survival for those patients who received all 3 planned cisplatin cycles at 100 mg/m^2 when compared to the group with ≤2 cycles of the same chemotherapy, and this benefit was associated with improved local and regional control but not distant metastases-free survival.

There were several limitations of our analysis. First of all, the number of studies included was small with serious methodological flaws were observed in some of them. Because the outcome is drastically different between definitive and postoperative studies, especially given the current status of human papillomavirus (HPV)-positive disease, which is mostly a nonsurgical disease, the number of available studies for statistical analysis was further reduced. Moreover, at least 2 factors might influence the net effect of a certain cumulative dose of cisplatin: a fractionation pattern of radiotherapy and drug scheduling. It is well documented that altered fractionated radiotherapy is more effective than conventionally fractionated radiation therapy.[38] It may be the case that concurrent administration of a specific dose of cisplatin yields a lesser benefit when combined with a more effective radiotherapy regimen. For example, there was no survival advantage observed when 2 cycles of cisplatin at 100 mg/m^2 and accelerated-fractionation radiotherapy were compared with 3 cycles of the same chemotherapy and standard-fractionation radiotherapy in the RTOG 0129 study, suggesting that the effect of more intensive radiotherapy approximates 1 cycle of cisplatin at 100 mg/m^2.[32,33] When comparing conventionally fractionated and hyperfractionated radiotherapy with and without daily

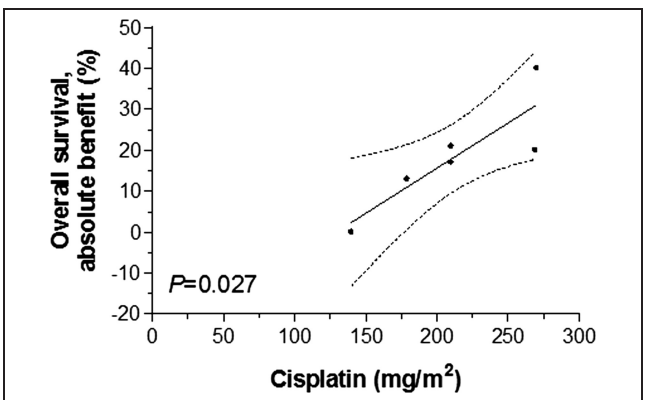

FIGURE 1. Overall survival absolute benefit in relation to a cumulative cisplatin dose in prospective randomized trials on concurrent chemoradiotherapy with single-agent cisplatin.

TABLE 3. Cumulative cisplatin dose in retrospective studies.

Author	TH type	Period	Sites/stage	No. of patients	Treatment	Cumulative CP dose, median, mg/m^2	Median follow-up, y	Survival at 2 y		
								LRC	EFS	OS
Fountzilas et al[25]	D	1991–1992	OC, OP, HP, L, NP, CUP	48	RT: 70 Gy, 1.8 Gy/d	300	2.2		N.S.	$p < .001$
			III, IV		CP: 100 mg/m^2/3 wk	G1: 200 ($N = 6$)		N.R.	G1: 50%	G1: 17%
						G2: 300 ($N = 42$)		N.R.	G2: 55%	G2: 75%
Gupta et al[26]	D	1996–2004	OC, OP, HP, L	264	RT: 66–70 Gy, 2–2.1 Gy/d	180	1.6	$p = .009$	$p = .011$	
			III, IV		CP: 30 mg/m^2/wk	G1: $\leq$150 ($N = 96$)		G1: 40%	G1: 39%	N.R.
						G2: $\geq$180 ($N = 168$)		G2: 57%	G2: 67%	N.R.
Lau et al[27]	D	2000–2002	OC, OP, HP, L, CUP	56	RT: 70 Gy, 2 Gy/d		1.3	N.S.		$p = .044$
			II–IV		CP: 20 mg/m^2/d 1–4,	G1: $\leq$80 ($N = 21$)		N.R.	N.R.	G1: 50.8%
					wk 1 and 5	G2: 160 ($N = 35$)		N.R.	N.R.	G2: 69.6%
Steinmann et al[28]	D, PO	2001–2006	OC, OP, HP, L, NP	78	RT: 50.4–70 Gy, 2 Gy/d	160	3	N.S.		N.S.
			I–IV		CP: 40 mg/m^2/wk	G1: $<$200 ($N = 43$)		G1: 69%*	N.R.	G1: 69%*
						G2: $\geq$200 ($N = 35$)		G2: 81%*	N.R.	G2: 70%*
								N.S.		N.S.
						G1: $<$160 ($N = 14$)		G1: 73%*	N.R.	G1: 66%*
						G2: $\geq$160 ($N = 64$)		G2: 86%*	N.R.	G2: 86%*
Rades et al[29]	D, PO	2000–2008	OC, OP, HP, L	160	RT: 60–72 Gy/2 Gy/d		2	N.S.		N.S.
			III, IV		CP: G1: 100 mg/m^2/3 wk	G1: 300 ($N = 74$)†		G1: 79%	N.R.	G1: 72%
					G2: 20 mg/m^2/d 1–5,	G2: 200 ($N = 86$)†		G2: 69%	N.R.	G2: 73%
					wk 1 and 5					
Espeli et al[30]	D, PO	2002–2009	OC, OP, HP, L, NP	94	RT: 66–70 Gy, 2 Gy/d		2.8		N.S.	$p = .041$
			I–IV		CP: G1: 100 mg/m^2/3 wk	G1: 232 ($N = 54$)		N.R.	G1: 52%	G1: 78%
					G2: 40 mg/m^2/wk	G2: 186 ($N = 40$)		N.R.	G2: 46%	G2: 51%
Geiger et al[31]	PO	2004–2010	OC, OP, HP, L, CUP, PNS	104	RT: 60–70 Gy, −2.2 Gy/d		5		N.S.	N.S.
			III–IV		CP: G1: 100 mg/m^2/3 wk	G1: 200 ($N = 51$)		N.R.	G1: 73%	G1: 88%
					G2: 25–30 mg/m^2/wk	G2: 150 ($N = 53$)		N.R.	G2: 74%	G2: 78%

Abbreviations: TH, treatment; CP, cisplatin; LRC, locoregional control; EFS, event-free survival; OS, overall survival; D, definitive; OC, oral cavity; OP, oropharynx; HP, hypopharynx; L, larynx; NP, nasopharynx; CUP, cancer of unknown primary; RT, radiotherapy; G1, group 1; G2, group 2; N.R., not reported; N.S., not statistically significant; PO, postoperative; PNS, Paranasal sinuses.

*At 18 months.

† Planned cumulative dose.

administration of cisplatin at 6 mg/m^2 (the same chemotherapy schedule in both combined-treatment arms), Jeremic et al[13] observed no benefit (either for local and regional recurrence-free survival or for distant metastasis-free survival) or only a trend (for OS; $p = .051$) of more aggressive hyperfractionated chemoradiotherapy over conventionally fractionated chemoradiotherapy. However, the GORTEC 9902 trial, comparing conventional chemoradiotherapy versus accelerated radiotherapy plus chemotherapy versus highly accelerated radiotherapy alone, concluded that chemotherapy has a substantial treatment effect when given concomitantly with radiotherapy and that acceleration of radiotherapy cannot compensate for the absence of chemotherapy. They found the most favorable outcomes for conventional chemoradiotherapy, suggesting that acceleration of radiotherapy is probably not beneficial in concurrent chemoradiotherapy schedules.[39]

With regard to cisplatin scheduling, weekly doses ranging from 30 to 40 mg/m^2 or daily administration at 5 to 7 mg/m^2 or at 100 mg/m^2 administered over several days have been increasingly used instead of a standard dose of 100 mg/m^2 every 21 days. The principle intent of this modification was to improve treatment compliance in order to increase the cumulative cisplatin dose and, consequently, the efficacy of combined therapy. Another rationale for more frequent administration of cisplatin would be to provide radiosensitizing chemotherapy during a larger proportion of the course of radiotherapy.[40] Retrospective comparisons of the efficacy, acute toxicity, and compliance of weekly and 3-week cisplatin schedules reported conflicting results.[29–31,41–44] However, a modeling study by Marcu et al,[45] showed that daily administration of cisplatin with radiotherapy is more efficient than weekly cisplatin, increasing tumor control by 35% and 6%, respectively, as compared to radiotherapy alone. The only published study randomizing patients between 2 different cisplatin regimens used concurrently with postoperative radiotherapy for high-risk squamous cell carcinoma of the oral cavity was reported by Tsan et al.[44] Because of slow recruitment, the study ended after only 55 patients had been recruited. In the standard 3-week cisplatin at 100 mg/m^2 arm, the mean cumulative dose was 208.5 mg/m^2, whereas in the weekly cisplatin at 40 mg/m^2 arm, it was 200.4 mg/m^2. After a median follow-up of 12 months, there was no advantage observed in terms of locoregional control or OS between the 2 arms.[44]

The relationship between HPV tumor status and cumulative dose of cisplatin is another area of interest. According to recent evidence, this important question relates not only to oropharyngeal cancer cases but also to other HNSCC sites.[46] Because of well documented survival advantage of HPV and/or p16 tumor positivity, several deescalation randomized trials are currently in progress. However, in none of these trials is the reduced dose of cisplatin used in the low-intensity arm compared to the standard-therapy arm.[47]

Carboplatin, a less toxic derivative of cisplatin, has also been used as an alternative to cisplatin-based chemoradiotherapy regimens. Studies suggest that patients may derive similar benefits with weekly or high doses of carboplatin with lesser toxicity, although randomized head-to-head trials comparing the efficacy cisplatin and carboplatin with radiation have not been conducted.[48–50] It may be reasonable to consider the substitution of carboplatin for cisplatin when toxicities preclude further administration of cisplatin with radiation. Two studies conducted at the University of Michigan in organ preservation of the larynx and oropharynx demonstrated no lack of efficacy when carboplatin was administered in place of cisplatin.[51,52] Moreover, the substitution allowed for 3 cycles of platinum to be administered with radiation, mollifying the concerns of the reduction in efficacy when $<$200 mg/m^2 of cisplatin could only be delivered.

Our study lends support to the idea that the cumulative dose of cisplatin in concurrent chemoradiotherapy protocols for HNSCC matters. However, the question of the optimal dose and schedule is still debatable, as the data available in the relevant literature are only indirect, often with a low level of evidence (ie, derived from nonrandomized, mainly retrospective studies). At the moment, the recommended cumulative dose of cisplatin that should be administered during radiotherapy seems to be at least 200 mg/m^2, but Figure 1 suggests that the more cisplatin administered, the higher the benefit. The importance of the schedule (ie, daily, weekly, or every 3weeks) is unclear from this analysis, as we concentrated on total dose. There are hints that cisplatin can induce very late (beyond 5 years) noncancer-related deaths,[17,23] and whether this risk is dose-related is unclear. The Japanese JCOG 1008 randomized trial in the postoperative setting, comparing 2 different chemoradiotherapy protocols with single-agent cisplatin, is ongoing in order to address the above-mentioned dilemmas. Hopefully, the outcome of this study might give support to the tendency to use the lower weekly dose schedules. However, in the era of intensive research in the field of HNSCC pathogenesis, including molecular mechanisms and targeted drug design, this question was felt by many to be less of a priority.

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