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Comparison of high-dose Cisplatin-based chemoradiotherapy and Cetuximab-based bioradiotherapy for p16-positive oropharyngeal squamous cell carcinoma in the context of revised HPV-based staging

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ABSTRACT

Aim: To perform a comparison of Cisplatin vs. Cetuximab in p16-positive oropharyngeal squamous cell carcinoma (OPSCC) in the context of the revised HPV-based staging.

Background: Previous reports comparing these agents in head and neck cancer have included heterogenous disease and p16-status.

Materials and methods: A retrospective review was conducted from 2006 to 2016 of patients with p16-positive OPSCC who underwent definitive radiotherapy concurrent with either triweekly Cisplatin ($n = 251$) or Cetuximab ($n = 40$). AJCC 8th Edition staging was adapted.

Results: Median follow-up for surviving patients was 40 months. On multivariate analysis for all-comers, comparing Cisplatin and Cetuximab, 3-year locoregional recurrence (LRR): 6% vs. 16% ($p = 0.07$), 3-year distant metastasis (DM): 8% vs. 21% ($p = 0.04$), 3-year overall recurrence rate (ORR): 11% vs. 29% ($p = 0.01$), and 3-year cause-specific survival (CSS): 94% vs. 79% ($p = 0.06$), respectively. On stage-based subgroup analysis, for stage I—II disease, 3-year LRR: 5% vs. 10% ($p = 0.51$), 3-year DM: 7% vs. 16% ($p = 0.32$), 3-year ORR: 10% vs. 23% ($p = 0.15$), and 3-year CSS: 95% vs. 82% ($p = 0.38$). For stage III disease, 3-year LRR: 10% vs. 40% ($p = 0.07$), 3-year DM: 9% vs. 43% ($p = 0.07$), 3-year ORR: 15% vs. 55% ($p = 0.04$), and 3-year CSS: 94% vs. 57% ($p = 0.048$).

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Conclusions: When given concurrently with radiotherapy, Cetuximab and triweekly Cisplatin demonstrated comparable efficacy for AJCC 8th Edition stage I–II p16-positive OPSCC. However, Cetuximab appeared to be associated with higher rates of treatment failure and cancer-related deaths in stage III disease. Upon availability of the RTOG 1016 trial results, analysis based on the revised HPV-based staging should be performed to confirm these findings.

1. Background

Human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC) is now established as a distinct clinical entity with favorable patient outcomes compared to other squamous cell carcinoma (SCC) of the head and neck that are commonly associated with heavy tobacco and alcohol use.[1] Because of this, there are ongoing attempts to de-intensify treatment to minimize treatment-related toxicities without compromising disease control. High-dose Cisplatin concurrent with radiation therapy is considered the standard of care for locally advanced SCC of the head and neck (LASCCHN) but is a regimen associated with considerable toxicity. Cetuximab, an epidermal growth factor receptor (EGFR) inhibitor, emerged as a potential alternative to Cisplatin-based radiotherapy after demonstrating a locoregional control and survival benefit when added to radiation for LASCCHN in a randomized trial.[2] This benefit was maintained specifically in p16-positive OPSCC.[3]

While the addition of Cetuximab to radiation is known to improve patient outcomes over radiation alone, there is no randomized evidence thus far comparing the efficacy of Cetuximab to high-dose Cisplatin. RTOG 1016 is a phase III randomized clinical trial designed to answer this question specifically for patients with HPV-associated OPSCC; it is now closed to accrual, but the results are not yet mature. Several institutions have retrospectively performed comparisons of Cisplatin and Cetuximab in LASCCHN with conflicting findings.[4–8] The majority of these reports comprise a heterogenous population of all LASCCHN without exclusively evaluating outcomes in patients with p16-positive OPSCC. To complicate matters further, the new AJCC 8th Edition Cancer Staging Manual now distinguishes p16-positive OPSCC as an entity separate from its p16-negative counterpart to more accurately prognosticate outcomes for this population.[9] Here, we report our institutional experience treating p16-positive OPSCC with definitive radiotherapy concurrent with either high-dose Cisplatin or Cetuximab in the context of revised HPV-based staging.

2. Materials and methods

2.1. Study design

A retrospective review was conducted at a single-institution from November 2006 through September 2016 after obtaining approval from the institutional review board. Consecutive patients eligible for inclusion underwent definitive management for TNM stage I–III (cT1-2N1-3 or cT3-4N0-3) (American Joint Committee on Cancer (AJCC) 8th Edition staging) histologically-confirmed p16-positive OPSCC with radiation therapy concurrent with either triweekly high-dose Cisplatin ($n = 251$) or Cetuximab ($n = 40$). Patients who received induction chemotherapy or oncologic surgery of any kind prior to definitive management were excluded from analysis, as were patients with prior head and neck radiotherapy or other known malignancies (excluding non-melanoma skin cancer) within the previous five years. Central pathology review was performed, with p16 immunohistochemical staining obtained for all patients, with positive cases interpreted to be strong and diffuse, >75% nuclear and cytoplasmic immunoreactivity.[10] A minimum of one year of follow-up was required for all surviving patients.

2.2. Treatment

Patients received intensity-modulated radiation therapy (IMRT) to a planned dose of 66–70 Gy with simultaneous-integrated boost technique concurrent with either high-dose Cisplatin (100 mg/m^2 triweekly) or Cetuximab (400 mg/m^2 loading dose followed by 250 mg/m^2 weekly). Reasons for receiving Cetuximab rather than Cisplatin were predominantly due to patient and physician preference with the exception of patients who were thought to be suboptimal candidates for high-dose Cisplatin due to baseline renal dysfunction or hearing impairment ($n = 9$). All patients underwent weekly on-treatment examinations. A treatment break was defined as one lasting two days or longer. At our institution, we did not prophylactically place gastrostomy tubes for nutritional support prior to treatment initiation. Rather, they were placed at the discretion of the treating physician if swallowing became significantly impaired during treatment or if patients experienced weight loss exceeding 10% of their baseline weight.

Evaluation with clinical exam and nasopharyngoscopy was performed one month following completion of treatment. Subsequent follow-up was scheduled initially every two to three months and gradually transitioned to every six months until five years at which point patients had the option of annual surveillance in head and neck clinic or routine care with their primary care provider. Post-treatment imaging studies were obtained periodically at the discretion of the treating including a baseline positron emission tomography (PET) scan in over 95% of the patients. No planned neck dissections were performed.