EDITORIAL

Recent advances in head and neck cancer: The beginning of the immunotherapy era in HNSCC

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After bringing unprecedented clinical benefits to patients with advanced melanoma, the field of immunotherapy has continued to break new ground and progressively transform the therapeutic landscape across many other cancers. The American Society of Clinical Oncology (ASCO), acknowledging the transformative impact and future potential of immunotherapy, has named it the “Advance of the Year” for the second consecutive year[1].

In head and neck squamous cell carcinoma (HNSCC), where only one targeted therapy had been approved by the U.S. Food and Drug Administration in almost a decade, the year 2016 marked a new era in the clinical landscape when two immunotherapy drugs, nivolumab and pembrolizumab, were approved for the treatment of recurrent or metastatic (R/M) head and neck cancer. In this editorial, we review the recent developments in the clinical landscape of HNSCC with a focus on immunotherapy and briefly describe the evolving areas of immunotherapy research, challenges, and future steps for the broad application of immunotherapy in HNSCC.

HNSCC comprises cancers originating from the mucosal lining of the upper aerodigestive tract and involves anatomical sites such as the oral cavity, hypopharynx, larynx, oropharynx, and nasopharynx[2]. Globally, more than 500,000 cases are diagnosed each year, making HNSCC the sixth most common malignancy in men worldwide, and approximately 50,000 new diagnoses occur annually in the United States. Roughly 3% of all cancer-related deaths can be attributed to HNSCC. While the overall incidence of HNSCC has been steadily declining over the past 30 years, a molecular subtype of HNSCC arising in the oropharynx and causally linked with infection by high-risk human papilloma virus (HPV) types 16, 18, and 33 has shown a sharp increase over the past decade[3]. This HNSCC subtype, denoted HPV-positive (HPV+ve) HNSCC, is considered a distinct biological and clinical entity and generally has a better prognosis compared to its HPV-negative (HPV-ve) HNSCC counterpart[4].

Treatment selection in HNSCC is based principally on the primary site, clinical stage, and HPV status, although the patient’s medical condition and treatment preference also play roles in decision making. Early-stage HPV-ve or HPV+ve disease typically has a good prognosis and is most often successfully managed with single-modality surgery or radiotherapy. Locoregionally advanced HPV-ve HNSCC is usually treated with combination therapy consisting of chemoradiotherapy or surgery, radiation, and chemotherapy. For the most part, chemoradiotherapy has predominated as the treatment for moderate to advanced cancers of the oropharynx, larynx, and hypopharynx over the past two decades. Despite such aggressive interventions, the 5-year progression-free survival (PFS) rate of advanced HNSCC has remained stagnant at 40%-50%, and the median time to relapse is less than 2 years[5,6]. The locoregional control and survival of patients with HPV+ve HNSCC is significantly better than that of those with HPV-ve HNSCC (2-year PFS rates: 87% v 56%; P = 0.05 and 2-year overall survival (OS rates: 94% v 58%;
For those with disease recurrence or distant metastasis, chemotherapy is the standard treatment of choice, but such cases have poor prognoses, with a median survival of 6–12 months. In addition to limitations in disease control, treatment-associated toxicity is also a concern, as multimodality treatment approaches for HNSCC can have debilitating effects on the quality of life of patients owing to impaired swallowing function, sensorineural hearing loss, and permanent xerostomia. The limited improvement in survival together with severe toxicities associated with the current treatments have shifted the focus in HNSCC research towards the discovery of less toxic and more effective treatments.

In recent years, cancer immunotherapy has become an area of intense investigation and has inspired widespread enthusiasm in the field, mainly due to the remarkable improvements seen in the survival outcomes of certain advanced cancer patients treated with immunotherapy. The basic premise underlying cancer immunotherapy is that it helps to overcome tumor escape strategies by enabling the functional restoration of immune signaling pathways of the host immune system. The revived host immune system then operates to neutralize a range of molecular and cellular tumor escape strategies, which include the impairment of tumor antigen processing and presentation, establishment of an immunosuppressive microenvironment, secretion of tumor-promoting cytokines, mediation of tumor escape via regulatory T cells (Treg cells) or myeloid-derived suppressor cells, and induction of T-cell anergy via an increase in co-inhibitory receptors, including cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death 1 (PD-1), or a decrease in co-stimulatory receptor expression.

Among the therapies counteracting tumor escape mechanisms, those targeting the co-inhibitory receptor pathway, i.e., CTLA-4 and PD-1, also known as “immune checkpoints,” are furthest along in terms of clinical investigation.

Multiple sources of evidence indicate that HNSCC is an immunosuppressive disease. For instance, Treg cells that suppress the induction and proliferation of effector T cells are commonly observed in HNSCC in a high proportion. Alteration of the immune microenvironment owing to enhanced secretions of immunosuppressive cytokines is another common feature of HNSCC tumors. For example, vascular endothelial growth factor, an inflammatory cytokine inhibiting dendritic cell function, is secreted at high concentrations in HNSCCs and is correlated with tumor relapse. A number of other diverse cytokines that mediate the recruitment of suppressive myeloid cells are found to be overexpressed in HNSCC. The presence of tumor-associated macrophages, a suppressive myeloid cell type, has been shown to be associated with poor treatment outcomes in advanced HNSCC. In oropharyngeal tumors, co-inhibitory receptor PD-1 expression in tumor-infiltrating lymphocytes (cluster of differentiation 4–positive [CD4+] and CD8+ T cells) is associated with HPV+ve viral infection. Overexpression of the PD-1 ligand (PD-L1) is frequently observed in HNSCC regardless of HPV status. These results suggest that immune dysregulation plays a crucial role in shaping HNSCC and further offer a strong rationale for immunotherapy intervention in HNSCC.

The year 2016 proved to be a landmark year in the treatment landscape of HNSCC, when two anti-PD-1 monoclonal antibodies, nivolumab and pembrolizumab, were approved for the treatment of R/M HNSCC. The approvals were based on the demonstration of superior OS in patients treated with nivolumab monotherapy when compared with the investigator’s choice of chemotherapy or cetuximab and the attainment of a durable objective response rate in the case of pembrolizumab. Among the therapies counteracting tumor escape mechanisms, those targeting the co-inhibitory receptor pathway, i.e., CTLA-4 and PD-1, also known as “immune checkpoints,” are furthest along in terms of clinical investigation.

Collective targeting of co-inhibitory or co-stimulatory pathways in effector lymphocytes is another approach to augment patient responses. On the basis of the promising activity seen in advanced melanoma patients, a number of studies have been initiated to evaluate combinations of anti-PD1/PD-L1 and anti-CTLA4 therapies in HNSCC. A phase III trial (NCT02551159), the KESTREL study, is currently evaluating the efficacy of durvalumab alone or durvalumab plus tremelimumab versus the standard-of-care EXTREME regimen (cisplatin, 5-fluorouracil, and cetuximab) for the first-line treatment of R/M HNSCC. Durvalumab is a high-affinity engineered human immunoglobulin G1 monoclonal antibody that inhibits binding of PD-L1 to
PD-1 and CD80, while tremelimumab is an anti-CTLA4 monoclonal antibody. CheckMate-651 (NCT02741570) is another phase III trial comparing nivolumab alone or in combination with ipilimumab (anti-CTLA4 monoclonal antibody) against the EXTREME regimen in the first-line R/M HNSCC. A phase III trial (NCT02369874), EAGLE, is evaluating the efficacy of durvalumab alone or in combination with tremelimumab against the standard-of-care regimen in platinum-refractory HNSCC. The CONDOR trial (NCT02319044) is comparing durvalumab alone, tremelimumab alone, and their combination in PD-L1-negative, platinum-refractory HNSCC patients. On the basis of encouraging preclinical data, immune-checkpoint inhibitors are also being tested in combination with therapies targeting other immunomodulatory receptors. Lymphocyte activation group-3 (LAG-3) receptors are a separate class of immunomodulatory receptors that suppress tumor cytotoxicity by averting attack from natural killer cells\cite{2, 23}. An early-phase clinical trial (NCT01968109) testing the combination of anti-LAG3 antibody with nivolumab in advanced solid tumors including HNSCC is in progress.

Other strategies for immune response amplification include targeting co-stimulatory receptors. For example, an agonist targeting the glucocorticoid-induced tumor necrosis factor receptor, which promotes CD8 effector T cell function, is being evaluated along with PD-1 blockade in solid tumors (NCT02740270)\cite{24}. Similarly, an agonist targeting the tumor necrosis factor superfamily receptor OX40, which augments T-cell effector responses, is currently being studied as a single agent in locally advanced HNSCC (NCT02274155)\cite{25}. The anti-4\(1\)BB agonistic antibody urelumab, which promotes T-cell activation and proliferation, is being assessed in combination with nivolumab in advanced solid tumors including HNSCC (NCT02253992). A study evaluating the combination of urelumab and cetuximab in advanced/metastatic HNSCC or colorectal cancer has been recently completed (NCT02110082). Because the tumor microenvironment is host to a number of immunosuppressive molecules, it serves as a rich source of immunotherapy targets. Indoleamine 2,3-dioxygenase (IDO), an immunosuppressive molecule expressed in tumor as well as infiltrating myeloid cells, promotes the inhibition of T-cell activation and proliferation\cite{26},\cite{27}. Agents inhibiting IDO in combination with the PD-1 inhibitor pembrolizumab are currently progressing in clinical trials of human malignancies including HNSCC (NCT02178722).

Oncolytic viruses are also being studied as anti-cancer therapy in HNSCC, either as monotherapy or in combination with standard or immune-checkpoint therapies. For example, talimogene laherparepvec, the most clinically advanced oncolytic immunotherapy, is being evaluated in combination with pembrolizumab in R/M HNSCC (NCT02626000). Other oncolytic viruses that are in early-phase clinical trials in HNSCC patients include the recombinant vaccine virus JX-594 and the recombinant avian fowl pox virus TRICOM (NCT00625456 and NCT00021424)\cite{2, 29}.

Another important area of investigation in immunotherapy is the use of anti-cancer vaccine therapies. Anti-cancer vaccine therapies work on the principle of generating an anti-cancer immune response by sensitizing the host immune system to tumor antigens. A number of anti-cancer vaccines are at various stages of clinical development in HNSCC. For example, the DNA vaccine INO-3112 and peptide vaccines Mucin-1 and AlloVax are in early stage clinical trials in HNSCC. A phase II trial evaluating the efficacy of a peptide vaccine (HPV16 E6 and E7) in recurrent or advanced HPV-related tumors, including HNSCC, has been recently completed, and the study results are awaited (NCT00019110). Combinations of vaccine therapies and immune checkpoint inhibitors are being assessed in a number of clinical trials. For example, a modified vaccinia virus Ankara vaccine expressing p53 in combination with pembrolizumab is being evaluated in a phase I trial of advanced solid tumors including HNSCC (NCT02432963). A phase I/II trial evaluating durvalumab alone or in combination with HPV-E7 tumor antigen–secreting live-attenuated Listeria monocytogenes (ADXS11-001) is ongoing in patients with R/M cervical and HPV+ve HNSCC (NCT02291055).

Over the past decade, we have significantly improved our understanding of strategies that are exploited by tumors to avoid immune detection and clearance. Seminal work delving into the mechanisms of immune responses has yielded breakthrough cancer therapies, such as the CTLA-4 and PD-1 targeting immune-checkpoint inhibitors, which have transformed the treatment landscape across many cancers. In 2016, the approval of immune-checkpoint inhibitors in HNSCC was an important step forward for the clinical management of the disease. While single-agent immunotherapies have afforded some clinical benefits to HNSCC patients, the response rates and the duration of response have not been optimal. The lack of insight into the factors guiding clinical responses has been chiefly responsible for the suboptimal performance of
immunotherapies in HNSCC. Studies designed to uncover the complexities of tumor response to immunotherapy will be helpful in addressing some of these clinical challenges. Another approach towards improving patient outcomes involves combining immune-checkpoint inhibitors with other immunomodulating therapies. Currently, there are a number of immunotherapy combination studies that are planned or enrolling patients in different HNSCC disease settings, including neo-adjuvant, concurrent definitive therapeutic, and post-operative adjuvant approaches. As new data emerge from these studies and we gain insight into rational immunotherapy combinations, it is likely that there will be improvements in the therapeutic outcomes of patients with HNSCC and that immunotherapy will become a standard for the treatment of head and neck cancer.

References


