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p16INK4a Status and Response to Induction Low-Dose Fractionated Radiation in Advanced Head and Neck Cancer

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Introduction

Induction therapy with low-dose fractionated radiotherapy (LDFRT) and chemotherapy were developed in analogy with our understanding of how human papillomavirus (HPV) affects response to therapy for squamous cell carcinoma of the head and neck (SCCHN). HPV-positive oropharyngeal carcinoma is a distinct head and neck cancer entity because patients with HPV-associated oropharyngeal carcinomas have improved response and survival to current standard treatment modalities compared with non-HPV associated SCCHN.^{1–4} p16INK4a (cyclin dependent kinase inhibitor 2a or p16) is a well-established surrogate for HPV infection. Kumar et al⁵ used response to induction chemotherapy to select patients for subsequent chemoradiation therapy (CRT) and found that high p16 expression was a predictor of good response to organ-sparing therapy and outcome.⁵

Encouraged by the impressive overall survival (OS) results of docetaxel, cisplatin, and 5-fluorouracil (TPF) in studies TAX 323 and 324, we developed and have previously reported response and long-term survival results of a unique induction therapy scheme for treating advanced head and neck cancer. Using LDFRT, paclitaxel, and carboplatin, we sought a less toxic regimen than TPF, without sacrificing efficacy. LDFRT was given as a chemopotentiator of the less toxic combination of carboplatin and paclitaxel. We studied 2 dose schedules of LDFRT in these induction regimens, with response rates of 86% to 90% at

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the primary site and overall response rate of 69% with decreased cytopenia and mucositis rates compared with TPF.⁶ We have recently reported 5-year survival data of one of these cohorts, showing excellent long-term outcomes.⁷

Low-dose fractionated radiation exploits a phenomenon called hyperradiosensitivity initially described by Joiner and colleagues^{8,9} 2 decades ago. Hyperradiosensitivity is the extreme sensitivity of cells to low doses of low-linear energy transfer radiation, which works through molecular mechanisms that are different from standard radiation fractions.¹⁰ Our institution evaluated the LDFRT potentiation of chemotherapy in in vitro and animal models.¹¹ We confirmed that the dosage range of 50 to 80 cGy of radiation creates an optimal potentiation in various human head and neck cancer cell lines.¹¹⁻¹⁴ The biomolecular mechanisms of this induction scheme are quite unique in laboratory experiments and in vivo models. We previously reported that LDFRT can be used in combination with paclitaxel to overcome the antiapoptotic effects of BCL-2 and nuclear factor κ B.¹³ These findings led to our phase II clinical trials using induction LDFRT as a chemopotentiator for locally advanced squamous cell carcinoma of the head and neck.^{6,7}

We felt it important to analyze the clinical impact that HPV/p16 status had on this unique form of treatment prior to designing future trials. We evaluated tumor p16 status in our cohort of patients treated with LDFRT/induction chemotherapy. We then analyzed the impact of this status on outcomes.

Methods

IRB approval was obtained for this retrospective study. Patients diagnosed with advanced-stage (stages III and IV) squamous cell carcinoma of the head and neck, previously treated on 2 separate LDFRT protocols (HN11 and HN15), were identified. The induction regimens were slightly different in HN11 and HN15.^{6,7} As previously reported, both protocols used 2 cycles of induction chemotherapy (carboplatin and paclitaxel) with 4 fractions of LDFRT. The total induction dose of LDFRT was 640 cGy for HN11 and 800 cGy for HN15. Patients were then evaluated for response to induction by a multidisciplinary team using physical examination and imaging studies and categorized into 4 groups based on RECIST criteria: complete response (CR), partial response (PR), stable disease, and progressive disease. The patients then went on to definitive treatment. The total radiation dose for patients undergoing definitive radiation therapy ranged from 66 to 70 Gy.

Surgical pathology slides from initial tumor biopsies before therapy were collected for immunohistochemical evaluation; 65 patients from both studies with advanced-stage SCCHN were enrolled, and 42 (65%) had analyzable tissue for p16 status determination. These 42 patients constitute the HPV study population for this retrospective analysis. Comparisons were made with the entire set of patients with oropharyngeal carcinoma as well as those patients with cancers of other head and neck subsites.

Serial sections of formalin-fixed and paraffin-embedded samples were deparaffinized in xylene and stepwise incubated in 100% to 70% ethanol. Epitope retrieval was performed by heating at 110°C for 10 minutes in 10 mM citrate buffer (pH = 6.0). Endogenous peroxidase

activity was blocked by incubating the sections in 3% hydrogen peroxide in PBS for 10 minutes. Primary monoclonal mouse anti-p16INK4A antibody (CINtec by MTM Laboratories, Tucson, Arizona, USA) was added to the slides for 60 minutes at room temperature followed by incubation with a secondary horseradish peroxidase-conjugated goat antimouse antibody (MTM Laboratories) at room temperature for 1 hour per manufacturer's instructions. After counterstaining of the peroxidase complex, sections were dehydrated and embedded with mounting medium. A blinded, independent pathologist reviewed and characterized the formalin-fixed, paraffin-embedded, immunostained sections. Tumors were classified as positive when >75% showed diffuse nuclear and cytoplasmic staining.¹⁵

Statistical Analysis

Of the 65 participants from protocols HN11 and HN15, 42 (65%) had tissue samples analyzable for p16 status and were included in this retrospective analysis. Descriptive statistics, including medians and ranges for continuous outcomes and percentages for categorical variables, for both baseline demographic and treatment-performance characteristics were calculated for this p16-determinable subset (n = 42). Wilcoxon rank-sum tests and Fisher's exact tests were performed where appropriate to test for unadjusted differences between variables regarding p16-positive/negative staining. Logistic regression modeling the odds of staining p16 positive was then performed to identify any significant baseline predictors. For time end points, including OS, disease-specific survival (DSS), and progression-free survival (PFS) outcomes, Kaplan-Meier curves were constructed to test for unadjusted differences for p16 staining, with corresponding log rank *P* values. Cox models were considered to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) while adjusting for any significant baseline covariates. Because of the small sample size of these analyses, model selection was utilized for both the logistic regression and Cox models using stepwise selection with entry and stay criteria equal to 0.15. Baseline variables considered for all models included age, sex, type of cancer (oropharyngeal vs all others), T-stage (T1-T3 vs T4), N stage, overall stage, and protocol the individual participated in. An additional subgroup analysis was also conducted using the same techniques described above for only those with oropharyngeal cancers (n = 17). All data analyses were conducted using SAS Version 9.3 for Windows (SAS Inc, Cary, North Carolina, USA).

Results

Patient Characteristics and p16 Outcomes

From 2000 to 2005, 65 patients with locally advanced SCCHN were enrolled in either the HN11 or HN15 protocol. Among them, 42 patients (65%) had tissue samples that were analyzable and were used for this analysis (Table 1). In this subset of patients with adequate tissue samples for p16 staining, 83% were male and the median age was 53 years (range = 36-81 years). The majority of patients (n = 33, 79%) had stage IV disease, and 60% were classified as N2b or N3. Primary sites were oropharynx (n = 17, 40%), larynx (n = 13, 31%), and other sites, including hypopharyngeal and oral cavity cancers (n = 12, 28%). The median follow-up for all patients was 83 months (range = 7-118 months). The median follow-up for survivors was 102 months (range = 66-118 months).

Logistic models to characterize differences between p16 staining and baseline characteristics were constructed as described in the section on statistical methods, and the best model using stepwise selection included adjusting for T-stage and tumor site. Those with a T-stage of T1 to T3 had larger odds of being p16 positive as compared with those with stage T4 (HR = 7.1; 95% CI = 1.2-41.9; $P = .03$). Additionally, those with oropharyngeal cancer had 5.8 times the odds of being p16 positive as compared with those with all other head and neck cancer types (95% CI = 1.3-25.7; $P = .02$).

Response to Induction

Generally, patients had a good response to induction therapy; however, no statistically significant results were found (Table 2). Those with p16-positive tumors ($n = 13$, 87%) had a CR or PR to induction as compared with those with p16-negative tumors ($n = 20$, 74%). Regarding definitive treatment, 20 patients underwent definitive chemoradiation therapy (CXRT; 48%); 12 had radiation therapy alone (XRT; 28%); and 10 had surgery with postoperative XRT/or CXRT (24%). There was no statistically significant difference between definitive treatment modality in the p16-positive versus p16-negative groups ($P = .77$).

There were no significant differences in response to induction or baseline characteristics for the oropharyngeal tumor subgroup of $n = 17$. An adjusted logistic model also did not identify any significant covariates associated with p16 status for the subgroup. Also, 90% of p16-positive oropharyngeal cancer patients had CR or PR, whereas none of those with p16-negative oropharyngeal cancers had a CR, and 71% had a PR ($P = .07$).

Survival

The rates of 5-year OS, PFS, and DSS for all patients whose tumors stained positive for p16 were 80%, 73%, and 73%, respectively, versus 58%, 50%, and 50% in p16-negative patients. Model selection adjusting for various baseline factors resulted in identifying p16 staining as the only covariate for survival outcomes, using the proportional hazards model. Only OS was statistically significant for p16 staining status, with p16-negative patients at higher risk of death as compared with those who were p16 positive (HR = 3.7, 95% CI = 1.1-12.7, $P = .025$; Figure 1).

In patients with oropharyngeal cancer, the 5-year OS, PFS, and DSS were 100% for all 3 parameters in the patients who stained positive for p16, whereas patients with negative p16 staining had 5-year OS, PFS, and DSS rates of 14%. These were all statistically significant, with log-rank values of $P < .001$ (Figure 2). Model selection using the Cox proportional hazard model did not identify any covariates that were associated with survival outcomes for this subset of oropharyngeal cancers.

Discussion

Some subtypes of SCCHN have different clinical responses to therapy. HPV-related tumors of the oropharynx and tongue base respond better to chemotherapy, radiation therapy, and surgery than their non-HPV counterparts.^{5,15-17} This has led most clinical trials to stratify for HPV/p16 status, although there are no changes in staging or treatment guidelines for

HPV-related disease. In studies of induction therapy, the HPV-related tumors have consistently demonstrated significantly better responses and outcomes.^{5,15-18}

LDFRT enhancement of chemotherapy is a unique biological phenomenon making it unclear how HPV/p16 status would play a role in response to therapy. Our study is the first to confirm differential effects on p16-positive and -negative SCCHN in the setting of induction LDFRT followed by definitive therapy, which reported results similar to other, more traditional chemotherapy and radiation studies in SCCHN. The patients in this study had good response rates to this unique and well-tolerated regimen, with 79% of all patients showing some measurable clinical response (CR and PR) to the initial induction therapy. p16-positive patients were more likely to have a CR to the LDFRT induction scheme, especially in the oropharyngeal subset, but no statistically significant effect on overall response to induction chemotherapy could be predicted ($P = .07$), likely because of our small sample size. We did some examination of responses at specific disease sites and saw no other obvious trends in response to this induction scheme. Our data are consistent with other reports regarding improved response to induction chemotherapy seen in HPV-associated disease.^{5,15,17}

In this study, we report the demographics and long-term survival of patients with oropharyngeal carcinoma, based on tumor p16 status. We report excellent results in our study, with 100% 5-year OS, PFS, and DSS in patients with p16-positive oropharyngeal disease, whereas p16-negative patients did significantly worse, with a 14% 5-year OS, PFS, and DSS. A subset analysis of the TAX 324 phase II clinical trial of induction chemotherapy followed by definitive CRT revealed a 5-year OS of 82% ($n = 56$) in patients with HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) versus 35% ($n = 55$) in those with HPV-negative OPSCC.¹⁸ In our entire cohort of patients, including all subsites treated, p16-positive status still predicted a significantly better OS than p16-negative status, with an 85% 5-year OS in p16-positive HNSCC versus 53% in p16-negative HNSCC.

HPV virus is prevalent in squamous cell carcinoma of the larynx and oral cavity with HPV expression in each subsite equaling 20% and 23.6%, respectively.¹⁹ Also, p16INK4a staining is a surrogate marker for HPV infection that is well recognized in oropharyngeal sites. But the impact of p16 status of nonoropharyngeal SCC on clinical outcomes is less clear. In nonoropharyngeal sites, p16 overexpression may not reflect transcriptionally active HPV. However, a recent study showed that patients with p16-positive nonoropharyngeal cancer have better outcomes than patients with p16-negative nonoropharyngeal cancers.²⁰ This finding is consistent with our results in the nonoropharynx p16-negative versus -positive cohort of patients.

Our results reveal that p16 overexpression resulted in improved OS in all subsites of the head and neck. Using other known methods to determine HPV status was not feasible because of the nature of the samples. Our study has limitations in terms of the heterogeneity of tumor site, stage, and postinduction treatment. The study protocols were designed and conducted during a time when p16 analysis was not part of our institutional standard of care. Some of the tissue blocks were unavailable or inadequate to study. Because of the small size, conclusions are limited. No statistically significant difference in postinduction treatment

modalities exists between p16-positive and p16-negative patients, with the majority of patients in both groups receiving concurrent CRT as definitive treatment. Despite the limitation in sample size, the p16 status remained a dramatic predictor of overall outcome. Furthermore, the improved response in the p16 groups nearly reached significance ($P = .07$) to this unique induction regimen of LDFRT with carboplatin and paclitaxel.

Despite years of study, the role of induction therapy in advanced-stage SCCHN remains uncertain. Some evidence points to induction reducing the rate of distant metastasis and increasing organ preservation and survival rates.²¹ The Meta-analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) study involved >12 000 participants in 87 randomized trials and showed a modest 2% improvement in survival from induction chemotherapy. TAX 323 and TAX 324 both compared induction TPF (docetaxel, cisplatin, and 5-fluorouracil) with PF but had different definitive therapies postinduction. TAX 323 demonstrated improvements in PFS and OS at 5 years in the TPF arm, whereas TAX 324 showed an improvement in 5-year OS in the TPF arm. Unfortunately, induction TPF has significant acute toxicity, with >75% of patients experiencing grade 3 or 4 neutropenia in both trials.²² This toxicity clearly affects the ability to deliver full courses of therapy and may affect how well the subsequent definitive therapy is tolerated. The use of LDFRT with induction chemotherapy may expand the number of patients able to complete all planned therapy. This and its effect on efficacy of the induction require further study.

In conclusion, the variations in patient treatment response to LDFRT induction chemotherapy correlates with the p16 status of SCCHN and is similar to those reported for induction chemotherapy. A positive p16 SCCHN status was associated with improved 5-year OS, PFS, and DSS in patients treated in these studies. These relationships must be considered as LDFRT induction chemotherapy is investigated further.

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Figure 1. Overall, disease-specific, and progression-free survival Kaplan-Meier curves categorized by p16 staining results for all tumor sites (N=42).

Figure 2.

Overall survival Kaplan-Meier curves categorized by p16 staining results for oropharyngeal cancers (N=17) (Disease specific and progression free survival are identical).

Table 1
Demographic Characteristics Categorized by p16 Staining Results

	All (N=42)			Oropharyngeal Only (N=17)		
	p16 Pos N=15 N (%)	p16 Neg N=27 N (%)	p-value	p16 Pos N=10 N (%)	p16 Neg N=7 N (%)	p-value **
Age – Median	52	53	0.41	63	54	0.32
Male	12 (80%)	23 (85%)	0.69	9 (90%)	7 (100%)	1.00
Type of Cancer	0.03 *			N/A		
Hypopharyngeal	0 (0%)	5 (19%)	0.03 *	10(100%)	7 (100%)	0.10
Laryngeal	2 (13%)	11 (41%)				
Oral Cavity	3 (20%)	4 (15%)				
Oropharyngeal	10 (67%)	7 (26%)				
N Stage	0.74			0.30		
N0-N2a	7 (47%)	10 (37%)	0.02 *	5 (50%)	1 (14%)	0.80
N2b-N3	8 (53%)	17 (63%)		5 (50%)	6 (86%)	
T Stage						
T1/T2/T3	13 (87)	13 (48%)	1.00	9 (90%)	3 (43%)	0.78
T4	2 (13%)	14 (52%)		1 (10%)	4 (57%)	
Overall Stage						
III	3 (20%)	6 (22%)	0.77	3 (30%)	1 (14%)	0.62
IVa	11 (73%)	19 (70%)		6 (60%)	5 (72 %)	
IVb	1 (7%)	2 (8%)		1 (10%)	1 (14%)	
Treatment						
Chemoradiation (CXRT)	7 (47%)	13 (48%)	0.08	4 (40%)	1 (14%)	
Radiation Alone	6 (40%)	8 (30%)		5 (50%)	5 (72%)	
Surgery w/post op	2 (13%)	6 (22%)		1 (10%)	1 (14%)	
XRT/or CXRT						
Protocol	0.08					
HN11	8 (53%)	22 (81%)	0.08	5 (50%)	5 (71%)	
HN15	7 (47%)	5 (19%)		5 (50%)	2 (29%)	

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* Significant at alpha level 0.05

** All p-values calculated using Fisher's Exact tests (age uses 2-sample Wilcoxon rank sum t-approximation test)

Table 2

Response to Definitive Treatment

	All (N=42)		Oropharyngeal Only (N=17)	
	p16 Pos N=15 N (%)	p16 Neg N=27 N (%)	p-value	p16 Pos N=10 N (%)
Local Regional Failure	2 (13%)	8 (31%)	0.28	0 (0%)
Distant Failure	2 (13%)	7 (27%)	0.44	0 (0%)
Status at last follow-up			0.01 *	
Died of other causes	0 (0%)	5 (19%)		0 (0%)
Died of disease	3 (20%)	12 (46%)		6 (86%)
No evidence of disease	12 (80%)	9 (35%)		1 (14%)
Response			0.06	
Complete Response	5 (33%)	2 (8%)		0 (0%)
Partial Response	8 (53%)	18 (69%)		5 (71%)
Stable Disease	1 (7%)	6 (23%)		2 (29%)
Progressive Disease	1 (7%)	0 (0%)		0 (0%)

* Significant at alpha level 0.05

** All p-values calculated using Fisher's Exact tests