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Cisplatin versus Cetuximab With Definitive Concurrent Radiotherapy for Head and Neck Squamous Cell Carcinoma: an Analysis of Veteran's Health Data

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Abstract

Background: Addition of cisplatin or cetuximab to radiation (RT) improves outcomes compared to RT alone in the non-operative management of head and neck squamous cell carcinoma (HNSCC), but limited data exist comparing these approaches. We compared outcomes of patients (pts) treated with RT plus cisplatin or cetuximab using Veterans Health Affairs (VHA) data.

Methods: We identified pts with stage III-IVb HNSCC treated non-surgically with RT and cisplatin or cetuximab from 2000 to 2016 in the VHA. Pts were analyzed by the drug used in their first treatment cycle (intent-to-treat). We compared overall survival (OS) by treatment group using Cox regression models, employing propensity score (PS) methods to account for treatment

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allocation bias. We determined the risk of toxicities, fitting logistic regression models in propensity-matched cohorts.

Results: A total of 4,520 pts were included in the analysis with a median follow-up of 3 years (yrs): 83% received cisplatin (20% ‘low dose’ – 30–50 mg/m²/week). Cisplatin pts were younger ($p<0.001$) and had fewer comorbidities ($p<0.001$). In an unmatched analysis, cetuximab was associated with inferior OS ($p<0.001$). After PS matching, cetuximab treatment remained statistically significantly associated with inferior OS (1.7 vs 4.1 yrs, HR 1.61, 95% CI 1.44–1.79, $p<0.001$). These differences remained significant across all primary HNSCC subsites and when compared to low dose and high dose cisplatin.

Conclusion: Cetuximab with RT yields inferior OS compared to cisplatin for non-operative management of Stage III-IVb HNSCC. Based on this study, cisplatin may be the most appropriate partner for RT in this setting.

Keywords

Cisplatin; Cetuximab; Head and Neck Cancer; Propensity Score; Chemoradiotherapy

Background

Head and Neck Squamous Cell Carcinoma (HNSCC) is a relatively common cancer, with nearly 50,000 new cases estimated in the United States in 2017.¹ Most patients present with locally advanced disease, which is treated with a combination of surgery, radiation therapy (RT), and systemic therapy. For patients opting for non-operative management, the standard of care is definitive RT with concurrent systemic therapy. There are currently two systemic treatments with Phase III data supporting their use – cisplatin² and cetuximab^{3, 4}. Each of these agents has been shown to lead to improved overall survival when compared to radiation alone. Guidelines view either option as a reasonable approach⁵ and, perhaps due to the impression that the toxicity profile is superior for cetuximab,^{2, 3, 6–11} many physicians opt for its use. There are scant prospective data comparing the relative efficacy of cisplatin and cetuximab in HNSCC, and it is unclear if cetuximab is actually less toxic. One published trial aimed to compare these two drugs when given with radiation but was significantly underpowered due to slow accrual – only 70 patients were randomized. In that analysis serious adverse events were, in fact, more common with cetuximab.¹² Multiple retrospective analyses have compared outcomes for platinum and cetuximab in this setting. While some showed cetuximab to be inferior to platinum sensitized RT,^{13–15} one series showed similar outcomes.¹⁶ All of these were limited by relatively small sample size, so they could not do robust subgroup analyses or control effectively for confounding by indication. The RTOG and TROG cooperative groups are currently performing Phase III studies comparing these agents among patients with p16(+) (HPV-related) oropharyngeal cancers. A press release was recently released indicating that cetuximab was inferior to cisplatin in the recently completed RTOG 1016 trial. Nevertheless, no randomized clinical trials are currently ongoing to address the relative efficacy of cisplatin versus cetuximab among patients with p16 (–) tumors. This is particularly relevant, as some data among patients with metastatic HNSCC indicate that epidermal growth factor receptor inhibition may have a more pronounced importance in p16 (–) tumors.¹⁷ An analysis of cancer registry

data linked to clinical information may be a practical way to inform clinical practice for this issue.

We have previously used clinical data from the Veterans Affairs (VA) Corporate Data Warehouse (CDW) to evaluate the effect of cisplatin dosing on clinical outcomes in HNSCC.¹⁸ The CDW contains registry-based cancer data linked to detailed clinical information for patients treated at VA medical centers across the United States. In contrast to claims data or other cancer registries, CDW includes pharmacy data describing chemotherapy dosing and frequency, as well as detailed comorbidity, behavioral and laboratory data, thereby providing detailed real-world comparative effectiveness data on cetuximab versus cisplatin with radiation for locally advanced HNSCC.

Methods

Patient Selection

Using the CDW, we identified patients with AJCC 7th Edition unresected stage III-IVb HNSCC treated with RT and either cisplatin or cetuximab (from 2000 to 2016 within the Veterans Affairs Health System. To be consistent with prior landmark trials in HNSCC,^{2, 10, 11} we evaluated patients with squamous cell carcinoma of the oral cavity, oropharynx, and hypopharynx/larynx. We excluded patients with nasopharyngeal, sinus, and other less common tumors. We also excluded patients who underwent definitive surgery before radiation, but did allow patients who underwent diagnostic procedures, such as lymph node biopsies (Figure 1).

Study Variables

VA databases were used to identify baseline sociodemographic variables. Comorbid illnesses present in outpatient and inpatient VA claims databases were identified using diagnostic codes in the 12 months prior to cancer diagnosis. Specific comorbidities relevant to treatment decision-making regarding systemic therapy choice were also identified (e.g. hearing loss and neuropathy) and we then calculated Charlson-Deyo scores for each subject to estimate the overall burden of comorbidities.^{19–21} Marital status and alcohol use was collected from VA oncology files and smoking status was classified using VA health factors data and augmented with registry data.²² Baseline creatinine values and estimated glomerular filtration rate (eGFR) estimates were ascertained using VA laboratory data. Cancer data were collected from VA oncology files, including diagnosis date, cancer stage, histologic subtype and anatomic site. Initial course of cancer treatment was determined using published methods for combined registry and administrative data; we supplemented oncology registry data using procedure codes to identify definitive surgical procedures and radiotherapy use.²³ We used the intravenous medication pharmacy files to ascertain systemic therapy use and dose. Given differential dosing practices surrounding cisplatin, we identified patients as receiving “high-dose cisplatin” (HDC, 80–120 mg/m²) or “low-dose cisplatin” (LDC, 30–50 mg/m²). Patients were analyzed in an intent-to-treat fashion based on the first regimen administered; e.g. patients who began receiving cetuximab and switched to cisplatin were assigned as recipients of cetuximab.

The primary outcome in this study was overall survival (OS). Secondary outcomes included the incidence of major treatment toxicities, as recorded using diagnostic coding in the CDW data files. Survival times for primary analyses were calculated using the date of first systemic therapy administration until the date of death or censoring on March 1, 2017. Time to event analyses of drug toxicities were calculated using the time from the initiation of either cetuximab or cisplatin until the earliest date of the event of interest, death or the end of the event window (60 days for acute events; last date of Veteran's Health Affairs (VHA) healthcare contact for chronic events). The study was approved by the institutional review board of the James J. Peters VA Medical Center.

Statistical Analysis

We tested for differences in baseline and clinical characteristics between cisplatin and cetuximab treatment groups using the chi square test for categorical variables and the t-test or Wilcoxon test for normal or non-normal continuous variables, respectively. In unmatched analyses we compared overall survival by fitting Cox regression models, first for all anatomic sites, and then stratified by anatomic site groups. Due to expected differences in the characteristics of patients receiving treatment with cisplatin or cetuximab (e.g. renal function, age, comorbidity), we used propensity score (PS) analysis to minimize allocation bias associated with the use of different therapies,²⁴ as has been successfully used to analyze the outcome of different cancer interventions.^{20, 25} We calculated PS for the study cohort by determining the probability of the use of cetuximab using logistic regression. Variables included in the PS were sociodemographic characteristics (age, race, sex, and marital status), smoking and alcohol use, comorbidity score, eGFR, baseline neuropathy and hearing loss, tumor characteristics (overall stage, T stage and N stage), year of diagnosis, and annual HNSCC treatment volume at the treating VA medical center. Variable types were included in the PS model as shown in Table 1, except for HNSCC treatment volume, which was categorized by quartiles. Smoking status, T-stage, N-stage, and alcohol use all had missing values (3%, 0.7%, %, 0.04%, and 6.1%, respectively); we used multiple imputation methods to estimate missing values for the propensity score calculation. Distribution of PS's were appropriate for comparison of treatments (Box plots; Supplemental Figure 1). A PS-matched cohort was then created, matching cetuximab-treated patients to up to 3 cisplatin-treated patients, yielding a cohort of 2,361 subjects (1,569 cisplatin and 792 cetuximab) using a PS caliper of 0.04.²⁶ We fitted Cox regression models comparing primary outcomes (survival and toxicity outcomes) between treatment groups in the matched cohort using robust standard errors.

In a secondary analysis, we also compared outcomes according to cisplatin dose. Although prior data found no differences in outcomes between HDC and LDC,¹⁸ many clinicians consider LDC or cetuximab for patients ineligible for HDC. For this analysis, we created additional PS-matched cohorts, matching 792 cetuximab patients to up to one LDC comparator (using a PS caliper of 0.05) yielding a matched cohort of 1,108 and matching 792 cetuximab patients to up to two HDC comparators (using a PS caliper of 0.05) yielding a matched cohort of 2,029. We then fit logistic regression models for toxicities between treatment groups in the matched cohorts (the overall cisplatin- and LDC-matched cohorts

described above) using robust standard errors. All analyses were performed using SAS 9.2 and STATA 15.

Results

Patient Characteristics

See Figure 1 for a CONSORT diagram of how we arrived at our analytic sample of 4,520 patients with Stage III-IVb HNSCC. Patients receiving cisplatin were younger (Table 1; $p<0.001$), more likely to be Caucasian ($p<0.001$), and current smokers ($p<0.001$). Patients receiving cisplatin had a different distribution of primary sites, with a higher percentage of laryngeal/hypopharyngeal cancers ($p=0.035$). There was no difference between treatment groups in terms of T or N stage. Cisplatin-treated patients had a higher baseline glomerular filtration rate ($p<0.001$), a lower prevalence of baseline hearing loss ($p<0.001$) and less neuropathy ($p<0.001$). Patients receiving cisplatin had a lower comorbidity score ($p<0.001$). The use of cetuximab increased over time ($p<0.001$). The median cumulative dose of cisplatin was 164 mg/m^2 (120 mg/m^2 among patients receiving LDC and 180 mg/m^2 among patients receiving HDC).

Survival Outcomes

In an unmatched survival analysis of all HNSCC cases, cetuximab treatment was associated with a lower OS relative to cisplatin (hazard ratio for death (HR) 1.70, 95% confidence interval (CI) 1.56–1.86, $p<0.001$). The median OS was 3.8 years for cisplatin versus 1.5 years for cetuximab (see Figure 2 a-d). Cetuximab was associated with lower survival in tumors arising in all primary sites. After PS matching, cetuximab continued to be associated with inferior OS in the full cohort (HR 1.61, 95% CI 1.44–1.79, $p<0.001$) and in all primary sites (Table 2 and Figure 3 a-d). The median OS in the PS matched cohort was 4.1 years for cisplatin versus 1.7 years for cetuximab. As described above, we generated separate PS matched cohorts to evaluate the relative efficacy of cetuximab versus LDC and HDC. Cetuximab was associated with lower survival than LDC (HR 1.54, 95% CI 1.34–1.77, $p<0.001$) and HDC (HR 1.68, CI 1.49–1.89, $p<0.001$) in these cohorts (Table 2 and Figure 4 a-b).

Toxicity Outcomes

In a PS matched analysis of all HNSCC cases, cetuximab was associated with less renal failure, nausea, diarrhea, and hearing loss. Conversely, cetuximab was associated with a higher incidence of rash and mucositis. Neutropenia was not seen with cetuximab, so a statistical comparison was not made for this adverse event. When comparing cetuximab to LDC in a PS matched analysis, cetuximab was associated with a lower rate of renal failure, percutaneous gastrostomy tube placement, nausea and hearing loss but a higher rate of rash. (See Table 3)

Discussion

In a large cohort of patients with HNSCC, we found that cetuximab concurrent with RT was associated with lower OS compared to cisplatin, even after accounting for potential

allocation bias in the use of these therapies. These disparities persisted in all tumor primary site subgroups and cisplatin dosing levels. Cisplatin was associated with more toxicity in general than cetuximab, but the disparity was lessened with the use of LDC.

Cisplatin and cetuximab are the only FDA-approved systemic therapies for concurrent use with RT for the treatment of HNSCC. Magrini et al randomized patients with locally advanced HNSCC to RT with either cetuximab or LDC.¹² While the goal was to randomize 130 patients, the study closed early due to slow accrual. Patients receiving cetuximab experienced more cutaneous toxicity but less hematologic and renal toxicity. There were more treatment-related serious adverse events with cetuximab treatment, including 4 deaths. They saw no difference in overall survival or locoregional control between cetuximab and cisplatin although the comparison was markedly underpowered and therefore no definitive conclusions can be drawn regarding the relative efficacy of these common treatment strategies. More recently, a press release describing the results of RTOG 1016 was released. This study randomized patients with HPV associated HNSCC to RT with either cisplatin (a limited administration schedule of HDC – 2 doses of 100 mg/m²) or cetuximab. In the press release, cetuximab was noted to be inferior to cisplatin in terms of overall survival. In our large registry-based analysis which included patients with HPV related and HPV unrelated tumors, we also found worse survival outcomes associated with cetuximab use. In the only other registry-based study, recently presented at ASCO, Zandberg et al used SEER-Medicare to compare outcomes for patients receiving cetuximab based bioradiotherapy to non-cetuximab regimens and radiation monotherapy.²⁷ While results from their analysis found that cetuximab was associated with inferior outcomes to other radiation sensitizing regimens, the authors did not use a PS analysis to account for bias by allocation. Given limitations of SEER, the investigators were unable to comment on chemotherapy dosing.

Our study showed that the toxicity profiles of cisplatin and cetuximab were distinct. As expected, cisplatin was associated with a higher rate of renal failure, nausea, and hearing loss. We were surprised to find that cetuximab was associated with a higher rate of mucositis than cisplatin. This is an important finding; the original Bonner study reported that cetuximab was not associated with a higher rate of mucositis than radiation alone,³ while cisplatin is known to lead to severe mucositis when combined with radiation.^{11, 28} Despite subsequent studies reporting severe mucositis with cetuximab-based bioradiotherapy,^{12, 29} the idea that cetuximab was not associated with mucositis has persisted.

Our comparison of cetuximab to LDC also demonstrated marked inferiority for survival. Current NCCN guidelines recommend consideration of LDC or cetuximab for patients ineligible for HDC,³⁰ but scant data differentiate between the therapies – only the underpowered trial described above prospectively addressed this question.¹² The findings of our study – improved OS for LDC compared to cetuximab and a similar toxicity profile for the two agents – may support LDC as a preferred treatment approach when comorbid disease is an important clinical consideration.

Our study has several strengths and limitations. First, the CDW does not provide complete radiation dosing data. We feel it is unlikely that radiation administration varies based on the type of systemic agent. In studies of bioradiotherapy and chemoradiotherapy for locally

advanced HNSCC, adherence to radiation dose is generally very high.^{3, 10, 11} There was no difference in radiation adherence between groups in the study by Magrini et al.¹². Second, we do not know the Human Papillomavirus (HPV) status for patients with oropharyngeal cancers. While this is a potentially important limitation, the prognostic impact of HPV is less pronounced among current or former smokers,³¹ who make up a substantial portion (90%) of our study population. Our group is currently using various informatics strategies to attempt to determine HPV status for future analyses. In this study, we saw inferior outcomes across both HPV related and unrelated primary sites. Third, the patients receiving cetuximab were older and had greater comorbidity compared to the patients receiving cisplatin. Although we controlled for differences in baseline characteristics with use of PS matching, as with any observational study, there is always the risk of unmeasured confounding. We are reassured by the extensive list of variables available to us in the CDW, as well as the appropriate PS correction seen on the box plots (Supplemental Figure 1a-d). Notably, an unmeasured confounder would need to be strongly associated with both treatment and death to have biased a clinically meaningful association between cetuximab or cisplatin to the results that we observed. Finally, CDW data only includes clinical information on veterans. Generalizability of our findings may be limited by the fact that veterans are more likely to be male and have more comorbid illnesses than the general population,³² which may yield generally inferior cancer-related outcomes. We are not aware of any data indicating that sex is predictive of response (or lack thereof) to cisplatin or cetuximab.

In summary, our registry-based study shows that cetuximab yields inferior overall survival when compared to cisplatin for the non-operative management of locally advanced HNSCC of the oral cavity, oropharynx, hypopharynx, and larynx. This was seen on both unmatched and PS matched analyses. Cetuximab was also inferior to both LDC and HDC in a PS matched analysis. As such, cisplatin may be the preferred systemic therapy concurrent with RT for locally advanced HNSCC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Included and excluded patients with Head and Neck Squamous Cell Carcinoma

Figure 2a-d.

A) Unmatched analysis of overall survival of all patients by treatment with cisplatin vs cetuximab

B) Unmatched analysis of overall survival of patients with oral cavity tumors by treatment with cisplatin vs cetuximab

C) Unmatched analysis of overall survival of patients with oropharyngeal tumors by treatment with cisplatin vs cetuximab

D) Unmatched analysis of overall survival of patients with hypopharyngeal/laryngeal tumors by treatment with cisplatin vs cetuximab

Figure 3a-d.

- A) Propensity score matched analysis of overall survival of all patients by treatment with cisplatin vs cetuximab
- B) Propensity score matched analysis of overall survival of patients with oral cavity tumors by treatment with cisplatin vs cetuximab
- C) Propensity score matched analysis of overall survival of patients with oropharyngeal tumors by treatment with cisplatin vs cetuximab
- D) Propensity score matched analysis of overall survival of patients with hypopharyngeal/laryngeal tumors by treatment with cisplatin vs cetuximab

Figure 4a-b.

A) Propensity score matched analysis of overall survival of all patients by treatment with high dose cisplatin vs cetuximab

B) Propensity score matched analysis of overall survival of all patients by treatment with low dose cisplatin vs cetuximab

Table 1.

Baseline cohort characteristics by treatment group

Characteristic	Cetuximab N=783	Cisplatin N=3,737	p-value	PS-adjusted p-value
Age , mean, (SD)	66.8 (9.5)	61.0 (7.3)	<0.001	0.90
Men , N (%)	779 (99.5)	3,700 (99.0)	0.20	0.93
Race/Ethnicity , N (%)			<0.001	0.99
Caucasian	586 (74.8)	2,951 (79.0)		
African American	134 (17.1)	611 (16.4)		
Hispanic	52 (6.6)	124 (3.3)		
Other	9 (1.2)	35 (0.9)		
Missing	2 (0.3)	16 (0.4)		
Year of diagnosis , N (%)			<0.001	0.97
2000–2005	1 (0.1)	856 (22.9)		
2006–2010	406 (51.9)	1,637 (43.8)		
2011–2016	376 (48.0)	1,244 (33.3)		
Smoking Status , N (%)			<0.001	0.82
Current	427 (54.5)	2,319 (62.1)		
Former	290 (37.0)	1,040 (27.8)		
Never	55 (7.0)	255 (6.8)		
Missing	11 (1.5)	123 (3.3)		
Alcohol Use , N (%)				
Yes	599 (76.5)	3,002 (80.3)	0.01	0.99
Missing	47 (6.0)	233 (6.2)		
Anatomic Site , N (%)			0.035	0.94
Oral Cavity	64 (8.2)	256 (6.9)		
Oropharynx	537 (68.6)	2,455 (65.7)		
Hypopharynx/Larynx	182 (23.2)	1,026 (27.5)		
Stage at Diagnosis , N (%)			0.76	0.98
III	184 (24.7)	924 (24.7)		
IVA	517 (66.0)	2,436 (65.2)		
IVB	82 (10.5)	377 (10.1)		
Clinical N , N (%)			0.30	0.99
0	138 (17.6)	660 (17.6)		
1	142 (18.1)	631 (16.9)		
2	461 (58.9)	2,218 (59.4)		
3	41 (5.2)	198 (5.3)		
Missing	1 (0.1)	30 (0.8)		
Clinical T , N (%)			0.83	0.97
1	68 (8.7)	325 (8.7)		
2	205 (26.2)	1,008 (27.0)		
3	252 (32.2)	1,241 (33.2)		

Characteristic	Cetuximab N=783	Cisplatin N=3,737	<i>p</i> -value	PS-adjusted <i>p</i> -value
4	258 (33.0)	1,161 (31.1)		
Missing	0 (0)	2 (0.1)		
GFR*, mg/dl, median (IQR)	81 (62–105)	92 (78–110)	<0.001	0.97
Baseline Hearing Loss	155 (19.8)	410 (11.0)	<0.001	0.91
Baseline Neuropathy	95 (12.1)	220 (5.9)	<0.001	0.94
Comorbidity Score, N (%)			<0.001	0.66
0	236 (30.1)	1,647 (44.1)		
0–1	180 (23.0)	933 (25.0)		
>1	367 (46.9)	1,157 (31.0)		

*
GFR: Glomerular filtration rate

Table 2.

Overall Survival by Treatment Group

Outcome	Median OS (years)		HR for OS (95% CI)	p value
	Cetuximab	Cisplatin		
Unmatched Full Cohort [n=4,520]	1.5	3.8	1.70 (1.56–1.86)	<0.001
Oral Cavity (n=320)	0.8	1.5	1.63 (1.22–2.18)	0.001
Oropharynx (n=2,992)	1.8	4.2	1.64 (1.47–1.82)	<0.001
Hypopharynx/Larynx (n=1,208)	1.1	3.4	2.05 (1.72–2.44)	<0.001
PS matched Full Cohort [n=2,358]	1.7	4.1	1.61 (1.44–1.79)	<0.001
Oral Cavity (n=150)	0.8	2.6	1.51 (1.03–2.22)	0.035
Oropharynx (n=1,602)	2.0	4.7	1.58 (1.38–1.80)	<0.001
Hypopharynx/Larynx (n=606)	1.3	3.7	1.88 (1.52–2.32)	<0.001
Cetuximab vs Low dose Cisplatin, PS matched [n=1,108]	1.7	3.9	1.54 (1.34–1.77)	<0.001
Cetuximab vs High dose Cisplatin, PS matched [n=1,671]	1.7	4.2	1.68 (1.49–1.89)	<0.001

Table 3.

PS Matched Toxicity by Cisplatin Dose

Toxicity	Odds Ratio for Toxicity with Cetuximab vs Cisplatin	95% CI	Odds Ratio for Toxicity with Cetuximab Vs. Low Dose Cisplatin	95% CI
Acute				
Renal Failure	0.36	0.26–0.49	0.62	0.40–0.95
Neutropenia	*	*	*	*
Mucositis	1.53	1.19–1.96	1.08	0.79–1.48
Nausea/Vomiting	0.42	0.31–0.57	0.50	0.35–0.73
Percutaneous Gastrostomy Tube Placement	0.86	0.71–1.05	0.71	0.55–0.91
Hypersensitivity	1.99	0.89–4.45	1.51	0.53–4.27
Diarrhea	0.60	0.39–0.91	0.80	0.46–1.37
Sepsis	1.00	0.62–1.60	1.55	0.83–2.90
Rash	6.94	4.77–10.09	9.16	4.84–17.36
Chronic				
Hearing Loss	0.57	0.44–0.74	0.72	0.52–0.98
Neuropathy	1.20	0.82–1.76	1.27	0.76–2.11
Dysphagia	0.79	0.46–1.33	0.72	0.35–1.47

* no neutropenia was observed with cetuximab (odds ratio not calculable) versus 2.5% of cisplatin patients