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Title: Paired phase II trials evaluating cetuximab and radiotherapy for low risk HPV associated oropharyngeal cancer and locoregionally advanced squamous cell carcinoma of the head and neck in patients not eligible for cisplatin

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Abstract

Background: Alternative therapeutic strategies are needed for localized oropharyngeal carcinoma. Cetuximab represents a potential option for those ineligible for cisplatin or, until recently, an agent for de-escalation in low risk HPV+ oropharyngeal carcinoma (OPSCC). Our objective was to define the toxicity and efficacy of cetuximab-radiotherapy.

Methods: We conducted paired phase II trials evaluating cetuximab-radiotherapy in two cohorts A) low risk HPV+ OPSCC and B) cisplatin ineligible. The mean follow-up was 48 months.

Results: 42 patients were enrolled on Cohort A with a two-year disease free survival (DFS) of 81%. 21 patients were enrolled onto Cohort B prior to closure due to adverse outcomes with a two-year DFS of 37%. Severe toxicities were seen in 60% of patients, 30% required enteral nutrition.

Conclusion: Amongst cisplatin ineligible patients, cetuximab treatment engendered poor outcomes. Rates of severe toxicities were on par with platinum based regimens suggesting that cetuximab is not a benign treatment.

Introduction

Head and neck squamous cell carcinoma is the sixth most common malignancy with the majority of patients presenting with advanced disease[1,2]. The addition of platinum based chemotherapy to radiotherapy is a standard of care for locally advanced disease[3,4]. However, the addition of cisplatin is associated with significant toxicities, prompting investigators to look for alternate therapeutic regimens[5].

In an era of HPV related (HPV+) oropharyngeal squamous cell carcinoma (OPSCC), long term toxicities related to cisplatin and radiation are concerning in a highly curable and often younger population[6]. Cetuximab is the only non-cisplatin radiosensitizing therapy for head and neck cancer supported by randomized phase III trial data[7]. Initial evidence suggested that the addition of cetuximab to radiation resulted in minimal increase in toxicity with significant improvement in locoregional control and survival. Furthermore, the degree of survival improvement seen in the subset with oropharyngeal cancer seemed to mirror that observed in cisplatin trials. Hence, substitution of cetuximab for cisplatin became a de-escalation strategy of interest to decrease the treatment associated toxicities while maintaining survival outcomes.

Beyond the HPV+ OPSCC population, there is also significant interest in finding alternatives to cisplatin in patients with baseline organ dysfunction, poor performance status, and medical comorbidities. Furthermore, meta-analyses suggest a lack of benefit to the addition of cisplatin patients ≥ 70 years old[4]. Although cetuximab may be a viable substitute, it is still associated with potentially severe toxicities including acneiform rash and infusion reactions which may impair the delivery of curative doses of radiation. At the five year follow-up analysis, a subset analysis suggested a lack of benefit in the addition of cetuximab to radiation in patients ≥ 65 years old as well as those with a KPS

performance status of 60-80%[7-9]. Although hypothesis generating, these observations were based on small numbers of patients. To date, no clinical trial has been performed specifically to evaluate the efficacy and tolerability of cetuximab in this setting.

Recognizing the potential therapeutic roles for cetuximab, we conducted paired, multicenter phase II trials to characterize the efficacy and toxicity in two distinct patient cohorts: 1) low risk HPV+ OPSCC; and 2) ≥ 70 years old or not-eligible for cisplatin.

Materials and Methods

Patient eligibility

These were paired multicenter phase 2 open label trials registered with the National Cancer Institute (NCT01663259, NCT00904345), independently reviewed, and approved by the Institutional Review Boards (IRBMED) of both participating centers; the University of Michigan Rogel Cancer Center (UMCC) and Ann Arbor Veterans Affairs Medical Center (AAVAMC). All patients provided written informed consent. This trial was conducted in full accordance with World Medical Association Declaration of Helsinki and local IRB ethical requirements.

Inclusion criteria for the low risk cohort (Cohort A) stipulated pathologically confirmed, previously untreated stage III-IV squamous cell carcinoma of the oropharynx, p16 expression on pre-treatment biopsy, smoking history less than 10 pack years, and ECOG ≤ 1. Patients' tumors were staged following the AJCC 7th edition criteria[10]. Tumors were defined as p16 positive if ≥ 70% of tumor cells demonstrated strong and diffuse nuclear and cytoplasmic staining[11].

Inclusion criteria for the non-cisplatin eligible cohort (Cohort B) consisted of pathologically-confirmed, previously untreated locally advanced squamous cell carcinoma of the larynx, hypopharynx, oropharynx, oral cavity, or unresectable head and neck cutaneous squamous cell carcinomas. Eligible patients were required to have met at least one of the following criteria 1) age ≥ 70 years old, 2) ECOG ≥ 1, 3) creatinine clearance < 30 cc/min, and/or 4) co-morbidities that precluded treatment with standard platinum-based chemotherapy as determined by the treating physician. Patients with nasopharyngeal squamous cell carcinoma were excluded.

In both cohorts, patients were required to have adequate hematopoietic and hepatic function defined as: WBC ≥ 3.5 $x10^9$ cell/ml, absolute neutrophil count ≥ 1.5$x10^9$ cell/ml, platelets ≥100,000 cells/mm^3, concentration of total serum bilirubin less than 1.5 times the upper limit of normal (ULN) as well as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) within 2.5x institutional upper limits of normal. Patients with a history of head and neck radiation or chemotherapy, prior head and neck malignancy, previous treatment with anti-EGFR directed therapy, or documented distant metastases were excluded.

Staging and Treatment

Pretreatment assessment of enrolled patients included a complete history and physical examination by all multidisciplinary teams (Otolaryngology, Radiation Oncology, and Medical Oncology), baseline laboratory studies (CBC with differential, comprehensive metabolic profile), and radiographic staging studies (PET-CT, CT or MRI of the head and neck as clinically warranted). All screening assessments were completed within 28 days prior to the start of treatment.

Radiotherapy started 5-7 days after loading dose of cetuximab and consisted of daily fractionated IMRT delivered over 35 fractions. In cohort A, total dose delivered to the planning target volume (PTV) high was 70Gy and PTVlow was 56Gy where gross tumor volume (GTV) was expanded by 3-5mm to create clinical target volume (CTV) 70. In cohort B, a PTVmid to 63Gy was used for high risk nodal volumes at discretion of treating physicians. PTV expansion was 3mm from CTV in all patients. Interruption in treatment was defined as greater than 4 scheduled radiation treatments missed ($\geq$ 54 days from initiation to completion of radiotherapy).

Cetuximab was delivered as a loading dose of 400 mg/m^2 administered 1 week prior to the start of radiotherapy. Premedication with acetaminophen, diphenhydramine, famotidine, and hydrocortisone was administered prior to every dose of cetuximab. Criteria for drug interruption and dose reduction were specified per protocol. Cetuximab 250 mg/m^2 was administered weekly during radiation. Patients were seen weekly by both Radiation Oncology and Medical Oncology during which toxicities were graded. Treatment-related adverse events were graded according to the Common Terminology for Adverse Events version 4.0 (CTCAE v4). At 12-14 weeks post completion of radiation restaging imaging (PET-CT or MRI at the discretion of the treating physician) was performed to evaluate clinical response to therapy. Patients were seen for study related follow-up at 1 month, 12-14 weeks, 1, and 2 years post completion of radiation at which point toxicities were recorded.

Statistical Analysis

Proposed sample sizes for each cohort (n=43 Cohort A; n=50 Cohort B) were pre-determined based on simulations using cohort specific preliminary data and objectives assuming 85% of accrued

patients would be evaluable for the primary endpoint, progression free survival. A previously published institutional clinical trial was utilized as a historical control. In this cohort, patients with oropharyngeal cancer were treated with daily fractionated IMRT and weekly carboplatin and paclitaxel for radiosensitization with survival on par with cisplatin regimens[12]. The primary objective of efficacy for Cohort A was powered to provide sufficient evidence to justify a future multi-institutional study and not formally test non-inferiority. Proceeding with a phase III multi-institutional study required that Cohort A demonstrate evidence of similar survival outcomes and lower rates of toxicities (including weight loss and enteral feeding tube use) compared to a historical control treated with platinum based therapy. Power for a test of biomarker association with progression-free survival was considered for Cohort B. All enrolled patients were evaluable for toxicity. Patients were evaluable for response if they completed the entire course of cetuximab and radiation or if radiation and/or cetuximab was stopped or modified due to toxicity.

Treatment-related adverse events (CTCAE v4) were graded for each trial and assigned an attribution. The highest grade observed for recurring toxicities was recorded. Adverse events definitely, probably, or possibly related to treatment were tabulated for comparison. Acute toxicities were defined as those occurring within 180 days of treatment completion. Freedom from local regional progression (FFLRP) was defined as time from enrollment to first local or regional failure. Disease free survival (DFS) was defined as time from enrollment to first event of either recurrent disease or death. Overall survival (OS) was defined as time from enrollment to death from any cause, or date of last follow-up for alive patients. Survival estimates were calculated using Kaplan-Meier methods, and the confidence intervals

were calculated by Greenwood method. All analyses were performed using SAS v9.4 software and R version 3.5.2.

Results

Patient Characteristics

From February 2009 to May 2016, a total of 63 patients were enrolled and treated with concurrent radiation and cetuximab. (Figure 1). The patient characteristics are summarized in Table 1. Overall, the median age was 61 years old (range: 39-85) and the majority of participants were male (n=53, 84%). Cohort A completed accrual while Cohort B stopped early due to concerns regarding toxicity and frequency of disease persistence.

Cohort A consisted of 42 patients, all of whom had HPV positive squamous cell carcinoma of the oropharynx. The majority were non-smokers, however 14% of patients had a greater than 10 pack year smoking history. Five percent of patients had T4 and 7% had ≥ N2c disease by AJCC 7th edition. Post hoc staging by AJCC 8th edition[13] demonstrated 81% (n=34) patients to have Stage I disease, 14% (n=6) with Stage II, and 5% (n=2) with Stage III.

Cohort B consisted of 21 patients of which nearly all patients were either current active smokers (n=7, 33%) or former smokers with greater than 10 pack year history (n=13, 62%). The pre-treatment Charlson Comorbidity Index (CCI) was calculated and most patients were found to have low level comorbidities (n=12, 57%); however, a significant number of patients had advanced level comorbidities (n=7, 33%). The most common primary site was the oropharynx (n=16, 76%). Characterization of the extent of disease by TNM staging demonstrated that most patients had Stage IVA disease (Stage III: n=6,

28%, Stage IVA: n=10, 48%, Stage IVB: n=5, 34%). HPV status was known in most patients (16/21) of which 10 were HPV positive (48%).

Treatment Compliance

Cetuximab based radiotherapy was administered per protocol in all 42 patients of the low risk HPV+ cohort (Table 2). A total of 23 patients (55%) who received at least seven doses of cetuximab and planned 70 Gy dose of radiation was delivered in all 42 patients. One patient (2%) had an interruption in radiation. A mean weight loss of 8% starting body weight was observed and 11 patients (26%) required enteral tube placement during therapy.

Among Cohort B, radiotherapy plus cetuximab was administered per protocol in 18 patients. Three patients did not complete study treatment with concurrent radiation and cetuximab. One patient discontinued cetuximab after a hypersensitivity reaction during the loading dose and was treated with radiotherapy alone. Three patients (14%) had radiation interruptions ranging from one to twenty-six days. Radiation and cetuximab were both discontinued in two additional patients (9%) due to radiation associated toxicities- one after 42 Gy and the other after 32 Gy. 18 patients (86%) had no interruption in their radiation therapy. Fourteen patients (63%) had at least seven doses of cetuximab. The mean weight loss was 11% (maximum of 14%) and eight patients (38%) required G-tube placement during treatment.

Treatment Toxicity

Amongst all 63 patients included in the study, ≥ grade 3 toxicities were seen in 60% of patients (Table 2). Select grade 3 toxicities of interest included mucositis in 43%, cutaneous toxicity in 11%, 19% dysphagia, and 9% hematologic toxicity (Table 3). Patients in Cohort A had a relatively higher rate of ≥ grade 3 toxicities (67%) relative to those in cohort B (48%). Distribution of toxicities was relatively similar between the two cohorts with more grade 3 hematologic toxicity seen in Cohort A (6 patients, 14%) whereas there was more grade 3 cutaneous toxicity (4 patients, 19%) in Cohort B. No grade 5 toxicities were seen in either cohort.

Outcomes

The median follow-up was 48 months. Kaplan-Meier survival analysis for overall survival (Figure 2A), disease free survival (Figure 2B), disease specific survival (Figure 2C), and freedom from locoregional progression (Figure 2D) were performed independently for each cohort. In the cohort A, the 1 and 2-year disease free survival were 86% (95% CI: 76-97%) and 81% (95% CI: 70-94%) respectively with corresponding 1 and 2-year overall survival of 98% (95% CI: 93-100%) and 95% (95% CI: 89-100%) (Table 4). One patient had a local failure, four patients had regional failure, and two patients had distant metastases.

At the time of analysis, in the non-cisplatin eligible cohort, eight patients are alive with a median follow up of 48 months. One patient was lost to follow up shortly after completion of treatment. Fifteen patients had planned reimaging three months after the completion of radiation. Two patients died prior to post-treatment restaging imaging and response assessment was missing for an additional four patients. Eleven patients (73%) had tumor clearance (radiographic complete response) on their

post-treatment imaging whereas four patients (27%) had persistent disease. The estimated overall survival was 68.8% (95% CI: 50.9-93.0%) at 1 year and 47.6% (95% CI: 29.7-76.3%) at 2 years. The estimated disease free survival was 47.8% (95% CI: 29.9-76.5%) at 1 year and 37.2% (95% CI: 20.7-66.8%) at 2 years. The disease specific survival at 2 years was 52.9% (95% CI:33.8-82.9%). Eleven patients developed recurrent disease. Patterns of recurrence varied significantly; six patients had both local and regional recurrence, one patient had local and distant recurrence, one patient had a regional failure, and three patients had distant metastases alone.

Discussion

These paired multicenter phase II trials characterize the outcomes of cetuximab based radiotherapy in both low risk HPV+ OPSCC patients and those ineligible for cisplatin. The findings of this study are timely given the publication of RTOG 1016 and the unanswered question of alternative agents for radiosensitization in specific cohorts of locally advanced HNSCC.

HPV+ OPSCC has been demonstrated to have better response to treatment compared to stage matched HPV- OPSCC. Low risk HPV+ OPSCC risk disease (defined as AJCC 7th Edition non-T4 and less than N2b with a <10 pack year history) has been shown to have a high overall survival of 93% at 3 years with cisplatin based radiation[14,15]. Amongst the cohort with low risk HPV+ OPSCC our study, the impressive overall survival was on par with previous findings[12,16]. Of note, due to evolving definitions of low risk[15], 2 patients were included whom would now be considered high risk HPV+ OPSCC and hence not eligible for de-escalation trials. The recent publication of two phase III trials (De-ESCALaTE and RTOG 1016) have highlighted the inferiority of cetuximab versus cisplatin. De-ESCALaTE was powered to

assess rates of severe toxicity with cetuximab versus cisplatin and indeed demonstrated equivalent rates of toxicities between the agents. However, treatment with cetuximab was found to be associated with a potentially impaired overall survival versus cisplatin (2-year overall survival 89.4% versus 97.5%)[17]. The non-inferiority trial RTOG 1016 definitively demonstrated the five year overall survival was significantly worse with radiotherapy plus cetuximab versus cisplatin (77.9 vs 84.9%)[18]. In comparison, we demonstrated a higher overall survival at one and two-year survival in patients treated with cetuximab roughly equivalent to the HPV+ subgroup analysis of IMC-9815[9]. Of note, RTOG 1016 included a significant population of patients which would not be considered low risk HPV+ OPSCC given their advanced stage disease (T4 or greater than N2b by AJCC 7th Edition) or smoking history (>10 pack years) which could potentially have affected these comparisons. Similarly, the overall survival in our trial was superior to published outcomes of cetuximab based radiotherapy in oropharyngeal cancer, albeit our study focused solely on patients with disease considered low risk[8].

Although a high overall survival rate was seen in Cohort A, the disease free survival seen in this low risk cohort was lower than that seen with historical cohorts treated with platinum based chemoradiation, but similar to previous reports of cetuximab based radiotherapy in HPV+ OPSCC[8,12,16]. This extends and supports the finding of decreased progression free survival in patients treated with cetuximab radiotherapy versus cisplatin in both RTOG 1016 and De-ESCALaTE[17,18].

Patients who are ineligible for cisplatin do not have evidence supporting the safety and efficacy of radiosensitizing therapeutics. Although age has previously been considered a contraindication to cisplatin, reviews of the National Cancer Database have shown an improvement in survival with the addition chemotherapy to radiotherapy regardless of age[19-21]. This emphasizes the need for

investigation of radiosensitizing therapeutics in older patients and those with contraindications to cisplatin. Cetuximab has been proposed given the lack of contraindications with solid organ impairment and differential mechanism of action compared to traditional cytotoxic agents. In fact, the IMC-9815 trial demonstrated no increased toxicities with the addition of cetuximab compared to radiotherapy alone[7]. Although data in Cohort B was limited due to early closure, both the overall and disease free survival rates were lower compared to those reported in either arm of IMC-9815. Our study exclusively targeted patients with a poor performance status and/or older than 65, a population which previously was suggested to have not garnered benefit with the addition of cetuximab[22]. Beyond impaired performance status and age, patients in cohort B were at high risk of recurrence as they were primarily stage IVA, current or past smokers, and had a large population of HPV- patients.

Toxicities are important to consider especially when dealing with both low risk or frail populations. De-escalation of therapy with alternate chemotherapeutics in low risk HPV+ OPSCC has been an intense area of interest. To be suitable for de-escalation, a regimen must decrease toxicity while maintaining excellent outcomes. Cetuximab has been considered as a potential agent for de-escalation in low risk HPV+ OPSCC given its previously reported efficacy and lack of increase in toxicity over radiotherapy alone. Our study supports that cetuximab is associated with significant rates of serious adverse events, albeit with a different profile[23]. RTOG 1016 demonstrated no difference in the rate of grade 3-4 toxicities between patients treated with cisplatin and those treated with cetuximab[18]. Severe mucositis was seen in 43% of patients overall (45% of the low risk cohort) which is seemingly lower than the rates of 53-56% reported with platinum based regimens[12,18,23]. Cutaneous toxicity is a known issue with cetuximab based radiotherapy reported in 23-43% of patients[7,18,23]. We observed a

much lower incidence of severe cutaneous toxicity, possibly due to the institutional use of prophylactic doxycycline and topical corticosteroids prior to initiation of therapy.

Outside of these commonly reported toxicities, weight loss and enteral nutrition can be significant contributors to impairment in quality of life. Reducing weight loss and the need for enteral nutrition are major aims when considering any treatment, especially those being used as an approach of de-escalation or in a frail population. In our study, patients lost an average of 7% of their starting body weight and many patients enteral nutrition. This rate of enteral nutrition is near identical to our previously reported rate in patients with OPSCC treated with carboplatin and paclitaxel based radiotherapy (30% in this study vs 29% previously)[12]. RTOG 1016 similarly reported no difference in the rate of enteral nutrition between patients treated with cisplatin versus cetuximab (57.3 vs 61.5%), although with higher overall feeding tube use. Feeding tube rates in our study may be lower due to smaller radiation target expansions and careful radiotherapy sparing of normal tissues known to be associated with dysphagia including pharyngeal constrictors.

Ongoing biomarker studies are underway to identify patient populations who may have a greater response to cetuximab. Tumor EGFR expression has not correlated with response, but p16+ patients with KRAS variant have been suggested to have greater benefit from cetuximab when added to RT/cisplatin, and loss of PTEN expression has been associated with decreased cetuximab response[24,25]. An immune mechanism for cetuximab response has also been suggested[26]. Immune markers and downstream markers of EGFR from tumor and normal tissue collected on our trial pre and post cetuximab administration are being investigated for correlation with tumor response and toxicity.

Although these paired clinical trials provide insight into the utility of cetuximab in important patient subgroups, our conclusions are limited given the relative sample size and single arm design. Although a significant limitation, the weakness of a lack of control arm was compensated by use of a relatively matched historical control. This control consisted of a prospective clinical trial performed at our institution in which patients with OPSCC were treated with radiotherapy plus carboplatin and paclitaxel and achieved excellent survival and functional outcomes. Although survival in Cohort A was on par with our historical control, the rate of severe toxicity was only modestly lower that platinum based therapy. Therefore, the evidence was insufficient to support a larger de-escalation trial utilizing cetuximab.

The challenges are similar in the cohort of non-cisplatin candidates which closed early due to high rate of failure and toxicity. The premature closure of the trial points to the potential for both poor outcomes and significant toxicities in this group at need of better treatment options. In the cohort of patients who were not eligible for cisplatin, cetuximab and radiotherapy was associated with poor patient outcomes including a high rate of toxicity and recurrent disease. The findings of NRG HN004 will be important in assessing the future utility of cetuximab and durvalumab in this non-cisplatin population. A future challenge may be the lack of a control arm of radiotherapy alone and/or an arm containing an alternative less toxic platinum regimen (ie weekly carboplatin and paclitaxel). Nevertheless, these findings will be pivotal in understanding how to best tailor therapy in LAHNSCC.

In conclusion, cisplatin remains the standard of care for concurrent chemoradiotherapy in the head and neck amongst eligible patients[27]. For those who are ineligible, further studies are necessary to identify optimal treatment alternatives.

Table 1: Patient and Tumor Characteristics

Table 2: Treatment Characteristics and Compliance

Table 3: Treatment Related Toxicities

Figure 1: Patient Flow Diagram

This figures illustrates the enrollment and follow-up status for all patients involved with the paired clinical trials.

Figure 2: Patient Survival Outcomes

These figures demonstrate overall survival (A), disease free survival (B), disease specific survival (C), and freedom from locoregional progression (D) for each cohort.

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