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A comparison of weekly versus 3-weekly cisplatin during adjuvant radiotherapy for high-risk head and neck cancer

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SUMMARY

Objectives: To compare cumulative cisplatin dose and toxicity between patients who received 3-weekly versus weekly cisplatin during adjuvant radiotherapy for high-risk head and neck squamous cell carcinoma (HNSCC).

Materials and methods: Consecutive HNSCC patients with involved resection margins and/or extra-capsular extension in two tertiary cancer centers with different institutional practices were identified. Cumulative cisplatin dose was calculated and information on toxicity reviewed and compared between patients who received 3-weekly versus weekly cisplatin.

Results: Of 270 high risk patients, 60 received 3-weekly 100 mg/m^2 and 48 received weekly 50 mg/m^2 cisplatin during adjuvant radiotherapy (60–66 Gy in 30–33 fractions). Fourteen patients received other chemotherapy schedules and 148 received no chemotherapy. Mean cumulative cisplatin dose was 199.4 mg/m^2 (standard error (SE) 5.4) in 3-weekly versus 239.8 mg/m^2 (SE 11.0, $P = 0.001$) in weekly treated patients. Cumulative cisplatin $\geqslant$200 mg/m^2 was given to 67.7% of patients in the 3-weekly cohort and 85.2% ($P = 0.039$) in the weekly cohort. The rate of feeding tube dependency 6 months after treatment, osteoradionecrosis, neutropenic fever, and persistent renal function decline were not statistically different.

Conclusions: About one half of high-risk HNSCC patients are not eligible for cisplatin during postoperative radiotherapy. Patients treated with weekly 50 mg/m^2 cisplatin received a higher cumulative dose with comparable toxicity as patients who received 3-weekly 100 mg/m^2 cisplatin. Efficacy and applicability to the frequently used weekly 40 mg/m^2 schedule remains to be evaluated.

Introduction

Patients with head and neck squamous cell carcinoma (HNSCC) treated with primary surgery have a very high risk of recurrence if resection margins are positive and/or if there is extra-capsular extension of lymph node metastases. Combined analysis of two phase 3 studies demonstrated that these patients derive benefit from adding high dose cisplatin (100 mg/m^2 at day 1, day 22 and day 43) to adjuvant radiotherapy with regard to loco-regional control, disease free and overall survival [1–3]. The combination of adjuvant radiotherapy and high dose cisplatin induces significant acute and long term toxicity, and even in a trial setting only 61% and 64% of the patients could complete 3 cycles of chemotherapy [1,2].

As an alternative, a weekly lower dose cisplatin schedule has been used, based on the assumption that a weekly regimen is less toxic and equally effective as 3-weekly high dose cisplatin. One

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small trial demonstrated a survival benefit of adding weekly cisplatin to postoperative radiotherapy [4]. However, weekly and 3-weekly cisplatin plus radiotherapy have not been compared directly in a randomized and adequately powered study. A single institution retrospective comparison of weekly ($n = 53$) versus 3-weekly cisplatin ($n = 51$) showed a trend for improved survival with 3-weekly high dose cisplatin. However, patients who received weekly cisplatin were older, had a lower rate of human papillomavirus (HPV) related tumors and a higher number of smoking pack-years, which are well known adverse prognostic factors [5]. These differences likely result from selection bias of less fit patients to receive the weekly schedule.

We therefore aimed to compare patient cohorts from 2 tertiary care centers where one center routinely treats high-risk HNSCC patients postoperatively with 3-weekly high dose cisplatin and the other center routinely gives weekly cisplatin. If weekly cisplatin is better tolerated than 3-weekly cisplatin, this might be reflected by a higher cumulative cisplatin dose in patients treated with a weekly schedule. We aimed to compare the cumulative cisplatin dose and toxicity between patients treated with a weekly schedule and patients treated with the high dose 3-weekly schedule.

Patients and methods

Study design, patients and treatment

For this retrospective cohort study all consecutive patients with HNSCC of the oral cavity, larynx, hypopharynx and oropharynx who underwent primary surgery and had positive resection margins (<1 mm) and/or extra-capsular extension of lymph node metastasis who started adjuvant radiotherapy between March 1st, 2005 and December 12th, 2012 at Princess Margaret Cancer Center (PM, Toronto, Canada) and between December 15th, 2008 and July 15th, 2013 at the University Medical Center Groningen (UMCG, The Netherlands) were included. Information on disease characteristics, treatment details and acute and late toxicity were extracted from prospective institutional databases and supplemented by reviewing electronic patient records [6,7]. For patients who received adjuvant radiotherapy alone, the reasons for not having chemotherapy were collected. Patients who received adjuvant radiotherapy at PM with up to 3 cycles of 3-weekly 100 mg/m^2 cisplatin and patients treated at the UMCG who received up to 7 weekly cycles cisplatin 50 mg/m^2 were included for cumulative chemotherapy dose and toxicity comparisons. The weekly dose of 50 mg/m^2 was chosen as institutional practice because this allows a cumulative dose of 300 mg/m^2 to be reached, which was the target dose in the landmark studies [1,2]. Patients who tolerated treatment well were offered a seventh cycle during the last week of radiotherapy. For both cisplatin schedules, patients were admitted overnight for equivalent hydration regimens. All patients received 3000–4000 mL of normal saline with magnesium and potassium supplementation and were premedicated with a 5-HT3 receptor antagonist, a neurokinin-1 receptor antagonist and dexamethasone.

Patients treated at PM received postoperative intensity-modulated radiotherapy (IMRT) as previously described [8]. High-risk patients treated at UMCG received IMRT with a simultaneous integrated boost technique. Patients received 66 Gy in 2 Gy fractions on high risk areas (lymph node areas with extracapsular extension and/or positive surgical margins), 59.4 Gy in 1.8 Gy per fraction on the intermediate risk areas (e.g. lymph node areas with positive nodes without extracapsular extension) and 52.8 Gy on the elective nodal areas.

All patients treated with 3-weekly high-dose cisplatin underwent prophylactic percutaneous endoscopic gastrostomy (PEG) feeding tube insertion, unless contraindicated or refused by the patient. In the weekly cisplatin cohort, all patients treated between December 2008 and December 2009 received a PEG tube. Thereafter standard treatment policy was changed and only patients with swallowing problems or significant weight loss before start of chemoradiotherapy received a PEG feeding tube. In the remainder of the weekly cohort a nasogastric feeding tube was placed during treatment if the caloric intake by mouth was insufficient.

This study was approved by the PM Institutional Review Board. In the UMCG a consent waiver was granted for this retrospective chart review.

Study endpoints and data analyses

The primary endpoint of the study was the cumulative cisplatin dose, defined as the total dose in mg/m^2 that a patient received during the course of adjuvant radiation. Secondary endpoints included the rate of tube feeding dependence at 6 months after chemoradiotherapy; the rate of osteoradionecrosis of the jaw after treatment; the rate of neutropenic fever during treatment; the worst change of serum creatinine according to the common terminology criteria for adverse events version 4.0 (CTCAE 4.0); and the change in body weight during treatment. For comparisons of endpoints and clinical characteristics between patients treated with weekly and 3-weekly cisplatin, the means of continuous variables were compared using two-sample *t*-tests and the frequency of categorical variables were compared using the chi-squared test or Fisher's exact test, whenever appropriate. Odds ratios and corresponding *p*-values were calculated using the binary logistic regression model.

The efficacy outcome was reported as the 1-year recurrence rate including type of recurrence for each group. No formal statistical testing was carried out to compare the clinical outcomes because this was a retrospective review with significant clinical heterogeneity between the two groups. All analyses were performed with SPSS version 19 (IBM, Chicago, IL).

Results

In total, 270 HNSCC patients with high risk features were identified. Out of 178 patients from PM, 104 (58%) received postoperative radiotherapy only. Likewise, 44 (48%) out of 92 UMCG patients did not receive chemotherapy (Fig. 1). The most frequently documented reasons for withholding chemotherapy were age, poor performance, cardiovascular morbidity and patient refusal (Table 5). Wound healing problems were mentioned as a contraindication for chemotherapy in 7 (4%) PM and 6 (7%) UMCG patients. Fourteen PM patients were excluded from the cumulative dose and toxicity comparisons because of treatment with weekly cisplatin ($n = 11$) or carboplatin ($n = 1$), or disease recurrence before start of chemoradiotherapy ($n = 2$).

Chemoradiotherapy comparison cohorts

Sixty patients were treated with 3-weekly high dose cisplatin and 48 patients received weekly 50 mg/m^2 cisplatin during adjuvant radiotherapy. The groups were balanced for age, sex and T-classification but not for tumor site, N-classification, smoking status, WHO performance status and type and extent of surgery (Table 1). All patients were treated with intensity modulated radiation therapy (IMRT). All patients except for one in the 3-weekly cohort completed radiotherapy. Patients treated with 3-weekly cisplatin received 60–72 Gy in 30–36 fractions.

All except one patient in the weekly cisplatin cohort received 66 Gy in 33 fractions (Table 2).