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Clinical outcomes and prognostic factors in cisplatin versus cetuximab chemoradiation for locally advanced p16 positive oropharyngeal carcinoma

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ABSTRACT

Objectives: Randomized trials evaluating cisplatin versus cetuximab chemoradiation (CRT) for p16+ oropharyngeal cancer (OPC) have yet to report preliminary data. Meanwhile, as a preemptive step toward morbidity reduction, the off-trial use of cetuximab in p16+ patients is increasing, even in those who could potentially tolerate cisplatin. The purpose of this study was to compare the efficacy of cisplatin versus cetuximab CRT in the treatment of p16+ OPC and to identify prognostic factors and predictors of tumor response.

Materials and methods: Cases of p16+ OPC treated with cisplatin or cetuximab CRT at our institution from 2010 to 2014 were identified. Recursive partitioning analysis (RPA) classification was used to determine low-risk (LR-RPA) and intermediate-risk (IR-RPA) groups. Log-rank/Kaplan-Meier and Cox Regression methods were used to compare groups.

Results: We identified 205 patients who received cisplatin (n = 137) or cetuximab (n = 68) CRT in the definitive (n = 178) or postoperative (n = 27) setting. Median follow-up was 3 years. Cisplatin improved 3-year locoregional control (LRC) [92.7 vs 65.4%], distant metastasis-free survival (DMFS) [88.3 vs 71.2%], recurrence-free survival (RFS) [86.6 vs 50.6%], and overall survival (OS) [92.6 vs 72.2%] compared to cetuximab [all $p < .001$]. Concurrent cisplatin improved 3-year OS for LR-RPA (97.1 vs 80.3%, $p < .001$) and IR-RPA (97.1 vs 80.3%, $p < .001$) groupings.

Conclusion: When treating p16+ OPC with CRT, the threshold for substitution of cisplatin with cetuximab should be maintained appropriately high in order to prolong survival times and optimize locoregional and distant tumor control. When cetuximab is used in cisplatin-ineligible patients, altered fractionation RT should be considered in an effort to improve LRC.

Introduction

Definitive chemoradiation (CRT) is an effective organ-preserving treatment for locally advanced oropharyngeal cancer (OPC) [1,2]. As median survival times increase, reducing the often debilitating short and long-term morbidities associated with the standard concurrent cisplatin-based approach has become the focus of multiple clinical trials. This is especially true in patients with p16 positive (p16+) disease who are generally younger, healthier, and have higher treatment response rates [3]. One approach to toxicity reduction has been replacing cisplatin with the targeted systemic agent cetuximab, which is an epidermal growth factor receptor (EGFR) inhibitor. In the IMCL-9815

Abbreviations: CRT, chemoradiation; DMFS, distant-metastasis-free survival; IR-RPA, intermediate-risk recursive partitioning analysis; LRC, locoregional control; LR-RPA, low-risk recursive partitioning analysis; OPC, oropharyngeal carcinoma; OS, overall survival; RFS, recurrence-free survival; RPA, recursive partitioning analysis; RT, radiotherapy

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trial, Bonner et al. showed that cetuximab concurrent with RT was associated with increased overall survival (OS) and locoregional control (LRC) compared to RT alone in the definitive treatment of locally advanced squamous cell carcinoma of the head and neck, with greatest effect in p16+ OPC and in those who received altered fractionation radiotherapy (AFRT) [4–6]. Randomized trials comparing cetuximab versus cisplatin CRT in p16+ OPC are underway but have yet to report preliminary data. Without a proper comparison of efficacy available, the appropriate threshold for substitution of cisplatin with cetuximab remains uncertain. Consequently, the notorious toxicity profile of concurrent cisplatin can be subjected to excess scrutiny, leading to increased off-trial use of cetuximab, even in patients who could potentially tolerate cisplatin [7]. The purpose of this study was to compare the efficacy of cisplatin versus cetuximab CRT in the treatment of p16+ OPC and to identify prognostic factors and predictors of tumor response in an effort to better guide treatment decision-making.

Materials and methods

Study design

In this Institutional Review Board-approved study, we retrospectively identified patients with histologically confirmed p16+ OPC squamous cell carcinoma who received curative intent CRT with concurrent cisplatin or cetuximab between 2010 and 2014. Pre-CRT neck dissection and/or surgery to the primary site were allowed in cases where extranodal extension (n = 11), positive margins (n = 10), or both (n = 6) were documented. Those who received induction or adjuvant chemotherapy, or those with a history of prior head and neck RT or active second malignancies were excluded. Two hundred and five patients were eligible for analysis. Clinical staging was determined using the TNM American Joint Committee on Cancer (AJCC) 8th Edition criteria which incorporates the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S) nodal staging system for human papilloma virus (HPV)-related disease. The recursive partitioning analysis (RPA) classification system previously established by Ang et al. [3] was used to determine low risk (LR-RPA) and intermediate risk (IR-RPA) groups. Pretreatment Eastern Cooperative Oncology Group (ECOG) performance status was available for all patients.

Radiation therapy

A contrast-enhanced computed tomography scan of the head and neck with a thermoplastic mask and custom-molded head rest for immobilization was used for treatment planning. Primary and nodal gross tumor volumes (GTV) were contoured, typically with the guidance of fused positron emission tomography imaging. Subsequent clinical target volume (CTV) and planning target volume (PTV) expansions were made to account for subclinical tumor extension and patient motion/set-up error respectively. Intensity modulated radiotherapy (IMRT) was used to deliver a median dose of 70 Gy (range 66–70 Gy) to the high-risk PTV, while treating elective nodal areas using a simultaneous integrated boost technique. Standard fractionation radiation (SFRT) consisted of 2 Gy daily fractions, 5 days per week. An accelerated treatment schedule delivering 6 fractions per week was the only form of AFRT utilized – the sixth fraction being given as an extra fraction on one of the first five days, allowing at least 6 h between fractions – as has been validated in previous clinical trials [8].

Chemotherapy

Concurrent cisplatin was given every 3 weeks (100 mg/m^2 days 1, 22, and 43; n = 71), weekly (40 mg/m^2; n = 59), or daily (6 mg/m^2; n = 7). When patients received AFRT, high-dose cisplatin was only given on days 1 and 22. Cetuximab was given weekly (400 mg/m^2 loading dose then 250 mg/m^2 thereafter; n = 68). Chemotherapy was switched to single agent carboplatin due to cisplatin-related toxicity in 17 patients.

Statistical analysis

Patient characteristics were compared using Chi-squared and t-tests. The interval from completion of RT to last oncologic follow-up or locoregional failure (defined as persistent or recurrent disease in the head and/or neck) was used to calculate LRC; time to last available information or death was used for OS. The interval from completion of RT to diagnosis of distant metastasis, last follow up, or death was used to determine distant metastasis-free survival (DMFS); similarly, time to first failure (locoregional and/or distant) was used to calculate recurrence-free survival (RFS). Three-year outcomes and univariate analysis were calculated using Kaplan-Meier and log-rank testing, variables included: ECOG-PS ($\geq$1), smoking ($>$ 10 pack-years), ICON-S nodal stage ($\geq$2), T-stage ($\geq$T3), age ($\geq$60 years), chemotherapy (cetuximab vs cisplatin), and RT fractionation schedule (altered vs standard). Variables with $p < .10$ on univariate analysis were included as covariates in Cox proportional hazards modeling to confirm results when adjusting for potential confounders. The AJCC 7th edition nodal staging ($\geq$N2b) was included in univariate analyses for comparison purposes but was not included in multivariate models. Analysis of cetuximab patients was performed separately using the same methods previously mentioned to identify prognostic factors and predictors of tumor response in this subgroup. A p-value $\leq .05$ was considered statistically significant. All calculations were performed using SPSS Statistics, version 23 (IBM Corp. Armonk, NY).

Results

Patient characteristics

Of the 205 eligible patients, 137 received cisplatin CRT and 68 received cetuximab. The median follow-up for survivors was 42 months (range 7–78) for patients who received cisplatin and 34 months (range 4–65) for patients who received cetuximab. Reasons for patients receiving cetuximab in place of cisplatin included: randomization on clinical trial (n = 22, 32%), hearing loss (n = 14, 20.5%), multiple medical co-morbidities (n = 13, 19%), patient choice (n = 12, 17.6%), or renal disease (n = 7, 10.3%). Patient, tumor, and treatment characteristics are described in Table 1. The groups were well-balanced with the exception of age, follow-up, and RT fractionation schedule; cetuximab patients were older ($p = .01$), had less follow-up ($p < .001$), and more commonly received AFRT ($p < .001$). Meaningfully, there were no statistically significant differences in baseline ECOG PS, T-stage, N-stage, or RPA groups.

Overall and recurrence-free survival

With a median follow-up of 36 months, 172 (83.9%) patients were alive with 15 (13.1%) and 18 (26.5%) deaths in the cisplatin and cetuximab groups respectively. Median OS was not reached. The 3-year OS for patients who received concurrent cisplatin was 92.6% and 72.2% for those who received cetuximab (Fig. 1A). The 3-year RFS rate for cisplatin patients was 86.6% and 50.6% for cetuximab (Fig. 1B). On univariate analysis (Table 2) the use of concurrent cetuximab was associated with decreased OS ($p < .001$) and RFS ($p < .001$). There were no significant differences in RFS ($p = .272$) or OS ($p = .516$) between those treated with high-dose cisplatin versus weekly cisplatin (Supplemental figure). When adjusting for potential confounding variables with multivariate analysis (Table 3), the use of cetuximab remained independently associated with decreased OS (hazard ratio [HR] 0.26; 95% CI 0.12–0.53; $p < .001$) and RFS (HR 0.21; 95% CI 0.12–0.38; $p < .001$). Additional covariates associated with decreased OS included smoking pack-years ($p = .04$) and advanced nodal disease

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