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Comparison of every 3 week cisplatin or weekly cetuximab with concurrent radiotherapy for locally advanced head and neck cancer

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SUMMARY

Background: Cisplatin dosed every 3 weeks (CIS) or weekly cetuximab (CTX) concurrent with radiotherapy are standards of care for locally advanced head and neck squamous cell carcinoma (LAHNC). Retrospective comparisons of CIS and CTX have offered mixed conclusions. We compared outcomes between CIS and CTX in this patient population.

Methods: Between January 2006 and December 2011, we identified 279 patients who underwent definitive radiotherapy and concurrent systemic therapy for LAHNC. The median age difference between the CIS and CTX groups was relatively small (58 vs. 62 years, respectively) and CIS patients had a slightly higher rate of N2 disease than CTX patients (74% vs. 61%, respectively).

Results: Median follow-up was 27 months. Systemic therapy consisted of CIS in 241 (86.4%) and CTX in 38 (13.6%). Actuarial locoregional control of the CIS and CTX groups at 2 years were 91% and 90% ($p = 0.74$), respectively. Actuarial 2 year distant metastasis rates between the groups were 8% and 12%, respectively ($p = 0.55$), and actuarial 2 year overall survival between the groups were 87% and 89%, respectively ($p = 0.47$).

Conclusions: We found no difference in locoregional control, distant metastasis rate, or overall survival between patients treated with concurrent CIS or CTX.

Introduction

Multiple phase III randomized trials have demonstrated that cisplatin given at 100 mg/m^2 every 3 weeks concurrent with radiotherapy (CIS) improves locoregional control over radiotherapy alone for locally advanced head and neck squamous cell carcinoma (LAHNC) [1–5]. A meta-analysis has also conclusively demonstrated improved survival with CIS compared with radiotherapy alone for LAHNC [6]. Similarly, weekly cetuximab concurrent with radiotherapy (CTX) also improves locoregional control and survival over radiotherapy alone in LAHNC, although this has only been demonstrated in one randomized trial [7,8]. The intensification of therapy by the addition of cetuximab to cisplatin concurrent with radiotherapy does not appear to improve outcomes over cisplatin and radiotherapy [9].

Concurrent cetuximab is well tolerated in patients with LAHNC, with an acneiform rash and infusion reactions comprising the major acute toxicities [8]. Given the perception that cetuximab with radiotherapy might result in less toxicity than combined systemic platinum chemotherapies with radiation, there is considerable interest in the utility of substituting CTX for CIS in LAHNC patients, especially in the HPV positive population. The Radiation Therapy Oncology Group (RTOG 1016) trial has recently closed to accrual, which is investigating concurrent bolus cisplatin every three weeks compared with concurrent weekly cetuximab and radiation therapy among patients with HPV positive, locally advanced oropharynx squamous cell carcinoma [10]. Unfortunately at present, there is little data available regarding the most appropriate agent (cisplatin or cetuximab) to use concurrently with radiation.

In order to attempt to add insight to this question until prospective data is available, we retrospectively compared outcomes from a single institution with definitive CIS versus CTX among a large cohort of patients with LAHNC.

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Materials and methods

Patient population and outcomes

An institutional head and neck cancer dataset was queried for patients who underwent treatment for squamous cancers of the head and neck from January 2006 through December 2011 ($n = 2517$). After excluding patients with prior definitive head and neck surgery, prior head and neck cancer, induction chemotherapy, concurrent chemotherapy with other chemotherapeutic agents or schedules, or metastatic disease, 279 patients remained for analysis. Institutional review board approval was granted prior to commencement of the study.

Patient disease and treatment details were abstracted from the chart. All patients with biopsy-proven locally advanced, American Joint Commission on Cancer (AJCC) stage III to IVA-B squamous cell carcinoma of the oropharynx, oral cavity, larynx or hypopharynx, underwent a pre-operative staging work-up with a computed tomography scan with intravenous contrast of the head and neck and thorax and/or positron emission tomography. HPV status was most often determined by p16 expression staining (>70% staining considered positive) and/or by using the INFORM HPV III Family 16 DNA Probe (Ventana Medical Systems, Inc., Tucson, AZ) which has an affinity for 12 high-risk HPV subtypes, including HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 66. HPV and/or p16 status was assessed in 112 (40.1%) patients beginning in 2009.

Radiotherapy

All patients were treated with intensity-modulated radiation therapy (IMRT) to a prescribed total dose of 70–76 Gy in 200 cGy daily fractions. Five patients who died on treatment and 3 additional patients who received less than the prescribed dose were included in the analysis. Two-hundred and thirty-three (83.5%) patients received once-daily radiation therapy while 46 (16.5%) of the patients received an accelerated radiation regimen, consisting of an additional 200 cGy fraction each week beginning the second week, given either as a twice-daily treatment with fractions separated by 6 h, or as an additional fraction on the weekend, as described by Overgaard et al. [11].

Systemic therapy

During the time-period of the study, bolus cisplatin at 75–100 mg/m^2 given every 3 weeks for 2–3 cycles was the standard systemic agent ($n = 241$ [86.4%]). Of 241 patients treated with cisplatin, 129 (53.5%) patients deviated from the planned cisplatin course because of toxicities including tinnitus, neuropathy, and/or cytopenia; 82 (34.0%) patients received a reduction in planned cisplatin cycles, 20 (8.3%) received a dose reduction, and 27 (11.2%) were changed to carboplatin during treatment. Despite these deviations from the planned course, 211 patients (87.6%) received a cumulative cisplatin dose $\geqslant$200 mg/m^2. Cetuximab was typically only offered to patients with pre-existing hearing or kidney damage ($n = 38$ [13.6%]). Cetuximab was initiated with a 400 mg/m^2 loading dose, followed by a planned 6–7 weekly cycles of 250 mg/m^2. Of 38 patients treated with cetuximab, 35 (92%) received the planned cetuximab course; 2 (5%) patients were switched to concurrent cisplatin and 1 (3%) to concurrent carboplatin after extensive cetuximab rashes.

Toxicity

Time to PEG tube removal was recorded as a surrogate for dysphagia toxicity. PEG tube removal was deemed appropriate both by the treating physician and a clinical nutritionist, typically after the patient had full oral intake without need for the tube in >30 days. PEG tubes were placed either prophylactically because of dysphagia or a >10% weight loss in the previous 6 months, or reactively because of an unacceptable weight loss of >10% or dehydration during treatment as determined by the treating physician. Patients who received a PEG tube prior to, or within, 10 days of initiation of chemoradiotherapy, were included in the prophylactic PEG tube group. A 10-day cut-off following commencement of CRT to define prophylactic PEG placement was empirically chosen *a priori* as most patients do not develop treatment related dysphagia within this time period.

Endpoints and statistics

The primary end-point was locoregional control. Secondary endpoints included distant metastasis rate, overall survival, a subset-analysis of HPV and/or p16 positive cases, as well as HPV and p16 negative oropharynx and non-oropharynx cases, and toxicity comparison among HPV and/or p16 positive cases as measured by time to percutaneous endoscopic gastrostomy tube (PEG) removal.

Statistical analysis was performed using Statistical Product and Service Solutions version 22.0 (SPSS®, Chicago, IL). Differences in patient and treatment characteristics between the CIS and CTX groups were evaluated using the Chi-square or Man-U Whitney test as appropriate. Actuarial rates of locoregional control, distant metastasis rate, and overall survival were calculated using the Kaplan–Meier method. Differences in rates based on systemic therapy treatment were assessed with the log-rank test. Multivariate analysis was performed using a Cox regression model with potential predictors from the log-rank univariate analysis. All clinical, tumor, and treatment variables were added to the Cox multivariate regression model. Continuous variables were split using clinically meaningful cut-points. An α (type I) error $\leqslant$0.05 was considered statistically significant.

Results

The median follow-up for surviving patients was 27 months (range 4–85). Patient, tumor, and treatment characteristics are shown in Table 1. CIS patients were significantly younger (median 58 yrs vs. 62 yrs, $p < 0.001$) but with a higher burden of nodal involvement ($\geqslant$N2 82.2% vs. 63.2%, $p = 0.01$) than CTX patients. There were no other significant differences between the CIS and CTX groups (Table 1). Actuarial LRC of the CIS and CTX groups at 2 years were nearly identical at 91% and 90%, respectively ($p = 0.74$; Fig. 1a). There was also no difference in actuarial distant metastasis rate (8% and 12%, respectively; $p = 0.55$; Fig . 1b) or overall survival at 2 years (87% and 89%, respectively, $p = 0.47$; Fig. 1c) between the groups. On Cox multivariate analysis, type of systemic therapy was not associated with LRC or OS (CTX HR 1.03 [95% CI 0.23–4.59, $p = 0.96$, and HR 1.31 [95% CI 0.43–3.96, $p = 0.64$, respectively). Five (2.1%) CIS patients died during treatment compared with no CTX patients, and 8 (3.3%) CIS patients died within 3 months of treatment completion, compared with one (2.6%) CTX patient ($p = 0.37$ and $p = 0.82$). Causes of death within 3 months of CIS treatment included an aortic aneurysm rupture, myocardial infarction, pneumonia, 4 patients with unknown causes of death, and one patient with disease progression; the single CTX patient died from progressive disease.

On subgroup analysis, 99 oropharynx patients (85 CIS and 14 CTX) had an HPV and/or p16 positive status. Among this cohort with more favorable outcomes, 2 year LRC was 97% and 93% ($p = 0.34$) and 2 year OS was 94% and 85% ($p = 0.26$) for CIS and CTX patients, respectively. Among 59 patients with HPV and p16