Chemoradiotherapy with Weekly Cisplatin 40 mg/m² in 103 Head-and-Neck Cancer Patients

A Cumulative Dose-Effect Analysis

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Background and Purpose: In patients with head-and-neck cancer treated with chemoradiotherapy (CRT), a cisplatin-based regimen is often used. Several treatment schedules are accepted with a cumulative cisplatin dose of 200 mg/m² (CisCD200) given during radiotherapy. The aim of this analysis was to investigate feasibility and efficacy of a weekly cisplatin 40 mg/m² regimen.
Patients and Methods: During 08/2001 and 12/2006, 103 patients with squamous head-and-neck cancer received concurrent CRT with intended weekly cisplatin 40 mg/m² and were analyzed retrospectively. CRT was definitive for a newly diagnosed primary in 62, postoperative in 16, and for recurrence in 25 patients. Most patients had carcinoma of the hypo- and oropharynx (81%). Patients received a median total dose of 70 Gy (range, 42–71.2 Gy).
Results: Only 42 patients (41%) received a CisCD200 predominantly due to hematotoxicity. Actuarial 12- and 18-month overall survival (OS) for patients with and without CisCD200 was 83.3% versus 72.1% (p = 0.19) and 66.7% versus 67.2% (p = 0.86), the 12- and 18-month locoregional control (LRC) 66.7% versus 78.7% (p = 0.325) and 59.5% versus 78.7% (p = 0.109), respectively. Multivariate analysis revealed only type of CRT (definitive vs. recurrent) and T-classification as significant variables predicting OS and LRC.
Conclusion: Feasibility and efficacy of CRT with weekly cisplatin 40 mg/m² were suboptimal in this analysis. However, the prospects of weekly cisplatin may be its more suitable integration into emerging trimodality concepts combining CRT with molecularly targeted agents.

Key Words: Chemoradiotherapy · Head-and-neck cancer · Cisplatin · Cumulative dose

Strahlenther Onkol 2009;185:682–8
DOI 10.1007/s00066-009-1989-5

Radiochemotherapie mit wöchentlichen Cisplatingaben von 40 mg/m² bei 103 Patienten mit Kopf-Hals-Tumoren. Kumulative Cisplatindosis und Überleben

Hintergrund und Ziel: Bei der Radiochemotherapie (CRT) von Patienten mit Kopf-Hals-Tumoren wird häufig eine platinhaltige Chemotherapie gewählt. Verschiedene Behandlungsschemata zielen auf eine kumulative Dosis von mindestens 200 mg/m² Cisplatin (CisCD200) simultan zur Bestrahlung. Ziel dieser Studie war es, die Wirksamkeit und Verträglichkeit wöchentlicher Cisplatingaben von 40 mg/m² zu untersuchen.
Patienten und Methodik: Im Zeitraum von 08/2001 bis 12/2006 erhielten 103 Patienten mit Kopf-Hals-Tumoren eine CRT mit geplanten wöchentlichen Cisplatingaben von 40 mg/m² und wurden retrospektiv ausgewertet. 62 Patienten bekamen eine definitive CRT bei primär diagnostizierten Tumoren, 16 Patienten wurden postoperativ und 25 Patienten in einer Rezidivsituation behandelt. Hypo- oder Oropharynxkarzinome lagen in 81% (Tabelle 1) der Fälle vor. Die mediane Gesamtdosis betrug 70 Gy (Streubreite 42–71,2 Gy, Tabelle 2).
Ergebnisse: Nur 42 Patienten (41%) erreichten die CisCD200 (Tabelle 3), hauptsächlich aufgrund erhöhter Hämatotoxizität. Das Gesamtüberleben (OS) nach 12 und 18 Monaten (Abbildung 1) betrug für die Patienten mit und ohne CisCD200 83,3% versus 72,1% (p = 0,19) und 66,7% versus 67,2% (p = 0,86). Die lokoregionäre Kontrolle (LRC) betrug nach 12 und 18 Monaten (Abbildung 2) 66,7% versus 78,7% (p = 0,325) und 59,5% versus 78,7% (p = 0,109; Tabelle 4). In der Multivarianzanalyse hatten nur die Behandlungsart der CRT (Primär- vs. Rezidivbehandlung, Abbildung 3) und das T-Stadium signifikanten Einfluss auf OS und LRC (Tabelle 5).

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Received: January 5, 2009; accepted: June 2, 2009

Schlussfolgerung: Die Durchführbarkeit und Wirksamkeit der CRT mit wöchentlichen Cisplatingaben erscheinen in dieser Analyse suboptimal. Der Vorteil wöchentlicher Cisplatingaben liegt vor allem in der besseren Integrierbarkeit in Konzepte, die eine CRT mit einer zielgerichteten Therapie verbinden.

Schlüsselwörter: Radiochemotherapie · Kopf-Hals-Tumoren · Cisplatin · Kumulative Dosis

Introduction

Only a minority of patients with locoregionally advanced squamous cell cancer of the head and neck (HNSCC) is able to undergo adequate surgical resection and treatment outcome is poor with respect to survival and ultimate locoregional tumor control (LRC) with a functional organ preserved [13, 24]. In these patients, definitive radiotherapy remains the treatment of choice and the addition of concurrent chemotherapy is able to improve treatment results [9].

Cisplatin is a potent radiosensitizer and the drug most commonly used for chemoradiotherapy (CRT) in HNSCC. A meta-analysis demonstrated that platinum-based chemotherapy might provide a survival advantage compared with non-cisplatin-containing radiation treatment regimens [10, 22]. The application of cisplatin 100 mg/m^2 q21 has been investigated in randomized trials and is the only evidence-based cisplatin regimen available in the definitive [1, 3, 15] and postoperative setting [4, 6, 12]. Common side effects in cisplatin-containing CRT trials are hemato-, nephro- and ototoxicity or oral mucositis, which make this treatment suitable for selected patients only. Despite improved survival and LRC compared to radiotherapy alone compliance with CRT regimens is suboptimal in many cases [1]. To limit toxicity, alternative schedules with reduced single doses of cisplatin have been established in HNSCC patients like 20 mg/m^2 d1–5 (week 1 and 5) [2, 23], weekly 30 or 40 mg/m^2 [5, 17] or even daily 6 mg/m^2 of cisplatin [18, 26], but to date published data are comparably rare. Common to all schedules is the aim to achieve a cumulative cisplatin dose of at least 200 mg/m^2 (CisCD200), although the adequacy of this threshold dose remains to be proven.

The aim of this retrospective analysis was to critically review our single-center experience with weekly cisplatin 40 mg/m^2 in HNSCC patients in terms of feasibility (CisCD actually achieved and toxicity profile) and efficacy (locoregional and systemic tumor control) with special emphasis on cisplatin-based dose-response relationship.

Table 1. Patients' characteristics.

Tabelle 1. Patientencharakteristika.

Age, median (range [years])	55 (30–73)
Gender (n)	
Male	84
Female	19
Primary site [n (%)]	
Oropharynx/oral cavity	34 (33)
Hypopharynx	49 (48)
• Multilevel including hypopharynx	27 (26)
Larynx	11 (11)
Nasopharynx	9 (9)
Classification [n (%)]	
T1/2	15 (15)
T3/4	88 (85)
N0/1	41 (40)
N2/3	62 (60)

Patients and Methods

Patients' Characteristics

Between 08/2001 and 12/2006, 103 patients with histologically proven locoregionally advanced HNSCC received concurrent CRT with cisplatin at our department and were analyzed retrospectively (Table 1). Staging consisted of panendoscopy, computed tomography (CT) scan of the head and neck, bone scan, chest X-ray, and ultrasound of the neck nodes and abdomen.

Radiotherapy

Three-dimensional treatment planning was performed after thermoplastic mask fixation based on a CT. A complex monoisocentric multifield (shrinking field) technique was used. Radiotherapy was delivered using 6-MV linac photons. The median total doses to the primary and macroscopically involved lymph nodes are shown in Table 2. The maximal dose to the spinal cord was limited to 45 Gy. 22 patients received a concomitant boost in treatment weeks 5 and 6 with a second fraction of 1 Gy resulting in a cumulative daily dose of 3 Gy in the boost volume (time interval to the first fraction of at

Table 2. Treatment-related data.

Tabelle 2. Therapiedaten.

Treatment category [n (%)]	
Definitive	62 (60)
Postoperative	16 (16)
Recurrence	25 (24)
• Reirradiation	17 patients
Radiotherapy median total dose (range [Gy])	70.0 (42.0–71.2)
Definitive	70.0 (56.8–71.8)
Postoperative	67.2 (54.0–70.0)
Recurrence	50.4 (45.0–71.6)
• Reirradiation	50.4 (42.0–71.6)
Treatment time median (range [weeks])	
Radiation treatment time	6.6 (4.2–10.9)

least 6 h). Median duration of CRT was 6.6 weeks (range, 4.2–10.9 weeks) for all patients completing radiotherapy. 17 of the patients with recurrence (n = 25) had received previous radiotherapy, five of them including platin-based chemotherapy.

Chemotherapy

Simultaneous cisplatin 40 mg/m^2 was administered as 1-h intravenous infusion once weekly up to six courses during CRT. Blood cell count, electrolytes, C-reactive protein (CRP), creatinine and liver enzymes were routinely checked before each application. Creatinine clearance was performed before onset and after three courses of cisplatin. Renal dysfunction (defined as creatinine clearance < 80 ml/min), leukopenia (< 3,000/µl) and thrombopenia (< 75,000/µl), infections or rising CRP values lead to postponement of the subsequent cisplatin application. At occurence of hematotoxicity grade 4 chemotherapy was terminated completely.

Table 3. Cumulative cisplatin dose (CisCD) achieved by all patients.
Tabelle 3. Erreichte kumulative Cisplatindosis (CisCD).

CisCD (mg/m^2)	Patients n (%)
40	2 (2)
80	5 (5)
120	14 (14)
160	40 (39)
200	27 (26)
240	15 (15)

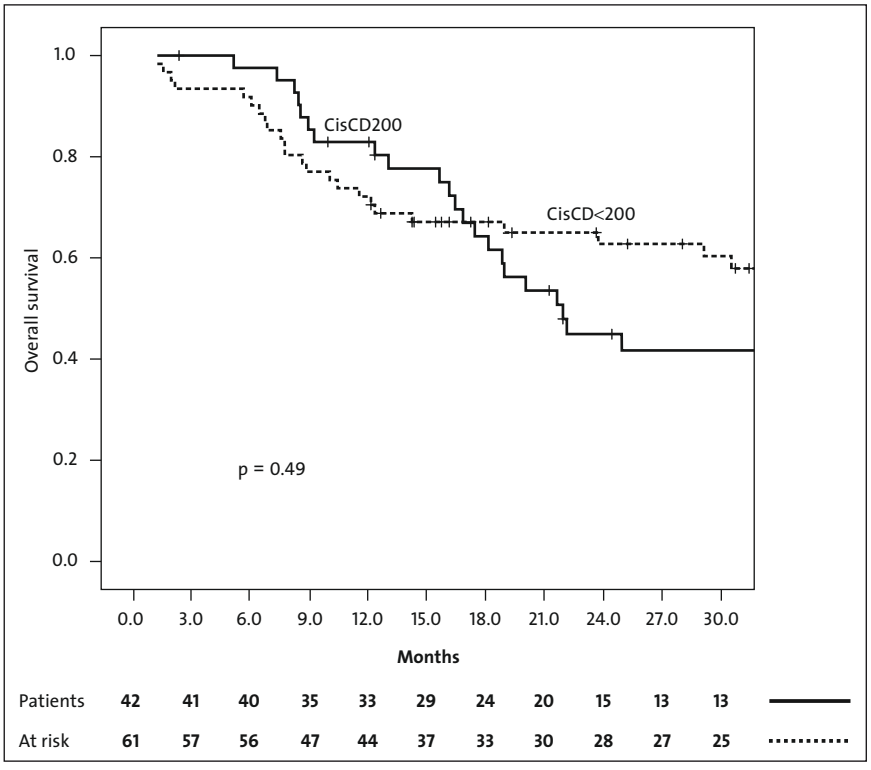

Figure 1. Actuarial overall survival of patients according to achieved CisCD200: yes (solid line) versus no (dotted line; Kaplan-Meier analysis, log-rank test).

Abbildung 1. Gesamtüberleben der Patienten in Korrelation zur erreichten CisCD200: ja (durchgezogene Linie) versus nein (gepunktete Linie; Kaplan-Meier-Analyse, Log-Rank-Test).

Assessment and Follow-Up

Patients' records and treatment protocols were used for retrospective analysis including the CisCD actually achieved and reasons for not achieving CisCD200. Clinical as well as radiologic and laboratory findings during follow-up were retrieved and systematically analyzed. Hematotoxicity was classified retrospectively applying the CTCAE v3.0 criteria [11].

Response to therapy was assessed by clinical examination including laryngoscopy and ultrasound examination of the neck at the Department of ENT. If necessary, additional diagnostics were carried out. Biopsy samples were taken from suspect findings.

Patients were revisited at regular intervals starting 6 and 12 weeks after the end of treatment, then followed 3-monthly during the first 2 years and 6-monthly thereafter. In patients, who did not show up at their follow-up visits, survival data were assessed by contacting the patient directly, the general practitioner, and/or the local cancer registry.

Statistical Analysis

Statistical analysis was performed using SPSS win 15.0 software. Survival time was measured from the time of onset of CRT. The following endpoints were analyzed: LRC with local or regional recurrence defined as event and overall survival (OS). The actuarial survival time was calculated by the method of Kaplan and Meier, differences were compared using the log-rank test. A multivariate stepwise Cox proportional regression analysis was used to identify the impact of known prognostic factors and treatment-related variables on outcome. The following parameters were included in the analysis as categorical variables: gender, site of primary (oropharynx/nasopharynx vs. hypopharynx including multilevel/larynx), T-stage (T1/2 vs. T3/4) and N-stage (N0/1 vs. N2/3), primary versus recurrent tumor, CisCD200 and CisCD160 (yes vs. no), hematotoxicity (Common Toxicity Criteria [CTC] class 0/I vs. II vs. III/IV), and radiation treatment time (< 6.7 vs. ≥ 6.7 weeks). A two-sided p-value < 0.05 was considered to be significant.

Results

Only 42 patients (41%; 36% of all women and 44% of all men) achieved the intended CisCD200. While 35 out of 78 patients (45%) with CRT for a newly diagnosed primary achieved a CisCD200, this was the case in only seven out of 25 patients (28%) with recurrence (p = 0.03). The median CisCD achieved was 160 mg/m^2 corresponding to median four cycles of cisplatin (range, one to six). However, 82 patients (80%) achieved a CisCD of at least 160 mg/m^2. Details are shown in Table 3.

3 months after the end of CRT clinical and imaging findings revealed complete remission in 68 and partial remission in twelve patients, while ten patients had locoregionally progressive disease. In ten patients locoregional treatment response could not be determined retrospectively due to incomplete records. In these patients only data on OS were available. Median follow-up of all patients was 19 months. For patients being alive at the time of data analysis (n = 50) it was 36.2 months. One patient with postoperative CRT was lost to follow-up (after 2.3 months).

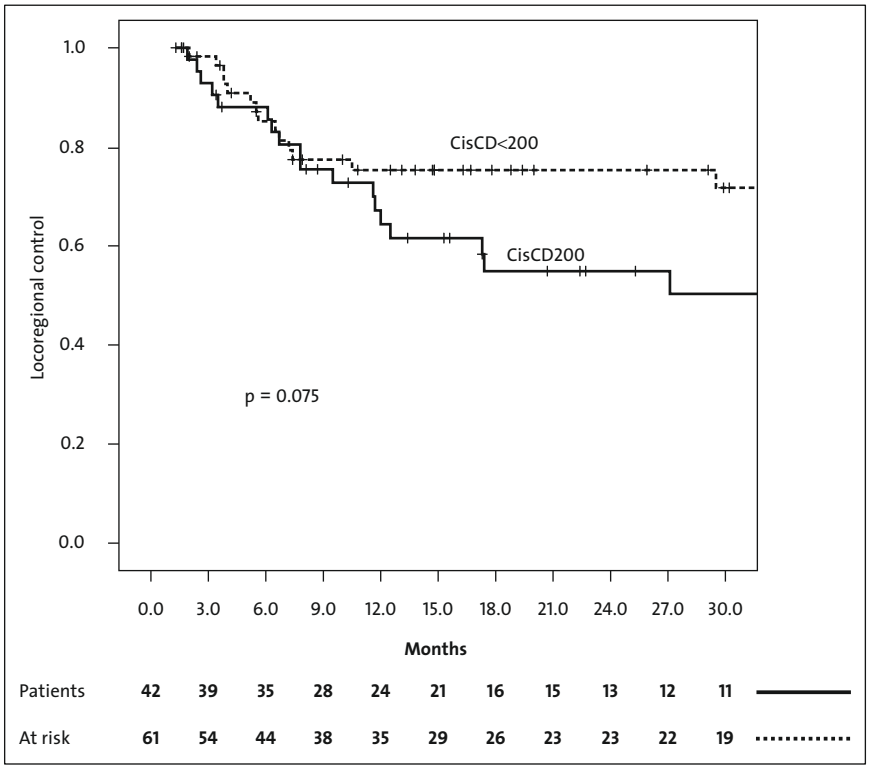

Figure 2. Actuarial locoregional control of patients according to achieved CisCD200: yes (solid line) versus no (dotted line; Kaplan-Meier analysis, log-rank test).

Abbildung 2. Lokoregionäre Kontrolle der Patienten in Korrelation zur erreichten CisCD200: ja (durchgezogene Linie) versus nein (gepunktete Linie; Kaplan-Meier-Analyse, Log-Rank-Test).

Table 4. Actuarial locoregional control (LRC) and overall survival (OS) at 18 months of all patients (n = 103) and patients with newly diagnosed primaries only (n = 78) with and without CisCD200 and CisCD160, respectively. CisCD: cumulative cisplatin dose.

Tabelle 4. Lokoregionäre Kontrolle (LCR) und Gesamtüberleben (OS) nach 18 Monaten aller Patienten (n = 103) und der primär therapierten Patienten (n = 78) mit und ohne CisCD200 bzw. CisCD160. CisCD: kumulative Cisplatindosis.

	CisCD200 (yes vs. no)		CisCD160 (yes vs. no)	
18 months	**LRC**	**OS**	**LRC**	**OS**
All patients (n = 103)	60% vs. 79% (p = 0.109)	67% vs. 67% (p = 0.857)	70% vs. 76% (p = 0.638)	66% vs. 71% (p = 0.768)
Newly diagnosed primaries only (n = 78)	69% vs. 81% (p = 0.276)	69% vs. 70% (p = 0.998)	73% vs. 86% (p = 0.392)	66% vs. 86% (p = 0.187)

Treatment-Related Toxicity

Reasons for not achieving CisCD200 were predominantly acute hematotoxicity in 34 patients (56%). 44 of all patients (including patients with CisCD200) developed hematotoxicity ≥ grade 3 with 14 experiencing hematotoxicity grade 4, and nine patients thrombopenia ≥ grade 3 (one patient grade 4). Three of these patients died due to pancytopenia with infection or bleeding despite intensive supportive care including application of granulocyte colony stimulating-factor and platelets substitution.

13 patients (21%) developed infections, septicemia or raised CRP values during CRT.

Renal dysfunction was the reason for postponement of subsequent cisplatin application in six patients with a decline of creatinine clearance as low as 66 ml/min (range, 66–75 ml/min). However, three of these patients (50%) achieved a CisCD200, the remaining three a CisCD160. No patient required hemodialysis. No interruption of radiation therapy was found due to treatment-related mucositis. A reliable classification of the degree of mucositis was not possible due to the imprecise description in the treatment records. The loss of body weight exceeded 5% in 51 patients and 10% in 16 patients.

Administrative reasons or patients' decision resulted in delayed onset of chemotherapy in 17 patients (28%) not achieving CisCD200.

Survival Data

OS and LRC of patients with and without CisCD200, respectively, were not significantly different (Figures 1 and 2, Table 4). Of note, an unexpected but not signifi-

cant inferiority in LRC was found in patients with CisCD200 with a follow-up ≥ 12 months (Figure 2). Comparable results were found when CisCD160 was chosen as a cutoff (Table 4).

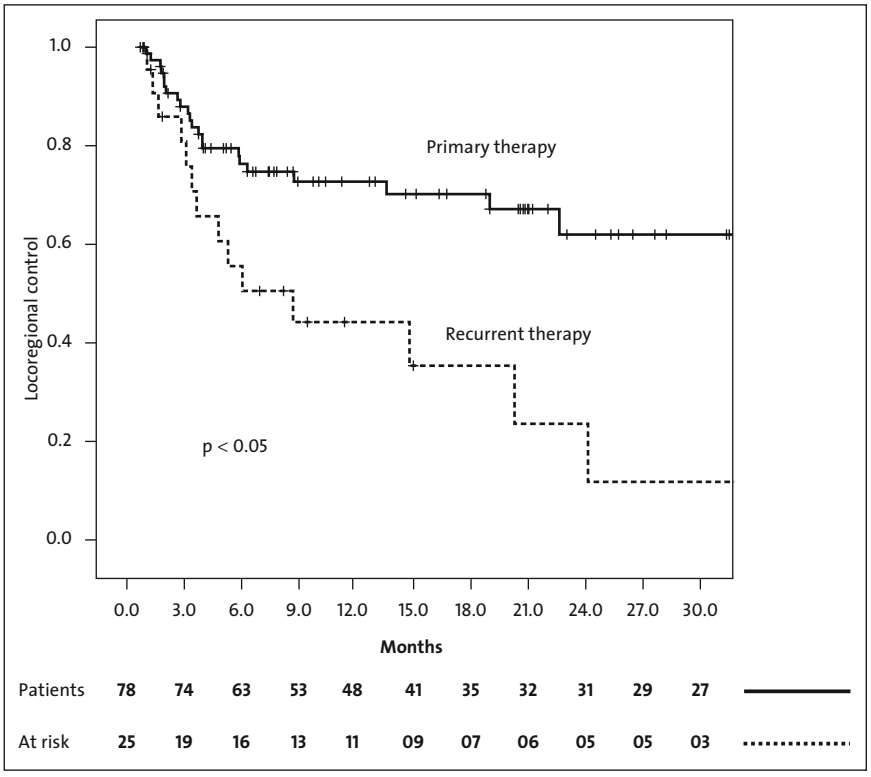

Figure 3. Actuarial locoregional control of patients with newly diagnosed (solid line) versus recurrent HNSCC (dotted line; Kaplan-Meier analysis, log-rank test).

Abbildung 3. Lokoregionäre Kontrolle der primär behandelten Patienten (durchgezogene Linie) versus Rezidivsituation (gepunktete Linie; Kaplan-Meier-Analyse, Log-Rank-Test).

Table 5. Influence of different patient- and treatment-related variables on locoregional control (LRC) and overall survival (OS). CisCD: cumulative cisplatin dose; CTC: Common Toxicity Criteria.

Tabelle 5. Einfluss verschiedener patienten- und therapiebezogener Variablen auf lokoregionäre Kontrolle (LRC) und Gesamtüberleben (OS). CisCD: kumulative Cisplatindosis; CTC: Common Toxicity Criteria.

Variable	LRC p-value		OS p-value	
	Univariate	Multivariate	Univariate	Multivariate
Gender	0.099	0.019	0.387	0.042
Tumor site	**0.017**	**0.037**	0.530	0.223
T-stage (T1/2 vs. T3/4)	**0.047**	0.976	**0.009**	0.966
N-stage (N0/1 vs. N2/3)	0.454	0.191	0.187	0.197
Hematotoxicity (CTC class 0/I vs. II vs. III/IV)	0.831	0.158	0.115	0.161
Radiation treatment time (< 6.7 vs. ≥ 6.7 weeks)	0.246	0.090	0.339	0.667
CisCD200 achieved (yes vs. no)	0.079	0.020	0.443	0.379
CisCD160 achieved (yes vs. no)	0.251	0.300	0.113	0.127

A separate analysis of the 78 patients with CRT for a newly diagnosed primary could not reveal a significant difference in OS and LRC between those with (n = 35) and without CisCD200 (n = 43, Table 4). 64 patients (82%) achieved a CisCD160. Again, no difference was found between those with and without CisCD160 in terms of OS and LRC (Table 4).

Multivariate analysis of patient- and treatment-related variables revealed a statistically significant influence for primary versus recurrent tumor on LRC (p = 0.002; Figure 3). When excluding patients with CRT for recurrence (n = 25), a statistically significant influence was found univariately on OS and LRC for T-stage and on LRC for tumor site. Details are summarized in Table 5.

Discussion

In this retrospective analysis only 42 patients (41%) actually received the intended CisCD200. On the other hand, 83 patients (80%) achieved a CisCD of at least 160 mg/m^2, corresponding to four cycles of weekly cisplatin 40 mg/m^2. Although we applied quite restrictive criteria to postpone or even suspend chemotherapy depending on the degree of leukopenia or thrombopenia, 44 patients (43%) experienced hematotoxicity ≥ grade 3 with three patients dying treatment-related.

In locoregionally advanced HNSCC concurrent CRT with three cycles of single-agent cisplatin 100 mg/m^2 q21 has been established as a standard dosing regimen based on the results of an RTOG phase II [20] and Intergroup phase III trial [1]. Compliance with the latter treatment regimen was 85% as measured by treatment completion, although no details of the achieved CisCD were stated. Treatment-related toxicity was high with 89% of evaluable patients in the high-dose cisplatin arm developing hematotoxicity grade 3–5. Four patients died due to toxicity.

In a prospective trial, Beckmann et al. investigated definitive CRT in 36 HNSCC patients using hyperfractionated radiotherapy and weekly cisplatin 40 mg/m^2. Only 19% of patients achieved the intended CisCD200 and

64% a CisCD160 [5]. Due to the lower CisCD only eight patients (22%) showed leukopenia and two patients (6%) thrombopenia ≥ grade 3 [5].

Ho et al. retrospectively compared weekly cisplatin 33–40 mg/m^2 (n = 24) and three cycles of cisplatin 80–100 mg/m^2 q21 (n = 27). Although more patients achieved a CisCD of at least 240 mg/m using weekly cisplatin 40 mg/m^2 or cisplatin 80 m g/m^2 q21 compared to cisplatin 100 mg/m^2 q21, the corresponding mean CisCD values (202 and 203 mg/m^2 vs. 180 mg/m^2) were not significantly different due to the small number of patients investigated [17]. Similar toxicity was found in both treatment groups with no further details stated.

Wolff et al. published data of daily 6 mg/m^2 cisplatin given concurrently with definitive or adjuvant radiotherapy in 50 patients with locally advanced HNSCC. 90% of their patients achieved at least 80% of the planned CisCD of 168 mg/m^2 [26], which compares favorably with the CisCD of 160 mg/m^2 achieved in 80% of our patients. Hematotoxicity ≥ grade 3 was reported in twelve patients (24%).

In contrast to HNSCC, CRT with 40 mg/m^2 cisplatin weekly has been used and reported extensively in patients with cervical cancer [16]. A randomized study compared 20 mg/m^2 (d1–5) in treatment week 1 and 5 with weekly cisplatin 40 mg/m^2 concurrently with pelvic radiotherapy [14]. The 20-mg/m^2 schedule turned out to be superior in terms of LRC and progression-free survival (PFS), with a higher proportion of patients achieving a CisCD of 200 mg/m^2 (91% vs. 81%) [14].

Possibly, the inferior adherence to weekly cisplatin 40 mg/m^2 in patients with HNSCC may be related to more troublesome acute side effects like oral mucositis or dysphagia and the frequently worse compliance due to unfavorable smoking and nutritional habits. Additionally, a discrepancy between patient compliance in randomized trials and under conditions of standard care exists. Torres et al. compared compliance and outcome of cervical cancer patients treated with concurrent cisplatin-based CRT in a multiinstitutional trial and under conditions of standard care. In patients routinely treated, more grade 2–3 neutropenia occurred leaving them less likely to achieve a CisCD200 compared to patients treated within a randomized trial (52% vs. 85%; $p < 0.001$) [25].

In this analysis we could not demonstrate a dose-response effect of CisCD within the range of 160–200 mg/m^2 in terms of OS or LRC. However, survival data of our patients with newly diagnosed primary (n = 78) compare favorably with published data of definitive CRT in locoregionally advanced HNSCC. The prospective trial with weekly cisplatin 40 mg/m^2 reported a 2-year PFS and OS of 67% and 58% [5] and the daily low-dose cisplatin regimen a 3-year PFS and OS of 78% and 67% [26]. By contrast, Adelstein et al. applying three courses of cisplatin 100 mg/m^2 q21 found a 3-year PFS and OS of only 51% and 37%, respectively [1]. Thus, the question remains unanswered which threshold of CisCD is optimal to maintain the best available therapeutic ratio. CisCD < 200 mg/m^2 may be adequate regarding the significant rate of treatment-related morbidity and mortality.

Another interesting aspect of weekly cisplatin is the emerging role of trimodal therapy incorporating targeted therapies into concurrent CRT [7, 8]. In an initial pilot study, Pfister et al. analyzed trimodality therapy in locoregionally advanced HNSCC with cisplatin 100 mg/m^2 q21 combined with cetuximab and hyperfractionated radiotherapy [21]. After accrual of 22 patients the study was closed prematurely due to significant adverse events. In a phase I dose-escalation trial a hyperfractionated radiotherapy with concurrent cetuximab and increasing doses of weekly cisplatin was combined [19]. Cisplatin 40 mg/m^2 weekly was established as the maximally tolerated dose in this trimodality trial representing the basis for an ongoing phase II trial.

Conclusion

Feasibility and efficacy of CRT with weekly cisplatin 40 mg/m^2 were suboptimal in this analysis. The appropiateness of this schedule should be reconsidered if confirmed by others. A CisCD < 200 mg/m^2 may be equally effective when given concurrently to high-quality radiotherapy. The prospects of weekly cisplatin may be its more suitable integration into emerging trimodality concepts combining CRT with molecularly targeted agents like cetuximab.

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