Mutational Burden: Impact on Head and Neck Cancer

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Overview
This activity is designed to inform physicians about the mutational burden impact on head and neck squamous cell carcinoma.

Target Audience
This activity is directed toward medical oncologists, primary care physicians, nurses, and nurse practitioners who treat and/or manage patients with head and neck cancer. Surgical oncologists, radiation oncologists, pathologists, internists, fellows, physician assistants, and other healthcare providers are also invited to participate.

Learning Objectives
After participating in this CME/CE activity, learners should be better prepared to:
- Explain the key unmet needs in the treatment of head and neck squamous cell carcinoma (HNSCC)
- Summarize immunotherapeutic approaches and the relevant study findings to the treatment of HNSCC
- Describe the most commonly mutated genes that have been identified in HNSCC and their clinical implications

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Introduction

Background

Head and neck cancer is the eighth most common cancer worldwide and the sixth most common cause of death from cancer, with an estimated 400,000 deaths each year (4.9% of total cancer deaths).[1] Annually, there are an estimated 600,000 new cases worldwide, with a 5-year overall survival (OS) rate between 50% and 60%.[2,3] Head and neck cancers comprise tumors of the oral cavity, larynx, pharynx, salivary glands, and nasal passages. These tumors usually originate from squamous cells that line the inside surface of the head and neck and are referred to as head and neck squamous cell carcinoma (HNSCC). Known risk factors for HNSCC include smoking and alcohol consumption,[4] and in some head and neck cancer types, human papilloma virus (HPV) infection.[5] HPV is, most notably, a causal factor in oropharyngeal squamous cell carcinoma (SCC). Approximately 30% of HNSCC is associated with high-risk, oncogenic HPV types.[6] HNSCC is widely viewed as having 2 distinct clinical entities: HPV-positive and HPV-negative tumors. Patients with HPV-positive HNSCC have a better prognosis compared with those with HPV-negative HNSCC.[7]

Standard therapies for head and neck cancer consist of surgery, chemotherapy, and/or radiation. Treatment depends on the anatomical location and stage of the disease. In a resectable patient when the prognosis is so poor that disfiguring surgery is not justified, and in nonresectable patients, combined concomitant chemoradiation is preferred.[8,9] Cisplatin-based chemoradiotherapy is the standard of care for locoregionally advanced disease. For those patients who are deemed inappropriate candidates for combined modality therapy, radiotherapy combined with cetuximab, the anti–epidermal growth factor receptor (EGFR) monoclonal antibody, may be an alternative. Increased levels of EGFR expression and activation have been associated with poor prognosis.[10] Therefore, cetuximab is commonly combined with radiation to improve OS compared with radiation alone.[11] The Erbitux in First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer (EXTREME) phase III trial compared platin-5-fluorouracil alone versus combined with cetuximab as first-line treatment in recurrent or metastatic HNSCC. The cetuximab arm of the study demonstrated a significant improvement in OS, progression-free survival (PFS), and response rate (RR). The quality-of-life analyses, however, had no significant differences between the treatment arms.[12]

Currently, there is no universally agreed upon second-line therapy. An open-label, randomized phase III trial comparing afatinib versus methotrexate in second-line recurrent or metastatic HNSCC demonstrated that afatinib was associated with significant improvements in PFS and had a manageable safety profile.[13] The clinical outcomes from this study did not adversely affect elderly patients (≥65 years) in a subgroup analysis.[14] Methotrexate plus cetuximab has been shown to be well tolerated and provide a significant survival benefit in the second-line setting in adult patients.[15] Ixabepilone, a novel tubulin-polymerizing agent, was examined in second-line HNSCC (NCT00033618). The primary endpoint was met with a RR of 16% in the ixabepilone arm, within the 90% confidence interval (CI), for a true response rate of 20%.[16] This study provides evidence that ixabepilone has activity in advanced HNSCC comparable to other active agents in the second-line setting. There have also been several phase II trials that examined the role of cetuximab in second-line HNSCC, all with similar outcomes regardless if it was used as a single agent or in combination with a platinum-based regimen. Responses were seen in 10% to 13% of patients, disease control rate was observed in 46% to 55% of patients, and median OS was 5.2 to 6.1 months.[17-19]

At the time they receive a diagnosis, many patients with head and neck cancer have comorbid conditions, several of which are significantly related to survival in head and neck cancer (eg, congestive heart disease, cardiac arrhythmia, peripheral vascular disease, pulmonary disease, renal disease).[20] Consideration of comorbid conditions can greatly impact the treatment and prognosis of HNSCC.

Although radiation for head and neck cancers can be curative, relatively high doses can damage any tissues within the head and neck. This toxicity profile can be significant, particularly when combined with chemotherapy. Common toxicities include mucositis, radiation dermatitis, xerostomia, dysphagia, and hypothyroidism.[21] Techniques for radiation dose distribution, such as intensity-modulated radiation therapy and proton therapy, have been proven to reduce toxicity in patients with head and neck cancer.[22,23] A key goal in the field has been to reduce treatment-related toxicities, improve patient quality of life, and reduce costs. These factors represent unmet needs in the field.

Novel Immunotherapy Approaches to Head and Neck Cancer Treatment

Several new therapeutic approaches to care for patients with HNSCC have been the focus of recent investigations. One such approach is the use of immune checkpoint inhibitors. HNSCC often expresses the ligand, PD-L1. In August 2016, pembrolizumab received an accelerated approval from the Food and Drug Administration (FDA) for patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy. This approval was based on the findings of the KEYNOTE-012 trial. A number of studies continue to assess pembrolizumab in the treatment of patients with HNSCC in various disease stages and patient subtypes (KEYNOTE-055, -048, and -040). Other checkpoint inhibitors under investigation include nivolumab (NCT02426892), avelumab (NCT01772004), and ipilimumab (NCT02488759).[24]

Oncolytic virus therapy is perhaps the next major breakthrough in cancer treatment following the success of immunotherapy using immune checkpoint inhibitors. Oncolytic viruses are engineered viruses that selectively replicate in and kill cancer cells without harming normal tissues.[25] To date, 2 genetically engineered oncolytic viruses have been approved for marketing as drugs: Oncorine (H101) for head and neck cancer and esophagus cancer in China and T-VEC (talimogene laherparepvec) for melanoma in the United States and the European Union. Currently, JX-594 (pexastimogene devacirepvec; Pexa-Vec), a genetically engineered vaccinia virus that has a mutation in the thymidine kinase (*TK*) gene, is being studied in HNSCC (NCT00625456).

Considering HPV is a significant cause of head and neck cancers, a treatment approach to HPV-positive HNSCC could include a neoantigen vaccine. At present, however, HPV vaccines mostly remain a preventive strategy. Although they protect against HPV strains responsible for the majority of HPV-related oropharyngeal SCC, in terms of a preventive measure to reduce the incidence of this cancer, the efficacy of HPV vaccines is unknown.[26] The use of HPV vaccines as a therapeutic tool in HPV-related oropharyngeal SCC has shown limited efficacy in several trials (NCT02002182, NCT01462838),[27] but there are several HPV vaccine therapies in clinical trials for HNSCC **(Table)**.

Genomic Landscape in HPV-positive and HPV-negative HNSCC Tumors

HPV has been implicated in the etiology of HNSCC tumors. Although genomic structural alterations are commonly seen in HNSCC regardless of HPV status, emerging data from HNSCC genome sequencing studies provide an opportunity to develop personalized therapy for patients based on their HPV status. The mutational frequency is similar in HPV-positive and HPV-negative HNSCC, but the types of gene mutations greatly vary.[28] A comprehensive list of distinct molecular abnormalities—in particular, therapeutically relevant genetic aberrations—has not been reported between these 2 entity types; however, there have been great strides in understanding genetic aberrations correlated to HPV status. HPV status, not necessarily anatomic site, is the most important factor determining tumor biology.[28]

Most studies examining the genomic landscape in head and neck cancer are conducted with largely HPV-negative patients with HNSCC. In some studies, approximately 85% of the patients are HPV-negative.[29,30] As a result, alteration of p53 signaling and cell-cycle pathway genes has been shown to occur almost exclusively in HPV-negative tumors.[28] Additionally, the mutational spectrum in HPV-negative HNSCC includes mutations in *TP53*, *CDKN2A*, *MLL2*, *CUL3*, *NSD1*, *PIK3CA*, and *NOTCH* genes, as well as copy-number increases in *EGFR*, *CCND1*, and *FGFR1*.[28,31] The importance of the mitogen-activated protein kinase pathway in HPV-negative HNSCC is demonstrated by *EGFR* amplification.[32]

Although evidence is lacking in large HPV-positive HNSCC cohorts, the results of recent studies demonstrate a distinct genetic profile in HPV-positive tumors that includes mutations in *DDX3X*, *CYLD*, and *FGFR* and enrichment for PI3K pathway alterations and rarer *KRAS* mutations.[28] Seiwer et al (2015) also explained that alterations in the following favored HPV-positive tumors: the DNA-damage pathway *(BRCA1, BRCA2, FANCG, FANCA, FANCD2,* and *ATM)*, FGF signaling (*FGFR2, FGFR3*, and *FGFR4*), JAK/STAT signaling *(STAT1, JAK1,* and *JAK2)*, and immunology-related genes *(HLA-A* and *HLA-B)*.[28]

Further, *TRAF3* mutations are observed in HPV-positive HNSCC, and *TRAF3* plays a critical role in antiviral response.[30,32] Both HPV-positive and -negative tumors share alterations, such as PI3K signaling, *NOTCH* aberrations, and mothers against decapentaplegic homolog (SMAD) signaling. The PI3K-PTEN-AKT-mTOR pathway is important in both HPV-positive and HPV-negative tumors by *PI3KCA* amplification; however, *PIK3CA* mutations are more frequently observed in HPV-positive subtypes.[28,30] Additional studies to examine the clinical implications of genomic mutations will be vital with respect to personalized medicine.

Barbara Burtness, MD, professor of medicine (medical oncology) at the Yale University School of Medicine and Yale Cancer Center, and the editor-in-chief of *Cancers of the Head and Neck*, offered her insights on the mutational burden and impact on head and neck cancer.

Moderator: What are some of the current unmet needs in head and neck cancer therapy?

Dr Burtness: There are many patients who are treated for head and neck cancer who are cured. However, the surgery, radiation, and chemoradiation that we use to get there can be associated with sequelae that are very long-lasting. Some of these sequelae can interfere with swallowing, nutrition, speech, the ability to interact with other people, and the ability to return to work. Even for those patients who have a good prognosis, we are always interested in ways to make our therapies less toxic. If we could avoid the most deforming surgeries, if we could reduce the doses of radiation so there's less chronic impairment of swallowing muscles and less neck fibrosis, and if we could avoid concurrent cisplatin, which seems to be associated with

TABLE. Clinical Trials for HPV Vaccine Therapies in HNSCC

Therapy	Vaccine Type	Immune Target	Stage	Clinical Trial Number(s)
INO-3112	DNA	HPV E6, E7	Phase I/II	NCT02163057
MAGE-A3/HPV16	Peptide	MAGE-A3, HPV-16-specific peptide	Phase I Phase I	NCT00257738 NCT00704041
ISA101	Peptide	Synthetic HPV E6 and E7 peptides	Phase II	NCT02426892
HESPECTA (ISA201)	Peptide	Two synthetic HPV16 peptides covalently linked to amplivant synthetic TLR 1/2 ligand	Phase I	NCT02821494
ADXS11-001	Biologic	Live, attenuated Listeria monocytogenes expressing HPV-E7-lysteriolysin-O fusion	Phase II	NCT02002182

HNSCC indicates head and neck squamous cell carcinoma; HPV, human papilloma virus; MAGE-A3, melanoma-associated antigen 3; TLR, toll-like receptor

an increased risk in noncancer mortality, the lives of head and neck cancer survivors would be improved.

We also know from cohorts of patients that some groups of patients do not have as high a chance of cure. Among the patients who have HPV-associated disease, if there is a significant history of tobacco consumption, those patients have a lower chance of cure from chemoradiation or surgery. In patients who have very bulky disease or HPV-negative disease, the current treatments do not cure the majority of people with locally advanced disease. I think we need new agents to incorporate into the standard management of people with intermediate- and high-risk disease. In metastatic disease, we have seen real breakthroughs in the past year. Nonetheless, the majority of patients who have metastatic head and neck cancer will succumb to that disease. Curative treatments in that setting are required.

What are some of the key biological differences between HPV-associated versus traditional head and neck cancer? What are the clinical implications of these different types?

The HPV-associated cancers do not have mutations in *p53*, and they do not have loss of heterozygosity at p16. Also, it appears that HPV-associated cancers may be less proficient at homologous recombination. They are quite sensitive to DNA-damaging strategies like radiation and cisplatin. HPV-associated cancers do not appear to be as hypoxic; hypoxia in HPV-negative cancers has been associated with treatment resistance. On the other hand, HPV-negative cancers are quite commonly hypoxic and very predominantly have loss of tumor suppressor function through mutation of *p53* and *NOTCH*.

What progress have we made with genomically personalized therapy in head and neck cancer so far?

The predominance of loss of tumor suppressor function is the underlying driver of head and neck cancer. There have been fewer potentially actionable genomic alterations in head and neck cancer than we've seen in some other solid tumors. There is very exciting evidence about the PI3K inhibitor, buparlisib, in a randomized phase II trial, where patients with platinum-refractory disease were treated either with paclitaxel or paclitaxel plus buparlisib, and the buparlisib arm did significantly better. We have not yet seen whether those results are tied to *PIK3CA* mutations.

The MATCH trial is a very large NCI trial (NCI-MATCH) in which patients who don't have a standard treatment option for their metastatic or recurrent solid tumor are biopsied and a genomic profile is generated from the tissue. There is an attempt to match the mutations in that genomic profile with a panel of targeted therapies, which have already been validated for that molecular target but in a different cancer. There are [several] arms within this trial that look promising for patients with head and neck cancer: FGFR inhibitor, PTEN loss, *PIK3CA* mutations. Among the first 795 patients who enrolled in the NCI-MATCH trial, there was a very low success rate in matching the patients with head and neck cancer to a targeted therapy. But with the recent expansion of the trial and the larger number of treatment arms, outcomes look more promising for patients with head and neck cancer.

We are moving the use of molecular profiling into the postoperative setting with a current ECOG-ACRIN trial, which is EA3132 (NCT02734537). As mentioned previously, the loss of the tumor suppressor function of p53 is difficult to target with a small-molecular inhibitor that would restore the function of p53. However, there is evidence that the radioresistance that develops or that's present in the setting of [a] p53 mutation or disruptive p53 mutation can be reversed, to some extent, by the addition of cisplatin. We have a trial for patients who have undergone resection of an HPV-negative head and neck cancer and who meet the usual criteria for receiving postoperative radiation, but do not meet the usual criteria for receiving postoperative chemoradiation. All trial patients received genomic profiling, which can be useful. If the cancer were to come back in the future, patients would already know their genomic profile.

The correlative co-chair of the study, Dr Christine Chung, analyzes the p53 sequence to determine if there is a mutation and whether the mutation would be predicted to produce a disruption of p53 function. Based on that, patients in the trial are randomized to radiation or cisplatin and radiation. Our hope is that we will be able to demonstrate disease improvement—that the addition of cisplatin to radiation reduces the risk of recurrence in this poor prognosis group of patients who have disruptive *p53* mutations.

Given the heterogeneous nature of head and neck cancer tumors, what strategies might work best when designing head and neck cancer therapies?

I think it is important to study the different types of head and neck cancer in separate trials. Trial outcomes vary based on the types of HNSCC being studied. Additionally, the research questions being addressed in each trial differ drastically. I would say good prognosis HPV-associated cancer, intermediate prognosis HPV-associated cancer, and HPV-negative cancer are 3 separate populations that should be studied in separate trials.

What are some of the most commonly mutated genes that have been identified in HNSCC with the help of next-generation sequencing?

The most commonly mutated gene in HPV-negative cancer is *p53*. *NOTCH1* is important in epithelial tissue, like head and neck epithelium, and essentially serves a tumor suppressor function. Mutation leads to a loss of tumor suppressor function. Although *PIK3CA* mutations and amplification are common both in HPV-positive and HPV-negative cancers, there are particular hotspots for *PIK3CA* mutations in HPV-positive cancers. *FGFR* and its ligands are commonly abnormal, whether through mutation or amplification or changes in expression. In HPV-positive cancers, abnormalities in *TRAF3* have been described. In HPV-negative cancer, PTEN loss may be present, either due to mutation or due to changes in expression, but is likely related to resistance to EGFR inhibitors. The chromatin modifier NSP1 may be very interesting in larynx cancer.

What is the rationale supporting the use of immune checkpoint inhibition in HNSCC? Further, does the HPV status have an impact on treatment response?

As I stated previously, the largest unmet need in the treatment of HNSCC is the need for new therapies that would be less toxic and less likely to lead to permanent sequelae. As part of that approach, we need new mechanisms of action in some of our poorer prognosis cancers. The advent of a major new strategy in anticancer therapies is important. It turns out that HNSCC [does] have many of the hallmarks of cancers that might be amenable to immune checkpoint inhibition. HNSCCs often express the ligand PD-L1. Tumor infiltrating lymphocytes are present and have been demonstrated to be related to outcome. It is known that viral antigens are continually expressed in the cancer cells in HPV-associated and Epstein-Barr virus–associated cancers of the oropharynx and nasopharynx. Viral antigens might provide a target for immune cells if the immune cells could be reactivated. In HPV-positive cancers, activation of the gene editing protein APOBEC3B leads to a higher mutational burden. There is some reason to believe that might be associated with better immune targeting. In tobacco-associated cancers, there's a high mutational burden probably related to the loss of *p53* function.

Pembrolizumab showed promising antitumor activity in recurrent/metastatic HNSCC in the KEYNOTE-012 study. Would you be able to briefly describe the key findings from this study and its clinical implications?

KEYNOTE-012 was an open-label, multicohort, multicenter, phase Ib trial with pembrolizumab. The trial looked at pembrolizumab in a number of different cancers that had not been well studied with immune checkpoint inhibitors up until that time. The cohort for patients with head and neck cancer was initially recruited with patients who were PD-L1–positive. Of the initial 104 patients who were screened for this study, 60 enrolled and treated patients were PD-L1-positive. This group of PD-L1–positive patients included both HPV-associated and HPV-negative cancers. The pembrolizumab treatment was well tolerated with about the same range of drug-related adverse events as had been seen with these [types of] agents in other cancers, and no drug-related deaths occurred in the initial cohort. The objective response rate was 18%, and in a recent update presented at ASCO last year, the durability of these responses with a 16-month follow-up was also reported.

The outcome of the PD-L1–positive cohort in the phase Ib trial led to an expansion cohort, which did not mandate PD-L1 expression. Similar outcomes were reported in this second cohort as the PD-L1–positive cohort. Pooled analysis of the total population across the 2 cohorts showed the overall response rate was 18%, and the durability for those patients who had response was quite good. These data led to FDA approval of pembrolizumab in platinum-refractory head and neck cancer. Additionally, a randomized trial [that] examined immune checkpoint inhibition in recurrent or metastatic HNSCC was reported in *The New England Journal of Medicine* in October. The CheckMate 141 study was a phase III trial with 361 patients and a 2:1 randomization (NCT02105636). Nivolumab showed improvement over an investigator's choice of palliative chemotherapy or cetuximab in platinum-refractory disease. Improvements in median OS were observed: from 5.1 months in the group that received standard therapy to 7.5 months in the nivolumab group. Interestingly, the response rate in the nivolumab group of patients, which had not been selected with PD-L1 testing, was 13%.

What are some of the most promising therapies for head and neck cancer on the horizon?

Immune checkpoint inhibitors are a promising therapy. They are clearly active, although modestly active, with response rates between 13% and 18%. I think that we need strategies that can couple the tolerability and the durable responses of immune checkpoint inhibitors with a greater ability to shrink cancers. This should be a focus of researchers, as many of our patients are symptomatic. I think that current trials that look at integrating immunotherapy with chemotherapy, targeted therapy, or radiation are promising. Another promising therapy is the previously mentioned buparlisib to second-line paclitaxel. There is intriguing randomized phase II data looking this therapy.

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