Novel Targets in Head and Neck Cancer: Should We Be Optimistic?

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Head and neck squamous cell carcinomas have distinct mutation and copy-number profiles depending on human papillomavirus status. Although several challenges remain in biomarker implementation and clinical trial feasibility, incorporating available genomic data will expedite the development of novel therapeutics and predictive biomarker-driven clinical trials. Clin Cancer Res; 21(3); 495–7. ©2014 AACR.

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In this issue of Clinical Cancer Research, Seiwert and colleagues (1) report mutation and copy-number variation (CNV) analyses in 617 cancer-associated genes from 120 tumor–normal tissue pairs from patients with head and neck squamous cell carcinoma (HNSCC). They confirmed the presence of frequent mutations and CNVs in HNSCC and identified additional mutations differentially associated with human papillomavirus (HPV)-positive tumors that were previously thought to be rare in HNSCCs. Further characterization of these mutational profiles may assist novel biomarker and targeted therapeutic development benefiting HPV+ and HPV− patients.

The most common risk factors for HNSCC development are heavy tobacco use and alcohol consumption, as well as HPV infection (2, 3). HPV+ and HPV− HNSCCs differ substantially in both epidemiology and clinical outcome. More specifically, HPV− patients have improved overall survival after initial diagnosis or following recurrent/metastatic disease (4, 5). Consistent with these notable clinical differences, recent comprehensive genetic analyses have revealed that the genetic landscapes of HPV+ and HPV− HNSCC differ greatly. There are three large genomic datasets available to date that evaluate these genetic variations using whole-exome sequencing (WES) or whole-genome sequencing (WGS) (6–9). However, earlier studies were dominated by HPV− samples, limiting the effective characterization of HPV+ tumors.

Building upon these previous studies, Seiwert and colleagues report three distinct findings: (i) HPV+ and HPV− tumors have a different profile of oncogenic mutations/CNVs; (ii) HPV+ tumors have frequent oncogene mutations previously described as rare in HNSCC; and (iii) no significant difference is evident in the frequency of mutations between HPV+ and HPV− tumors. These findings may have resulted from several key differences with previous three studies. First, HPV status was balanced between the two cohorts with HPV+ tumors representing 42.5% of total tumor samples. Across the previous studies, HPV+ tumors accounted for only ~13% of the samples. Second, tissue and clinical data collection occurred at a single institution for all samples included in the study. In addition, concurrent chemoradiation was uniformly administered across all patients in the study (1, 6–9). Furthermore, utilizing a targeted sequencing approach increases the sensitivity for detecting somatic mutations in genes of interest rather than genome-wide studies designed to maximize coverage (1). Exomic or genomic deep sequencing is time-consuming, labor-intensive, informatically challenging, and relatively expensive. To avoid these issues, Seiwert and colleagues opted for a targeted approach investigating 617 cancer-specific genes to provide a sequencing depth nearly twice that of The Cancer Genome Atlas (TCGA; refs. 6–9). Consequently, somatic mutations present at low allelic frequencies may have been missed in the previous studies due to insufficient coverage depth.

The identification of HPV-specific mutation profiles has far-reaching clinical implications as they represent potential therapeutic targets and predictive biomarkers. Currently, we rely on prognostic biomarkers (such as HPV status) that are associated with outcome regardless of the treatment provided. If we intend to improve patient outcomes, a shift toward predictive biomarker-driven clinical trials must be undertaken to maximize clinical benefits. The most successful predictive biomarkers in recent years are activated oncogenes. These are commonly point mutations, such as c-KIT in gastrointestinal stromal tumors; however, copy-number gain and gene upregulation, such as HER2 amplification in breast cancer, also represent powerful biomarkers. Based on current genome-wide sequencing and copy-number data, several oncogenes in HNSCC are immediately targetable with agents in clinical development (Fig. 1). Current data suggest that the frequency of oncogene mutations is relatively higher in HPV+ than in HPV− tumors, and the oncogene profiles differ based on the HPV status. For example, EGFR, CCND1, and FGFR1 amplifications are more common in HPV+ tumors, whereas FGFR2/3 mutations are more common in HPV− tumors.

Currently, there are concerted efforts to conduct predictive biomarker-driven clinical trials using targeted agents incorporating genomic, therapeutic, and clinical trial data to achieve the ultimate goal of personalized medicine. Because selecting patients with specific mutations results in small, fractionated cohorts, the
use of site-specific phase II/III trials is no longer feasible. Consequently, novel designs are required, such as multi-arm trials enrolling patients with a specific mutation in one of many simultaneous arms with a given targeted agent (also called umbrella, bucket, or basket trials). There are several multiple-arm clinical trials currently under way, and patients with HNSCC will be able to participate in the Molecular Analysis for Therapy Choice (MATCH) trial. In this study, patients with recurrent/metastatic cancers (regardless of organ site) will undergo pre- and posttreatment biopsies to sequence 200 preselected targetable genes to match with one of the targeted agents evaluated in the trial. In the MATCH trial. This study, patients with recurrent/metastatic cancers (regardless of organ site) will undergo pre- and posttreatment biopsies to sequence 200 preselected targetable genes to match with one of the ~25 targeted agents evaluated in the trial. Although this technology is promising, significant challenges are inherent to mutational biomarker data. For example, previous studies suggested HPV- tumors have fewer mutations than HPV+ tumors, whereas the current study failed to demonstrate this difference. This result suggests that mutations in HPV+ tumors (including clinically relevant mutations) may be present at lower allelic frequencies than is observed in HPV- tumors, requiring increased sequencing depth to detect these key differences. If validated, this finding would help establish the ideal depth of coverage for routine mutation testing to be utilized for effective biomarker detection. To date, the threshold of cancer cells harboring a targetable mutation that is required for a clinically meaningful response is unknown. If we follow the current Response Evaluation Criteria In Solid Tumors (RECIST) criteria, an activating mutation may be required to occur at cancer cell fraction greater than 0.3 (corresponding to approximately >30% of tumor mass) to observe a positive therapeutic response. For the amplified genes, the threshold of copy-number gain to consider significant is again unknown in HNSCC. Accurate mutational and CNV detection aside, the therapeutic agents matched to these targets must be effective at inhibiting...
oncoprotein. There is significant variability even within the same class of targeted agents with respect to efficacy and toxicity. Additional issues include determining the most clinically significant oncogene in a landscape of aberrations, the emergence of resistant clones from heterogeneous tumors, obtaining tumors for testing from inaccessible anatomic locations, and access to drugs still in developmental pipeline in cases of trial ineligible patients. For HPV patients, more creative approaches to target tumor suppressor loss or the relevant downstream consequences of negative regulator loss must be ascertained. Furthermore, whereas early therapeutic response can be assessed in multi-arm trials agnostic to disease site, confirmatory trials in patients with newly diagnosed or recurrent/metastatic HNSCC with survival benefit as the primary endpoint will be required. In the confirmatory trials, separate cohorts based on HPV status should be investigated; thus, HNSCC provides significant, but not prohibitory, challenges in future agent evaluation and trial feasibility.

In conclusion, effectively incorporating sequencing data into the clinic will allow us to move beyond HPV status as our sole prognostic biomarker and necessitate novel clinical trial design and validation of biomarkers. However, the quest for personalized medicine will be easier when a comprehensive map of HNSCC is created that accurately encompasses the full breadth of heterogeneity provided by this challenging disease. We remain cautiously optimistic that we will be able to take advantage of this and future genomic studies to meaningfully benefit our patients.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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Conception and design: G.S. Krigsfeld, C.H. Chung
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): G.S. Krigsfeld, C.H. Chung

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**References**

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