Precision Medicine in Head and Neck Cancer: Myth or Reality?

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ABSTRACT: Standard treatment in head and neck squamous cell carcinoma (HNSCC) is limited currently with decisions being made primarily based on tumor location, histology, and stage. The role of the human papillomavirus in risk stratification is actively under clinical trial evaluations. The molecular complexity and intratumoral heterogeneity of the disease are not actively integrated into management decisions of HNSCC, despite a growing body of knowledge in these areas. The advent of the genomic era has delivered vast amounts of information regarding different cancer subtypes and is providing new therapeutic targets, which can potentially be elucidated using next-generation sequencing and other modern technologies. The task ahead is to expand beyond the existent armamentarium by exploiting beyond the genome and perform integrative analysis using innovative systems biology methods, with the goal to deliver effective precision medicine-based theragnostic options in HNSCC.

KEYWORDS: Head and neck cancer, liquid biopsy, gene expression profiling, circulating tumor cell, indel burden

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Introduction

Current treatment options for head and neck squamous cell carcinoma (HNSCC) have limited success particularly in the recurrent or metastatic setting. Therapeutic decisions are by and large based on tumor location and disease staging rather than specific tumor biology. For early-stage disease, surgery and radiotherapy are the mainstay of treatment. Surgery is usually preferred for tumors of the oral cavity with adjuvant radiotherapy or chemoradiotherapy given based on risk of recurrence. Radiotherapy is generally given as primary treatment for oropharyngeal, hypopharyngeal, and laryngeal tumors to aid organ preservation. Concurrent cisplatin-based chemotherapy with radiation is the treatment of choice for locoregionally advanced disease. For patients who are deemed unfit for cisplatin-based chemotherapy, the anti-epidermal growth factor receptor (EGFR) monoclonal antibody cetuximab can be given concurrently with radiotherapy. In the case of recurrent or metastatic disease, platinum-based chemotherapy is the cornerstone of treatment, and the addition of cetuximab to standard cytotoxic chemotherapy offers some benefit in the first-line setting but at the price of increased toxicity.[1] Until recently, no standard options existed for second-line therapy in recurrent or metastatic platinum refractory HNSCC. The US Food and Drug Administration has granted approval and accelerated approval for 2 immune checkpoint inhibitors both targeting programmed cell death protein 1 (PD-1), nivolumab and pembrolizumab, respectively, and thus expanded therapeutic choices in this patient population.[2,3]

In recent decades, some countries have had a decrease in oral cavity cancer incidence correlating to decreased tobacco use. However, other countries, such as the United States, United Kingdom, Canada, Denmark, Norway, Sweden, and the Netherlands, have seen an increase in the rate of oropharyngeal and oral cavity cancers despite declining smoking rates, likely related to increased rates of human papillomavirus (HPV)-associated cancers.[4] High-risk serotypes of HPV, such as HPV16 and HPV18, have changed the epidemiology of HNSCC, particularly oropharyngeal cancer. Human papillomavirus–related HNSCC has shown improved clinical outcome with standard therapy compared with HPV-negative disease.[4–6]

Unfortunately, despite recent therapeutic progress in HNSCC such as the emerging role of immunotherapy and the changing epidemiologic landscape as demonstrated by the rising incidence of HPV-related tumors, the mortality rates of locoregionally advanced disease, as well as recurrent or metastatic disease, remain poor. Therefore, the application of precision medicine holds promise to further improve the control and curability of HNSCC. The aim of precision medicine is to personalize treatment according to molecular alterations or cellular features within a tumor.[7] Actionable biomarkers for precision medicine in HNSCC that alter management decisions are limited at present, but ideally the increasing amount of genomic, transcriptomic, proteomic, and epigenetic data will increase knowledge regarding the pathogenesis of the disease and provide novel targets for therapy. Head and neck cancer and cancers in general arise due to the accumulation of environmentally induced and genetically inherited aberrations in key signaling and survival pathways. The hope is that targeting aberrantly functioning pathways will provide clinical benefit to patients.

Target Identification

The Human Genome Project identified a total of 20 000 to 25 000 genes,[8] approximately 3000 of which are considered to be part of the "druggable genome." The druggable genome is the portion of the human genome that is susceptible to pharmacologic interaction while also being involved in pathologic mechanisms leading to disease.[9,10] Most of the drugs exert their therapeutic effect by interacting with genome-encoded proteins. The number of potential drug targets in the human genome is the intersection between the druggable genome and those genes that are related to disease. It has been estimated that only 10% of the druggable genome can be targeted by a small-molecule drug.[9]

The Cancer Genome Atlas (TCGA) has genetically profiled 10 000 cancer genomes including 500 HNSCC tumors. The initial data from 279 of these tumors showed that both HPV-positive and HPV-negative tumors harbor amplifications of 1q, 3q, 5p, and 8q and deletions of 3p, 5q, and 11q. Amplification of 3q26/28 region containing squamous lineage transcription factors *TP63, SOX2*, and *PIK3CA* is seen in both but more frequently in HPV-positive tumors. Also, in HPV-positive tumors, recurrent deletions of *TRAF3* and 11q including *ATM1* and focal amplification of *E2F1* are seen but 9q21.3 containing *CDKN2A* is usually intact. Meanwhile, in HPV-negative tumors, 9p21.3 is frequently deleted, whereas 11q13 containing *CCND1, FADD*, and *CTTN* and 11q22 containing *BIRC2* and *YAP1* are amplified. The 7p region that includes *EGFR* is less amplified in HPV-positive tumors.[11] From a practical point of view, these results would indicate that HPV-positive tumors may be more susceptible to blockade of PI3K and FGFR3 pathways, whereas HPV-negative tumors may be more susceptible to treatment with cell cycle inhibitors. A potential limitation in the TCGA data is that most of the sequenced tumors were procured from early-stage surgical tumor samples rather than disease in the recurrent or metastatic setting. The latter likely has different genetic profiles due to various phenomena including clonal evolution and treatment selection pressures.

A solution to this issue may come from the collection and examination of data derived from real-world genetic sequencing. Cancer genomic data are aggregated through the American Association for Cancer Research Project Genomics Evidence Neoplasia Information Exchange (AACR Project GENIE) and are made available to the global community.[12] This is an international data-sharing project that catalogues cancer genomic data from multiple international institutions' cancer sequencing efforts combined with clinical outcomes. To date, the AACR GENIE data set includes nearly 32 000 de-identified genomic records collected from patients treated at each of the Consortium's participating institutions. The combined data set now includes data for 59 major cancer types including samples from nearly 700 patients with HNSCC, and almost 40% represent those collected in the metastatic disease setting. This database provides the statistical power to improve clinical decision making, and importantly it further enriches the knowledge base in the genomic landscape of HNSCC[13] (Figure 1). In addition to TCGA and AACR GENIE, the Catalogue of Somatic Mutations in Cancer (COSMIC) also contains genomic sequencing data of HNSCC.[16] The relative frequencies of the most common somatic mutations in each of the 3 databases are quite similar, and some of the frequently mutated genes have readily available targeted therapies that may be used to treat HNSCC cases with specific aberrations (Table 1).

Personalized Treatment Strategy

The ultimate goal of genomic sequencing studies is to translate findings directly to patient care through aiding prognostication and to tailor therapeutic decision making. To date, only cetuximab targeting EGFR,[17,18] pembrolizumab,[19] and nivolumab[20] targeting PD-1 have been approved in recurrent or metastatic HNSCC and none of these systemic treatment decisions is biomarker driven. Genomically selected treatment has demonstrated unquestionable benefit and has been incorporated into the routine management of multiple solid tumors[21–23] as well as hematologic malignancies.[24] As the list of putative biomarkers being investigated increases due to widespread molecular profiling efforts and data-sharing initiatives such as the AACR Project GENIE, the outstanding question remains as to the maximal proportion of patients who can benefit from a personalized approach.

Many large academic institutions across the globe have published their "first-generation" experience in matching patients including those with HNSCC, who have undergone genomic testing to specific targeted agents, as an important step to define the clinical utility of precision medicine.[25–30] Most of these initiatives have performed such genotype matching based on opportunistic enrollment into early-phase clinical trials that are active in the respective institutions, others have recruited patients into prospectively designed biomarker-driven studies in search of prescreened patients with particular aberrations. To date, the results of these trials have been somewhat disappointing. Although driver mutations felt to stimulate tumor progression were identified in 30% to 50% of patients, only 5% to 15% of patients received treatment that was selected based on genomic analysis. A limitation of these trials is that they are simply matching the most obvious mutations to drugs but ignoring the totality of the information garnered from molecular profiling. Cancer cell biology is vastly more complex than simply relying on specific mutations to produce a phenotype. As one moves to "next-generation" precision medicine–based programs, such as the National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH) study,[31] with expanded scopes including broader and deeper exploitation of the cancer genome; evaluation of the transcriptome, proteome, epigenome, and immunome; and integrated data analysis using systems biology–based approaches,[32] the outlook of precision medicine remains optimistic.

Figure 1. The list of common mutations identified in head and neck squamous cell carcinoma in The Cancer Genome Atlas and the frequency of each mutation to date in samples catalogued in the AACR GENIE (American Association for Cancer Research-Genomics Evidence Neoplasia Information Exchange) database.
Courtesy of AACR GENIE[12] via cBioPortal.[14,15]

An additional avenue for early adoption of targeted therapy into HNSCC is to evaluate the off-label use of agents approved for other cancers under the auspice of a clinical trial or a registry. These agents have already been rigorously investigated in other cancer subtypes with specific mutations and the suggestion is that use in HNSCC with similar genetic aberrations may achieve benefit. A new series of basket trials are now being opened including American Society of Clinical Oncology's (ASCO) Targeted Agent and Profiling Utilization Registry (TAPUR),[33] the Netherland's Drug Rediscovery Protocol (DRUP)[34] and the Canadian Clinical Trials Group's (CCTG) Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)[35] that will involve assigning patients to receive off-label use of approved therapies based on specific mutations present in their tumor. These trials involve multiple treatment arms, so hopefully this strategy will increase the number of patients being matched to a targeted therapy and help to further determine whether treating cancer based on specific genetic changes is effective.

Another exciting development that has recently been launched is the first biomarker-driven umbrella master protocol in recurrent or metastatic HNSCC. The European Organisation for Research and Treatment (EORTC) 1559-HNCG study (UPSTREAM) is a multicenter pilot study offering personalized biomarker-based treatment strategy or immunotherapy in patients with recurrent or metastatic HNSCC.[36,37] In this study, patients will be allocated to receive standard of care, targeted therapy, or immunotherapy based on comprehensive molecular characterization of their cancer. Treatment stratification will occur based on the result of a combination of next-generation sequencing and specific immunohistochemistry assays.

New Targets or Drugs of Interest in HNSCC

NTRK

Most of the molecular profiling programs in the past have concentrated on common or frequent genetic aberrations that are known to be recurrent in cancers. An interesting development is the discovery of occasional rare variants, which are often not part of routine genetic testing, that could potentially act as therapeutic targets. One such example is the rearrangement of the neurotrophic tropomyosin receptor kinase (*NTRK*) gene. Multiple different *NTRK* gene fusions have been identified across different cancer subtypes. In common cancers, these fusions tend to occur infrequently, but in some rare cancers, *NTRK* fusions appear to be the defining characteristic and are present in nearly every case. Novel compounds have been

Table 1. Comparison of frequency of somatic mutations identified in the TCGA as being present in HNSCC from COSMIC, TCGA, and GENIE databases and potential treatment options available.

GENE	COSMIC, %	TCGA, %	GENIE, %	POTENTIAL DRUGS TO INHIBIT TARGET
TP53	41	72	41	WEE-1 inhibitors
CDKN2A	16	22	19	CDK inhibitors
PIK3CA	8	21	19	PI3K inhibitors
KMT2D	5	18	19	
NOTCH1	10	19	14	NOTCH inhibitors
FAT1	5	23	14	
CASP8	5	9	7	
NFE2L2	5	6	7	
FBXW7	3	5	7	
PTEN	3	2	6	
RB1	1	3	5	
TGFBR2	1	4	5	
HRAS	8	4	4	RAS inhibitors (FTI)
NSD1	4	10	4	
PIK3R1	3	1	2.1	PI3K inhibitors
HLA-A	2	3	0.6	
CUL3	2	4	0.5	
TRAF 3	0	1	0	
AJUBA	0	6	0	

Abbreviations: COSMIC, Catalogue of Somatic Mutations in Cancer; FTI, farnesyltransferase inhibitor; GENIE, Genomics Evidence Neoplasia Information Exchange; HNSCC, head and neck squamous cell carcinoma; TCGA, The Cancer Genome Atlas.

developed that are selective inhibitors of the constitutively active fusion proteins that arise from the molecular alterations. Larotrectinib is a pan-TRK inhibitor with compelling antitumor activity as demonstrated in a phase 1/2 study of 55 patients with 17 cancer subtypes where the objective response rate was 76% and the compete response rate was 12%.[38] *NTRK*1, 2, and 3 fusions in HNSCC are present at a rate of 3%, 1.6%, and 3%, respectively, in the AACR GENIE database.[12]

HRAS

Farnesyltransferase (FT) catalyzes the posttranslational attachment of farnesyl groups to signaling proteins that are required for localization to the inner cell membrane and downstream signaling. All RAS isoforms (KRAS/NRAS/HRAS) are FT substrates; however, only HRAS is exclusively dependent on farnesylation. Tipifarnib is a potent and highly selective inhibitor of FT which is currently being investigated in an ongoing multi-institutional, open-label phase 2 study in patients with *HRAS*-mutated solid tumors. Early efficacy signal has been noted in *HRAS*-mutated HNSCC and as a result there is ongoing enrichment for this patient population.[39] *HRAS* mutations are present at a rate of 4% in HNSCC in the AACR GENIE database.[12]

Antibody-drug conjugates

Antibody-drug conjugates are monoclonal antibodies conjugated to cytotoxic agents.[40] They use antibodies targeting particular cell surface proteins conferring tumor specificity. Ongoing efforts are focused on identifying better targets, more effective cytotoxic payloads, and improved antibody-drug linkage. Examples of antibody-drug conjugates currently approved for use include ado-trastuzumab emtansine in HER-2–positive breast cancer[41] and brentuximab vedotin for Hodgkin lymphoma and anaplastic large-cell lymphoma.[42] Numerous agents are being developed and investigated which target cell surface proteins which may be of clinical use in HNSCC with examples such as ABBV-221 and AVID100,[43,44] which target EGFR; BAY1129980,[45] which targets C4.4a; IMMU-132,[46]

which targets TROP-2 antigen; and tisotumab vedotin,[47] which targets human tissue factor.

DNA damage repair

The DNA damage response (DDR) is a potential target for anticancer therapy. Tens of thousands of DNA damage events occur daily in normal body cells and multiple pathways have developed to correct them. Most cancers will have lost one or more DDR pathway or capability during their development leading to greater genetic instability and increased dependence on the remaining pathways. Drugs have been developed that target different proteins involved in DDR which show efficacy in treating cancer. Identifying tumors with a defective DDR pathway through genomic sequencing may provide a potential target that can be exploited with a single agent, an approach known as synthetic lethality.[48,49] The most well-known examples are the poly (ADP-ribose) polymerase inhibitors in *BRCA1/2*–mutated cancers. There is an increasing catalogue of DDR pathway inhibitors that interrogate DNA damage–signaling proteins such ATM,[50] ATR,[51] DNA-PK,[52] WEE1,[53] and CHK1&2.[54] The frequency of alterations in DDR-related genes in HNSCC is approximately 8% based on the AACR GENIE database.[12]

Tumor mutational burden

Cancers with a high mutational burden tend be more immunogenic due to increased expression of tumor-specific antigens on the cancer cell surface. As a result, these cancers tend to be more susceptible to immuno-oncology approaches.[55,56] However, selecting patients most likely to respond to immunotherapy is still in an early phase of development with no validated biomarkers as yet. A recent large study across a variety of tumor subtypes used comprehensive genomic profiling to assess tumor mutation burden. This study defined high mutational burden as >20 mutations per megabase of DNA, and this threshold is found in 25% of patients with HNSCC who may therefore benefit from immunotherapy.[57]

Challenges and Solutions

Although there are existent druggable targets in HNSCC and more are being discovered due to emerging knowledge and innovative technologies, several challenges exist that should be considered as precision medicine is brought to bear in this malignancy. Tumors are quite adept at developing resistance to targeted therapy; research to identify mechanisms of drug resistance is essential to discover mechanisms to prevent escape. A combinatorial approach to therapy is a possible way to circumvent escape mechanisms or at least delay the development of resistance. The challenge is to choose between the plethora of available drugs and test them safely and efficiently. New computational methods and technologies are making it increasingly possible to conduct large-scale searches for rational combinations.[10,58] Once promising combinations are identified, laboratory models are established to predict and measure the efficacy of the combinations to determine which combinations are likely of most benefit to patients. In HNSCC, reliable models that are predictive of clinical efficacy remain scarce.

For precision medicine to be effective, it needs to adapt to the evolution of the cancer to the presence of a targeted therapy. This requires dynamic monitoring of the changing molecular landscape to enable the discovery of resistant clones early and appropriate reaction when resistance develops likely before clinical or radiological progression. A developing technique to facilitate monitoring is the serial measurement of circulating tumor DNA (ctDNA). The ctDNA consists of short fragments of double-stranded DNA shed from tumors; it is characterized by unique mutations not present in normal cells. It is shed during necrosis or apoptosis during cell turnover and released into the circulation. The utility of ctDNA is being investigated in multiple settings including surveillance for disease recurrence after curative intent treatment and to identify the development of resistance mutations during systemic treatment with a targeted therapy. It also potentially has a role in longitudinal clinical monitoring of patients on treatment to ensure that there is an ongoing clinical response. In the case of patients who have received treatment with curative intent who have also had their tumor sequenced at baseline, ctDNA could potentially be used to monitor for early disease relapse and lead to reflex use of genotype-matched agents once ctDNA is detected.[59,60] A recent feasibility study has shown that quantification of rare mutations in ctDNA in plasma from HNSCC using droplet digital polymerase chain reaction (ddPCR) is possible. *TP53* mutations were identified in surgically resected primary tumors of 6 patients with HNSCC, and blood samples were obtained prior to surgery and were tested for the presence of ctDNA. Mutation-specific ddPCR assays were designed and the results indicated that detection was possible.[61] Further investigation is required, however, to fully appreciate the utility of this technology in HNSCC.

Another practical issue is the limited number of therapeutic targets available. An ongoing effort by Tsherniak et al.[62] aims to compile a comprehensive catalogue of genetic vulnerabilities in cancer, to increase the repertoire of druggable alterations. Their recently published study identified more than 760 genes on which multiple types of cancer are strongly dependent for growth and survival. Cancer cells can harbor a broad variety of genetic errors; if an error shuts down a critical gene a cancerous cell will compensate by adjusting other genes' activity often resulting in dependence on these adaptations. Many of the dependencies are specific to certain cancer types but about 10% are common across multiple cancers. Therefore, it is possible that a relatively small number of therapies targeting these dependencies may treat multiple different types of cancer. More than 80% of dependencies with biomarkers were found to be related to changes in gene expression rather than mutation. Identifying these

dependencies provides opportunities to gain further insight into cancer development and determine new therapeutic targets, including in HNSCC.

Conclusions

There has been a substantial increase in the dissection of genetic landscapes underlying the pathogenesis of HNSCC; however, translation of scientific discoveries to clinical applications remains slow. Research in both preclinical and clinical settings is actively ongoing and will deliver further insight into potential treatment options for HNSCC. Collaboration between scientists and researchers at the bench and bedside, as well as international data-sharing efforts, is germane to make precision medicine a tangible goal in the management of HNSCC.

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