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A single-institution comparison of cetuximab, carboplatin, and paclitaxel induction chemotherapy followed by chemoradiation (CRT) versus CRT for locally-advanced squamous cell carcinoma of the head and neck (LA-SCCHN)

Surbhi Grover, M.D.^{*}, Nandita Mitra, Ph.D.[†], Fei Wan, M.S.[†], J. Nicholas Lukens, M.D.^{*}, Sonam Sharma, M.D.^{*}, Jessica Bauman, M.D.[‡], Farzad Masroor, M.D.[‡], Roger B. Cohen, M.D.[‡], Arati Desai, M.D.[‡], Kenneth Algazy, M.D.[‡], Michelle Alonso-Basanta, M.D., Ph.D.^{*}, Peter Ahn, M.D.^{*}, Boon-Keng Kevin Teo, Ph.D.^{*}, Ara Chalian, M.D.[¶], Gregory S. Weinstein, M.D.[¶], Bert W. O'Malley Jr., M.D.[¶], and Alexander Lin, M.D.^{*}

^{*}Department of Radiation Oncology, University of Pennsylvania, Philadelphia, PA

[†]Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, PA

[‡]Department of Internal Medicine, University of Pennsylvania, Philadelphia, PA

[¶]Department of Otorhinolaryngology, University of Pennsylvania, Philadelphia, PA

Abstract

Objectives—Comparisons of induction chemotherapy (IC) against upfront chemoradiation (CRT) for locally advanced head and neck cancer (LA-HNSCC) have demonstrated no differences except greater toxicity with IC. Effective induction regimens that are less toxic are therefore warranted. To inform future efforts with IC, we present our institutional experience comparing a less toxic IC regimen to CRT.

Methods—We included patients with LA-HNSCC treated with organ-preservation CRT (+/– induction) between 2008–2011. Patients were age >18, ECOG performance status 0–1, and minimum 6 months follow-up. IC consisted of 8 weekly cycles of cetuximab, carboplatin, and paclitaxel followed by CRT. The CRT regimen was platinum-based, with cetuximab reserved for patients contraindicated to receive platinum.

Results—Of 118 patients, 24 (20%) received IC and 94 (80%) received CRT. Median follow-up was 17 (IC) and 19 (CRT) months ($p=0.05$). There were no differences in toxicity between the groups. IC patients were more likely male, with more advanced tumor and nodal stage. Even when controlling for these factors, IC was still associated with worse locoregional control (LRC) (HR 3.6 $p=0.02$), distant-metastasis free survival (HR 5.3, $p=0.02$), and overall survival (OS) (HR 5.1, $p < 0.01$).

Corresponding Author: Alexander Lin, M.D., Perelman School of Medicine, University of Pennsylvania, Department of Radiation Oncology, 3400 Civic Center Boulevard, TRC 2 West, Philadelphia, PA 19104, Telephone: (215) 662-3198, Fax: (215) 349-5445, alexander.lin@uphs.upenn.edu.

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Conclusions—IC patients had greater disease burden than those receiving CRT. IC was well-tolerated, but with significant rates of locoregional and systemic failures. Given the retrospective nature of the study, our findings are not meant to be definitive or conclusive, but rather suggestive in directing future efforts with IC. For now, we favor CRT as the standard option for treatment of inoperable LA-HNSCC.

Keywords

head and neck cancer; induction chemotherapy; radiation therapy; combined modality therapy; chemoradiation

Introduction

It is estimated that in 2013, over 53,000 individuals will be diagnosed with head and neck cancer in the U.S., with an estimated 11,500 deaths (1). Approximately 47% of patients will present with advanced stage disease (1).

One established treatment approach for patients with locally-advanced squamous cell carcinoma of the head and neck (LA-HNSCC) is organ-preservation with concurrent chemoradiotherapy (CRT) (2–6). Based on the results of the TAX studies (7, 8), induction (IC) chemotherapy followed by RT or CRT became a 2nd widely used approach in the treatment of these patients. The TAX studies compared one induction regimen (docetaxel, cisplatin, fluorouracil; TPF) versus another (cisplatin, fluorouracil; PF). Direct, randomized comparisons of IC vs CRT have been attempted (most notably the DeCIDE and PARADIGM trials), but their interpretation has been complicated by poor accrual, premature study closure, and significant acute toxicity secondary to induction chemotherapy. Most important, the hoped for favorable impact on overall survival via the addition of IC to CRT has not been realized in the data analyzed to date (9–11), despite a decrease in distant failures observed with IC in DeCIDE (9).

Given the very real toxicities of docetaxel-based IC, a number of recent efforts have focused on developing equally effective, but less toxic IC regimens. One of the most promising regimens evaluated to date consists of weekly cetuximab, carboplatin, and paclitaxel (PCC), which in non-randomized phase II clinical trials has demonstrated very high response rates, similar to those seen with TPF, but with less toxicity (12, 13). Given the high hospitalization and toxicity rates observed with the TPF regimen, a decision was made by the medical oncologists at our institution to treat patients with PCC induction beginning in 2008. The published results of our institutional experience with PCC induction (14) demonstrate response rates (97% response rate: 30% complete response, 67% partial response) at least comparable to that observed in the two phase II studies of this regimen (12, 13). However, a comparison of PCC induction followed by chemoradiation versus upfront chemoradiation has not yet been made.

There are numerous theoretical factors for and against the use of IC. Proponents of induction therapy cite the ability to deliver multiple agents at higher doses pre-CRT or RT, with the thought that this may salvage a subset of patients who otherwise would develop systemic cancer dissemination. Other arguments for induction include the ability to assess biologic

response in adaptive treatment paradigms (referring the non-responding patients to radical surgery, for example) and even reduce the volume of disease that would need to be irradiated. Opponents of induction cite concerns about delaying the onset of definitive radiation, potential compromises in the delivery of chemoradiation secondary to the acute toxicity from induction, and changes in tumor vasculature and microenvironment caused by IC, which could promote radiation-resistance. These concerns are not without merit, given worse locoregional control with IC compared to CRT shown in the Pignon meta-analysis of chemotherapy in head and neck cancer (2).

Here we present the retrospective results of our institutional experience comparing IC (with cetuximab, carboplatin, and paclitaxel) versus upfront CRT.

Methods and Materials

This was an Institutional Review Board approved retrospective review of consecutive patients with AJCC (7th edition)(15) stage III, IVa or IVb squamous cell carcinoma of the oropharynx, larynx, or hypopharynx treated at The Hospital of the University of Pennsylvania between 2008–2011 with definitive CRT, with or without induction chemotherapy. Only patients of age > 18 years, with ECOG performance status of 0 or 1, with at least partial response to IC, and minimum 6 months of follow up were included.

Treatment

Induction chemotherapy with cetuximab, carboplatin and paclitaxel was administered over eight weeks, with an additional loading dose of 400 mg/m² i.v. cetuximab administered the week prior to starting the three-drug regimen. During subsequent weeks, patients received cetuximab 250 mg/m² in combination with weekly carboplatin AUC 2 and paclitaxel 90 mg/m², with standard pre-medications of dexamethasone 12 mg i.v., diphenhydramine 50 mg i.v. and ondansetron 24 mg i.v. Treatment cycles were repeated weekly for up to 8 weeks and doses were withheld or modified at the provider's discretion depending on the types of toxicities experienced.

Radiotherapy was initiated approximately 3 weeks after completion of induction chemotherapy. Target volumes, duration of therapy, and total radiation dose were determined by the treating radiation oncologist based on the standard of care. For all patients receiving IC, target delineation of the gross tumor volumes (GTV) at the primary site and involved neck nodes were based on pre-IC disease extent, as captured on a PET-CT simulation performed prior to initiation of IC. An intensity-modulated radiation therapy (IMRT) technique with dose painting was used for all patients, with a total dose of approximately 70 Gray delivered over 7 weeks (one fraction per day, 5 days per week).

Concurrent therapy during radiotherapy was determined at the discretion of the provider. Depending on the performance status and prior toxicities, the regimens used included either high-dose cisplatin (100 mg/m²) administered every 3 weeks for three doses, weekly cetuximab (250 mg/m²), weekly cisplatin (30 mg/m²), or weekly carboplatin (AUC 2) and paclitaxel (30 mg/m²). If toxicities were encountered during chemoradiotherapy, providers either reduced the dose of the chosen regimen or changed to a less toxic regimen including

weekly cetuximab (250 mg/m²), weekly carboplatin (AUC 2) or weekly cisplatin (30 mg/m²). Chemotherapy modifications that were made during radiation were made irrespective of whether a patient received IC or not, and were based on standard guidelines and routine laboratory evaluation of blood counts and kidney function. These standardized approaches were reflective and consistent of how the various trials of the respective regimens were performed. Because the therapy was given with curative intent (IC or CRT), all efforts were made within standard guidelines to avoid dose reductions/deletions.

Data Collection

Once patients were identified, we reviewed the electronic medical charts to extract data for baseline patient characteristics (age, marital status, gender, performance status, smoking history), disease characteristics (T stage, N stage, gross tumor volume, p16 status, tumor sub-site), treatment and toxicity data (total treatment days, whether induction chemotherapy was given, weight loss during treatment, need for PEG at last follow-up, and changes in radiation or chemotherapy dose, schedule or regimen due to toxicity). Initial radiation and medical oncology consultation notes were reviewed to determine why the patients in the IC group received induction (such as concern for tumor bulk or physician preference). Many patients in both groups had unknown p16 status, as they were treated at a time prior to p16/HPV testing becoming the standard of care at our institution. Imaging studies for those patients with locoregional recurrence were reviewed and fused with the initial radiation treatment plan to determine whether the recurrence was in-field vs. marginal.

Statistical Analysis

Chi-squared tests and independent two-sample t-tests were used to assess differences in demographic, disease, treatment and toxicity variables between the IC and CRT groups. Differences in overall survival, distant-metastasis free survival and locoregional control between the IC and CRT groups were determined using the Kaplan-Meier approach and the log-rank statistic. Cox proportional hazards models with stepwise variable selection ($p < 0.10$ for inclusion/exclusion) in combination with clinically-relevant factors were used to adjust for potential confounders such as differences identified in patient-, disease-, or treatment-related factors between both groups. The proportional hazards assumption in these models was assessed using Schoenfeld residuals test, with statistical significance defined as $P < 0.05$. All analyses were conducted using SAS 9.2 (SAS Institute Inc., Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria) software.

Results

We identified a total of 118 eligible patients. Twenty-four patients (20%) received IC followed by CRT and 94 (80%) received upfront CRT. Median follow up in the IC and CRT groups was 17 and 19 months, respectively ($p = 0.05$). Patient characteristics are described in Table 1. Disease features and treatment details are presented in Table 2.

Induction patients were more likely to be male, have higher tumor and nodal stage disease, and less tobacco pack-year exposure (Tables 1 and 2). The documented intent by the attending medical and/or radiation oncologists for those receiving IC was bulky primary or

nodal disease for 18 (75%) patients, and provider preference for 6 (25%) patients. The total treatment time for IC was 16–17 weeks (8 weeks induction, 1–2 weeks off, 7 weeks chemoradiation) and 7 weeks for CRT. Otherwise, the groups were well balanced with respect to the other disease and treatment-related factors presented in Table 2.

Compared to upfront CRT, the use of induction therapy did not affect the total duration of RT, weight loss during RT, delivered RT dose, or the likelihood of lowering the dose of chemotherapy or changing chemotherapy agents during chemoradiation due to toxicity. There were no differences between the groups in the incidence of PEG tube reliance at the date of last followup.

Among the 24 patients receiving IC, 7 (29%) had locoregional recurrence, with or without distant metastatic disease, versus 14 out of a total of 94 (15%) receiving CRT. All locoregional recurrences were in-field, within the high-dose RT region, an example of which is shown in Figure 1.

At 18-months followup, patients receiving induction chemotherapy had worse overall survival (73% (58–93) vs 94% (90–99), $p = 0.003$, Figure 2a), locoregional control (58% (36–75) vs 80% (69–88), $p = 0.04$, Figure 2b), and distant-metastasis free survival (73% (52–93) vs 96% (92–100), $p = 0.007$, Figure 2c).

Using multivariable Cox regression to adjust for variables that were imbalanced between the two groups (T stage, N stage, pack-year smoking history), patients treated with induction chemotherapy had significantly higher risk of locoregional recurrence (HR 3.6, $p = 0.02$, Table 3), distant metastases (HR 5.3, $p = 0.02$, Table 2), and worse overall survival (HR 5.1, $P < 0.01$, Table 3).

Discussion

The results of this study suggest that concurrent chemoradiation should remain the standard organ-preservation treatment option for patients with locally-advanced head and neck cancer, as previously established (2–6). The publication of the TAX studies (7, 8) led to the validation of induction as an alternative approach and TPF as the induction chemotherapy regimen of choice, which was recently validated by a meta-analysis (16). Acceptance of induction followed by CRT occurred despite the absence of a head-to-head comparison to CRT. The disappointing results from the DeCIDE (9) and PARADIGM (10) randomized trials have tempered the enthusiasm for induction with TPF. A significant limitation of TPF is acute toxicity. In TAX 324, 21% of patients did not proceed to protocol-defined chemoradiotherapy, and 7% of patients did not proceed to any potentially curative therapy (8), while in DeCIDE, there was a significant increase in deaths due to acute toxicity from induction (9). If the proper role of induction chemotherapy is to be further studied, it is clear that alternatives to current induction regimens will need to be developed.

One such alternative consists of weekly cetuximab, carboplatin, and paclitaxel. This was first studied in a phase II clinical trial published by Kies *et al* (12), in which response to induction was 96%, and all 47 patients proceeded to potentially curative therapy. After a median followup of 33 months, progression-free and overall survival were 87% and 91%,

respectively. Wanebo *et al* (13) used a similar regimen in 74 patients, in which 65% of patients obtained a pathologic complete response (as assessed by serial biopsies) after induction and a 100% CR rate after subsequent chemoradiation. Based upon these data, the treating clinicians at our institution selected this regimen as a less toxic and potentially more active alternative to TPF, adopting this latter regimen in 2008 as our preferred approach to induction chemotherapy in the treatment of locally-advanced head and neck cancer. Our institutional experience with this regimen has demonstrated it to be well-tolerated, with response rates similar to those seen with TPF (14).

It is within this context that we present the results of our retrospective, institutional comparison of IC versus CRT, which is notable for its use of a demonstrably less toxic, yet clinically effective alternative induction regimen. We found that patients who received induction chemotherapy had higher rates of locoregional and systemic recurrences, and worse overall survival. Acute toxicity cannot account for the differences in our results. Proponents of the induction approach have cited the ability to give multiple chemotherapy agents at full doses as a way to decrease distant metastases, and by so doing, improve long-term overall survival. A documented liability of TPF, however, is the potential for severe acute toxicity, which may limit subsequent patient compliance with the planned course of chemoradiation (8), and occasionally lead to early treatment-related deaths (9). In our experience, the induction regimen of weekly cetuximab, carboplatin, and paclitaxel, was well-tolerated. All patients who received induction in our series proceeded to planned chemoradiation. These patients tolerated chemoradiation as well as their upfront CRT counterparts, as reflected in the similar rates of required changes in chemotherapy dosing or regimen due to toxicity, as well as similar full doses of RT delivered, without treatment delay.

We acknowledge that our study findings may be attributable to potential shortcomings such as the retrospective nature of the study and its susceptibility to potential selection bias. Our patients were not randomized, with physician concern about the bulk or volume of the primary and/or nodal disease being the main reason that patients were recommended to receive IC. We controlled for differences in patient-, disease- and treatment related factors in a multivariable analysis, and found that IC still appeared to be associated with a higher risk of poor disease outcome compared to upfront CRT; however, we acknowledge that even these findings may be due to selection of intrinsically poorer prognosis patients for IC and potential confounding due to unmeasured covariates. Therefore, we do not primarily intend for our study to be a direct head-to-head comparison of IC versus CRT, but rather to direct future discussions on potential novel treatment approaches for LA-HNSCC.

A strength of our study is that it examines the results of IC in a high-risk population. A possible explanation of the negative results from DeCIDE and PARADIGM may be patient selection, as a significant proportion of the patients enrolled may have had a high-likelihood of long-term disease control with or without IC (HPV-positive oropharynx patients). Therefore, the benefits of IC may be best realized in a population with high-risk disease features (high T and/or N stage) treated with an induction regimen that is well-tolerated and with response rates comparable to the standard, but highly-toxic regimen of TPF. The patients in our study who received IC fit such a description. Yet, despite receiving IC, these

patients still had suboptimal results, with high rates of locoregional and/or systemic disease recurrence, and poor overall survival.

In conclusion, this study examines treatment with upfront chemoradiation versus a contemporary, promising, and generally well-tolerated induction chemotherapy regimen for locally-advanced head and neck cancer. Despite induction being well-tolerated and not compromising subsequent chemoradiation, we observed that patients receiving IC had inferior locoregional and systemic control and overall survival compared to patients receiving upfront CRT; however, given the retrospective nature of this study, selection bias is a potentially significant confounder of our results. Therefore, our findings are strictly hypothesis-generating, rather than definitive statements. We did observe that the use of IC in a population selected for high-risk disease features did not appreciably yield significant improvements in disease outcomes. We hope that our results will inform and direct potential future investigations for patients who are at significant risk of disease relapse. We believe that induction chemotherapy may play a role in the treatment of high-risk, LA-HNSCC, but that its use should be in the setting of a randomized, controlled trial. For the time being, we believe concurrent chemoradiation should remain the standard approach for non-surgical organ preservation in locally-advanced head and neck cancer.

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Figure 1.

49 year-old patient with stage IVa, T2N2b left tonsillar cancer, treated with induction chemotherapy prior to chemoradiation. PET/CT (fused to initial RT plan) obtained 2 years after completion of treatment demonstrating a massive in-field recurrence located within high-dose 7040 cGy isodose line outlined in red.

Figure 2.

2a: Overall survival 2b: Locoregional control 2c: Distant-metastasis free survival (CRT = chemoradiation, IC = induction chemotherapy)

Table 1

Patient Characteristics

	CRT^{††} (n = 94)	IC[*] (n = 24)	p value
Average Age (yrs) (SD)	60.40(10.62)	57.00(10.19)	0.16
ECOG Performance Status			0.73
0	55(58.5%)	17(70.8%)	
1	37(39.4%)	7(29.2%)	
Unknown	2(2.1%)	0	
Gender			0.01
Female	20(21.3%)	0	
Male	74(78.7%)	24(100.0%)	
Marital Status			0.84
Single	36(38.3%)	10(41.7%)	
Married	57(60.6%)	14(58.3%)	
Unknown	1(1.1%)	0	
Average pack-year tobacco (SD)	35.81(27.49)	21.24(21.63)	0.04

Abbreviations:

* = induction chemotherapy;

†† = chemoradiation

Table 2

Disease and Treatment-Related Characteristics

	CRT^{††} (n = 94)	IC[*] (n = 24)	p value
p16 status			0.38
Negative	8(8.5%)	2(8.3%)	
Positive	19(20.2%)	8(33.3%)	
Unknown	67(71.3%)	14(58.3%)	
Subsite			0.16
Oropharynx	64(68.1%)	21(87.5%)	
Larynx/Hypopharynx	28(29.8%)	3(12.5%)	
Unknown	2(2.1%)	0(0%)	
T stage			<0.01
T1	13(13.8%)	0(0%)	
T2	22(23.4%)	11(45.8%)	
T3	29(30.9%)	1(4.2%)	
T4a	22(23.4%)	12(50.0%)	
T4b	6(6.4%)	0(0%)	
Unknown	2(2.1%)	0(0%)	
N stage			<0.01
N0/N1	33(35.1%)	0(0%)	
N2	57(60.6%)	21(87.5%)	
N3/unknown	4(4.3%)	3(12.5%)	
Overall Stage			0.01
III	27(28.7%)	0()	
IVa	60(63.8%)	22(91.7%)	
IVb	7(7.4%)	2(8.3%)	
Total RT duration (days) (SD)	49.98(8.51)	47.33(3.25)	0.14
% Weight loss during RT (SD)	7.44(5.87)	6.04(4.38)	0.28
Change in chemotherapy regimen during RT			0.07
No	38(40.4%)	5(20.8%)	
Yes	56(59.6%)	19(79.2%)	
PEG at last followup			0.45
No	82(87.2%)	19(79.2%)	
Yes	11(11.7%)	5(20.8%)	
Unknown	1(1.1%)	0()	
Median RT dose received (Gy) (SD)	70.3 (1.28)	70.7 (1.03)	0.14

Abbreviations:

* = induction chemotherapy;

$\dagger\dagger$ = chemoradiation

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Table 3

Multivariate Analyses of Locoregional Control, Distant-Metastases Free Survival and Overall Survival Using Cox Proportional Hazards Model

Locoregional Control		
Variable	Hazard Ratio (95% CI)	P value
Induction (Yes vs. No)	3.6 (1.3–10.6)	0.02
N2 (vs. N0/N1)	0.3 (0.1–0.9)	0.05
N3 (vs. N0/N1)	2.4 (0.4–12.9)	0.3
T3/4 (vs. T1/2)	0.3 (0.1–0.7)	0.02
Smoking (>vs 10 pack-years)	2.7 (1.0–8.5)	0.09
Distant-Metastases Free Survival		
Induction (Yes vs. No)	5.3 (1.3–25.9)	0.02
N2 (vs. N0/N1)	0.4 (0.7–2.0)	0.21
N3 (vs. N0/N1)	9.2 (0.8–107.3)	0.13
T3/4 (vs. T1/2)	0.5 (0.1–1.9)	0.36
Smoking (>vs 10 pack-years)	2.9 (0.7–16.7)	0.24
Overall Survival		
Induction (Yes vs. No)	5.1 (1.6–19.7)	<0.01
N2 (vs. N0/N1)	0.4 (0.08–1.3)	0.09
N3 (vs. N0/N1)	15.1 (1.9–131.0)	0.02
T3/4 (vs. T1/2)	0.6 (0.2–2.0)	0.47
Smoking (>vs 10 pack-years)	5.7 (1.5–30.7)	0.05