Immunotherapeutic Strategies for Head and Neck Cancer

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KEYWORDS

• Biologics • Monoclonal antibodies • Immunotherapy • Otolaryngology • Cancer • PD-1

KEY POINTS

- Immunotherapy for head and neck squamous cell carcinoma (HNSCC) consists primarily of biologic agents, including monoclonal antibodies, vaccines, and whole immune cells.
- Inhibitors of the programmed cell death protein 1 (PD-1) immune checkpoint pathway are in use for recurrent/metastatic HNSCC and are currently under investigation for previously untreated, locally advanced disease.
- Preventive vaccines for human papilloma virus (HPV) are not useful for treatment of pre-existing HPV-related oropharyngeal carcinoma, but several therapeutic vaccines for HPV-related HNSCC are in development.
- Combinations of immunotherapy with chemotherapy, radiation, or surgery have shown encouraging results in HNSCC. The combination of anti–PD-1 therapy plus cytotoxic chemotherapy has been US Food and Drug Administration approved for recurrent/metastatic disease.

INTRODUCTION

Surgery, radiation, and cytotoxic chemotherapy have been used for decades to treat head and neck squamous cell carcinoma (HNSCC). In recent decades, immunotherapy has revolutionized the treatment of cancer, including HNSCC. Most immune therapies consist of biologics, including monoclonal antibodies, vaccines, and cell therapy. This article reviews basic tumor immunology, then provides an overview of immunotherapeutic strategies in use and under investigation for HNSCC. For further

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information, some of these strategies are covered in more detail elsewhere in this issue.

DISCUSSION

Basics of Tumor Immunology and Immunotherapy

Cancer can be viewed as a genetic disorder in which cellular stress/inflammation induced by carcinogens (eg, tobacco) leads to genomic instability and impaired ability to undergo cell death. Innate and adaptive immunity exist, in part, to eliminate nascent malignant cells. However, clinically significant tumors evolve ways, under the harsh selective pressure of the immune system, to escape and thrive.

The innate immune system is the first line of defense against the stress signals that lead to tumor formation. Stressed, inflamed cells release damage-associated molecular patterns (DAMPs),[1] which result in the trafficking of immune cells into the tumor milieu. Natural killer (NK) cells recognize and kill cells that show generic stress signals. Innate immunity is a rapid, nonspecific response. In contrast, adaptive immunity is antigen specific and durable. In general, for a robust adaptive immune response, tumor neoantigens, proteins perceived as foreign that can be recognized by antigen-specific T cells, are required. In HNSCC, these antigens can consist of proteins that are expressed at high levels (eg, epidermal growth factor receptor), mutated proteins (eg, p53), or viral material, such as human papillomavirus (HPV) oncoproteins. In order for these neoantigens to be presented to a T cell, they must first be processed inside the cell, loaded onto a major histocompatibility complex (MHC; also known as human leukocyte antigen [HLA]) molecule in the endoplasmic reticulum, then shuttled to the surface of the cell. The peptide-MHC complex is then bound by antigen-specific T-cell receptors (TCRs; **Fig. 1**). For antigen-presenting cells such as dendritic cells, antigen processing and presentation is a full-time job. These cells engulf proteins found in the environment, process the material, and present potential antigens to T cells. Once the TCR is linked to a peptide-MHC complex, activation of costimulatory receptors (CD28) is an important second signal for T-cell activation. The third important signal is production of cytokines, which leads to T-cell proliferation and differentiation.

However, cancer cells have evolved numerous ways of escaping under the selective pressure of the immune system. Tumor cells can adapt to express fewer neoantigens over time, a process known as immunoediting. Tumor cells that do express neoantigens can downregulate expression of MHC-I and other cellular components needed for antigen processing and presentation to immune cells. Even if neoantigens are present and properly processed, immune cells must be present to respond to them; tumors that exclude immune effectors (said to be immunologically cold) or are heavily infiltrated by immunosuppressive cells may also escape immune surveillance. In addition, the expression of coinhibitory checkpoints, such as programmed cell death 1 (PD-1) on T cells and its ligand PD-L1 on tumor and other tumor infiltrating cells, also inhibits antitumor immunity (**Fig. 2**). The evolved purpose of coinhibitory checkpoints is to prevent exaggerated immune responses (eg, autoimmunity), but cancer cells can exploit this system by expressing high levels of PD-L1 to avoid killing by T cells.

Most immunotherapeutic treatments work by enhancing the action of immune effector cells (“stepping on the gas”) or by inhibiting these mechanisms of immune escape (“releasing the brakes”; **Table 1**). Combination therapies may use both strategies at once. For example, radiation and cytotoxic chemotherapy preferentially kill cancer cells, releasing antigens and DAMPs, and creating an inflammatory response;

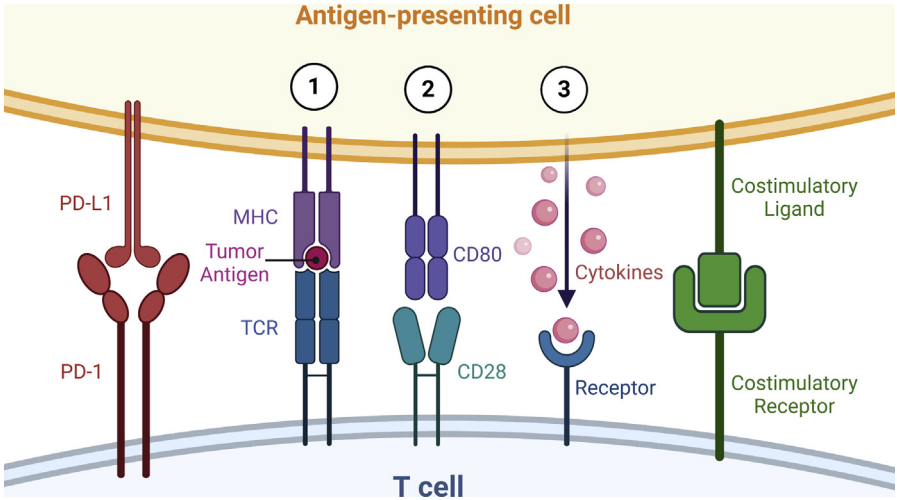

Fig. 1. Three steps are required for initiation of a T-cell response. First, interaction of the TCR with an antigen-MHC complex induces T-cell stimulation (1). Next, interaction of cluster of differentiation (CD) 28 and CD80 leads to T-cell activation (2). In addition, production of cytokines by the antigen-presenting cell (3) leads to T-cell proliferation and differentiation. Interaction of coinhibitory receptors (eg, programmed cell death 1 [PD-1]; *red*) with their ligands (eg, PD-L1) inhibit the T-cell response, whereas the interaction of costimulatory receptors (eg, CD40, CD137, OX40) with their ligands (*green*) promote the T-cell response. Created with BioRender.com.

the activity of responding immune cells can then be further enhanced by inhibiting checkpoints such as PD-1. Specific therapeutic strategies are detailed further in the rest of this article and elsewhere in this issue.

Immunotherapeutic Strategies for the Treatment of Head and Neck Cancer

Tumor antigen-targeted monoclonal antibodies

Cetuximab is a chimeric mouse-human immunoglobulin (Ig) G1 monoclonal antibody targeting epidermal growth factor receptor (EGFR), which is overexpressed in most HNSCCs. Cetuximab is US Food and Drug Administration (FDA) approved in combination with radiation for previously untreated disease; this combination is primarily used in cisplatin-ineligible patients. It is also approved as monotherapy or in combination with cytotoxic chemotherapy (cisplatin/fluorouracil) for recurrent or metastatic disease.[2,3] Interestingly, only a subset of patients respond well to cetuximab, and its mechanisms of action are thought to be related to enhanced antitumor immunity rather than EGFR inhibition.[4,5] In support of this idea, tumor antigen-specific T cells correlate with responses to cetuximab in HNSCC.[6,7] The mechanisms of action and indications for cetuximab are further reviewed by Trivedi and Ferris in Epidermal Growth Factor Receptor Targeted Therapy for Head and Neck Cancer.

Immune checkpoints

Coinhibitory checkpoint pathways exist to prevent exaggerated immune responses, but, as noted earlier, tumor cells may exploit these pathways as a mechanism of immune escape. Although several different coinhibitory checkpoints have been identified and studied, PD-1 and cytotoxic T lymphocyte–associated protein 4 (CTLA-4) pathways have been most widely studied thus far. Monoclonal antibodies blocking these

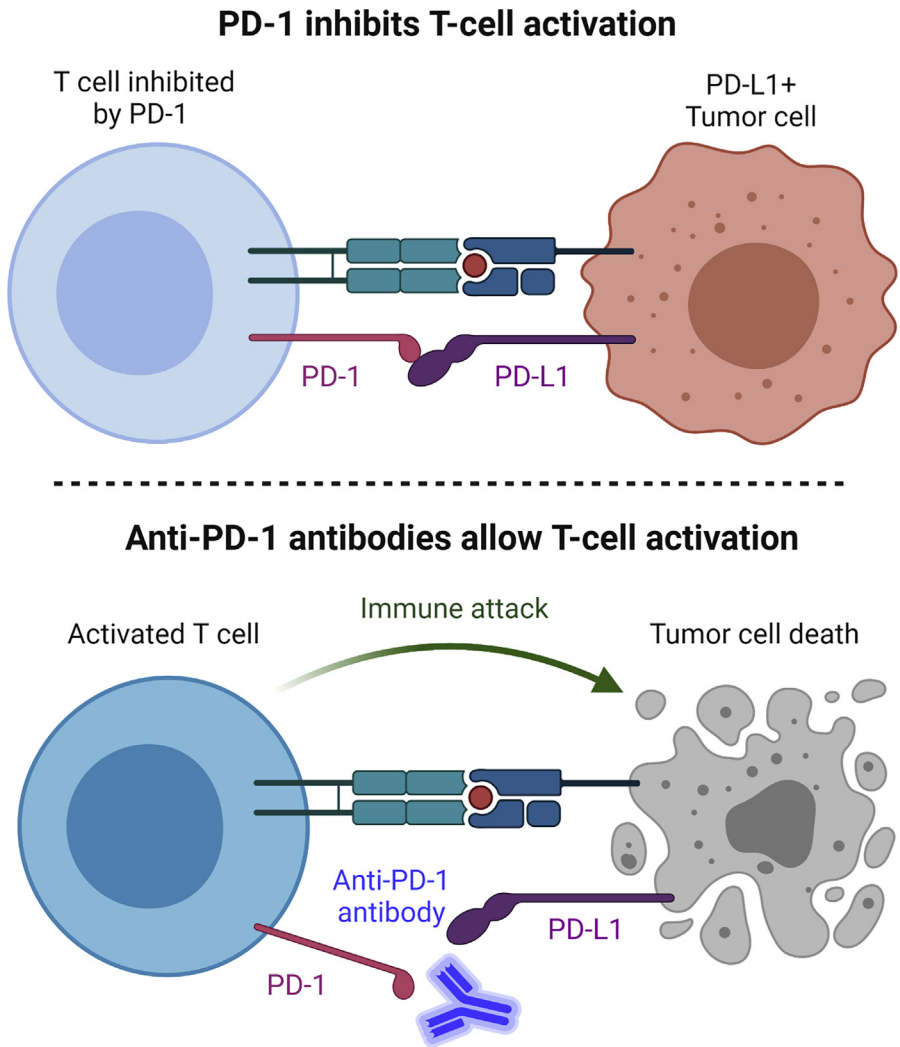

Fig. 2. The interaction of PD-1 on a T cell with its ligand (PD-L1) on a tumor cell inhibits T-cell activation. T-cell activation can be restored by blocking this interaction with anti–PD-1 or anti–PD-L1 antibodies, leading to T-cell killing of the tumor cell. Created with BioRender.com.

pathways have shown encouraging results, first in melanoma, and more recently in HNSCC and other solid tumors.

Programmed cell death 1 pathway. The best-studied immune checkpoint pathway thus far for HNSCC is the PD-1 pathway. Multiple monoclonal antibodies targeting PD-1 or its ligand, PD-L1, are now available. Two PD-1 inhibitors, pembrolizumab and nivolumab, are currently approved for use in recurrent/metastatic (R/M) HNSCC. The standard first-line therapy for R/M HNSCC was the EXTREME regimen, which includes cisplatin, fluorouracil and cetuximab. Approximately one-third of patients respond to the EXTREME regimen, with a median overall survival of 10 months.[8]

Table 1
Immunotherapeutic strategies and current phase of study for head and neck squamous cell carcinoma

Enhancement of Immune Effector Cells (Stepping on the Gas)		Overcoming Immune Escape Mechanisms (Releasing the Brakes)	
Strategy	**Phase of Study**	**Strategy**	**Phase of Study**
Tumor antigen-targeting antibodies (cetuximab)	FDA approved	Checkpoint inhibitors (anti–PD-1/PD-L1)	FDA approved
Costimulatory agonists	Early phase	Inhibition of immunosuppressive cells (MDSCs, Tregs)	Early phase
Vaccines (peptides, viral or bacterial vector)	Early phase	—	
Adoptive cell therapy	Early phase		
Agonists of innate immunity	Early phase		

Abbreviations: FDA, US Food and Drug Administration; MDSCs, myeloid-derived suppressor cells.

However, EXTREME is associated with significant toxicity. In the KEYNOTE-012 trial, patients with R/M HNSCC who had failed first-line, platinum-based therapy were treated with the anti–PD-1 antibody pembrolizumab.[9,10] About a third of the enrolled patients showed a response or stable disease, despite having failed multiple prior rounds of therapy. Some of the responses were durable, often lasting up to 2 years. In the first phase III, randomized, placebo-controlled trial of PD-1 therapy for HNSCC (CheckMate-041), patients with R/M disease who had failed platinum chemotherapy were randomized to receive the anti–PD-1 antibody nivolumab or investigator's choice of second-line therapy (other forms of cytotoxic chemotherapy or cetuximab monotherapy). The trial was stopped early after meeting its primary end point of increased 1-year overall survival, which increased from 17% with standard second-line therapy to 36% with nivolumab.[11] Both anti–PD-1 antibodies were very well tolerated, and these 2 trials led to FDA approval of pembrolizumab and nivolumab for the treatment of platinum-refractory, R/M HNSCC in 2016.

Multiple subsequent trials with PD-1 inhibitors have followed, with similar results: good responses in a subset of patients and stable disease in others, despite failing multiple prior lines of therapy, and a favorable toxicity profile.[12,13] The consistent finding of responses in a minority of patients has sparked tremendous interest in finding biomarkers of response and resistance (see the review by Maroun and Mandal, "Anti-PD-1 immune checkpoint blockade for head and neck cancer: Biomarkers of response and resistance", in this issue). The one predictive biomarker already in wide clinical use is tumor expression of PD-L1.[10,14] The combined positive score (CPS) is the number of PD-L1–positive cells (lymphocytes, macrophages, tumor cells) divided by the total number of viable tumor cells, then multiplied by 100. The CPS was established in order to standardize the assessment of PD-L1 staining for prediction of responses.[12] Although it has been suggested that HPV-related tumors may be more likely to respond to PD-1 inhibition versus HPV-negative tumors, results from clinical trials have been mixed.[9,14–17]

Other coinhibitory and costimulatory receptors. Inhibitors of CTLA-4 are approved for use in melanoma[18] but have shown disappointing results for HNSCC.[19] Multiple preclinical mouse model studies have shown an encouraging rationale for the use of

antibodies blocking other coinhibitory checkpoints, including TIM-3, LAG-3, and TIGIT, in addition to PD-1.[20–26]

Rather than release the brakes by targeting coinhibitory receptors, 1 way of stepping on the gas is to enhance T-cell function by activating costimulatory receptors, such as OX40, CD137 (also known as 4-1BB), or CD40. This strategy has been tested in multiple preclinical mouse model studies, and multiple early-phase clinical trials of costimulatory agonists are underway for solid tumors, including HNSCC.[27–29]

Vaccines and oncolytic viruses

Vaccination is the process of introducing a specific antigen or antigens to the immune system with the intent of developing a durable, antigen-specific immune response. Tumor vaccines can be made from peptides, DNA, whole tumor cells, or antigen-presenting cells loaded with a specific tumor antigen. Tumor vaccines can also be delivered by viral or bacterial vectors. The presence of viral antigens in HPV-related disease is a strong rationale for the development of vaccines and other antigen-specific immune therapies for HPV-driven tumors. Preventive vaccines are highly effective for prevention of future HPV infection but not useful for treating established HPV-associated tumors. Several therapeutic vaccines have been developed for cervical cancer and other HPV-related malignancies. However, vaccines consisting of E6, E7, $p16^{INK4A}$, or other HPV-16 peptides have shown modest results so far.[30–33] Vaccines using viral or bacterial vectors to deliver HPV-specific antigens have also been studied. Multiple early-phase trials using a *Listeria*-based HPV-16 antigen vaccine (ADXS11-001) are enrolling patients with oropharyngeal cancer and other HPV-related cancers.[31,34]

Oncolytic viruses preferentially infect and lyse tumor cells more than normal cells, subsequently releasing tumor antigens from dying cells to the tumor microenvironment where they can be recognized by immune cells.[35] Clinical trials with the T-VEC vaccine (an HSV-1 virus) and other oncolytic viruses for melanoma, HNSCC, and other solid tumors have shown encouraging results.[36–38]

Adoptive cell therapy

Another way to step on the gas is by administering immune effector cells, which is known as adoptive cell transfer. Most commonly, this involves the use of CD8+ T cells, which can be isolated from patients, expanded ex vivo, and then reinfused into the patient. Modifications are often made to make the T cells more effective before expansion and reinfusion. Thus far, most clinical trials involving T-cell transfer in HNSCC have focused on HPV-related disease[39,40] (see the comprehensive overview of adoptive T-cell therapy for HNSCC by Norberg and Hinrichs, in this issue).

However, some tumors do not respond to adoptive transfer of T cells because of a lack of neoantigens or the machinery required to process and present these antigens. These limitations might be overcome by using NK cells or chimeric antigen receptor (CAR) T cells instead. NK cells do not react to specific antigens and do not need to be HLA matched to the host. CARs are artificial TCRs that are engineered to recognize specific antigens and also contain T-cell activation domains. For example, CAR T cells have been engineered to express receptors for ErbB dimers, which are often upregulated in HNSCC, and the 4ab receptor, which converts IL-4 into a signal for T-cell expansion.[41] The use of off-the-shelf NK cell or CAR T-cell products offers attractive strategies that are currently in early-phase clinical trials.[41,42]

Agonists of innate immunity

Toll-like receptors (TLRs) play an important role in the antiviral immune responses, inflammation, and innate/adaptive immunity.[43] TLR agonists act, in part, by maturing

antigen-presenting cells to present antigen in an inflammatory context to T cells. In mouse models of HNSCC, agonists of TLR7, TLR8, and TLR9 have shown additive or synergistic activity when combined with cetuximab or PD-1 antibodies.[44–46] A phase 1b trial of a TLR8 agonist (motolimod) combined with cetuximab for R/M HNSCC showed some partial responses and enhanced NK cell activation,[47] but another trial comparing motolimod versus placebo combined with the EXTREME regimen showed no difference in survival.[48] A phase 1b/2 study combining intratumoral injection of a TLR9 agonist (SD-101) with pembrolizumab for R/M HNSCC showed an encouraging disease control rate of 48%.[49]

Type 1 interferons are produced following activation of a protein called stimulator of interferon genes (STING). The STING protein can be activated by cyclic dinucleotides (CDNs), which can be natural or synthetic. Injection of CDNs in mouse models of HNSCC resulted in robust antitumor immune responses, which were further enhanced by adding anti–PD-1 therapy.[50,51] Clinical trials of CDNs in combination with checkpoint inhibitors are currently underway.[51,52]

Inhibition of immunosuppressive cells

Some of the immune cells found within the tumor microenvironment are primarily immunosuppressive. These cells include myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and M2 macrophages. Strategies under investigation for inhibiting MDSCs include specifically depleting them, preventing them from trafficking into the tumor, and impairing their function.[53–55] Treatments designed to deplete or inhibit Tregs or M2 macrophages have also been explored.[56,57]

Combination therapies

Based on the small proportion of patients with R/M disease who respond favorably to immune checkpoint blockade, more recent clinical trials have attempted to increase response rates by combining multiple forms of immunotherapy, or by combining immunotherapy with standard therapies. It has also been recognized that immunotherapy could be used strategically to increase response and survival rates in patients with high-risk, previously untreated, HPV-negative HNSCC, or to deescalate therapy for patients with HPV-related HNSCC.

Combinations of immunotherapy. Immunotherapeutic combinations may consist of multiple coinhibitory checkpoint inhibitors, or a coinhibitory checkpoint inhibitor in combination with a costimulatory agonist. Although combinations of anti–PD-1/PD-L1 and anti–CTLA-4 therapies have been useful for melanoma, similar combinations have shown disappointing results in HNSCC.[15,58] Combinations of the IDO1 inhibitor epacadostat with anti–PD-1 antibodies have shown some responses and favorable toxicity profiles.[59,60] As detailed earlier, STING and TLR agonists have also been used in combination with PD-1 inhibitors.

Immunotherapy combined with standard therapy. Standard therapies, such as chemotherapy and radiation, may enhance the antitumor immune response in HNSCC and other cancers. When radiation or chemotherapy are used, dying cancer cells release antigens and DAMPs, which can then be detected by immune cells. As a result, the tumor itself serves as an in situ vaccine. Preclinical studies in mouse tumor models have shown that radiation and platinum-based chemotherapy can enhance immunogenic cell death, antigen processing/presentation, and adaptive immunity.[61–69] Radiation used at one tumor site can result in responses at distant tumor sites outside the radiation field, a phenomenon known as the abscopal effect. The abscopal effect is mediated in large part by CD8+ T cells and may be enhanced by

combining radiation with immune checkpoint blockade.[70–73] Multiple clinical trials have used reirradiation in combination with checkpoint inhibitors in the recurrent/metastatic setting for HNSCC and other solid tumors. For patients with previously untreated, locally advanced disease who are not eligible to receive cisplatin, anti–PD-1/PD-L1 antibodies alone or in combination with anti–CTLA-4 therapy have been used with radiation, so far with favorable results.[74–76] Larger studies are needed to compare the efficacy of these regimens with standard radiation plus cisplatin or cetuximab.

Platinum chemotherapy has been used successfully in combination with PD-1 inhibitors, first in lung cancer, and more recently in HNSCC. Initially, PD-1 inhibitors were only FDA approved for patients who had failed treatment with platinum-based chemotherapy. In the KEYNOTE-048 trial, patients were randomized to 1 of 3 arms: (1) the EXTREME regimen (cisplatin, fluorouracil and cetuximab), (2) first-line pembrolizumab (anti–PD-1), or (3) pembrolizumab (instead of cetuximab) in combination with cytotoxic chemotherapy (platinum/fluorouracil). At the second interim analysis, improved overall survival was noted with pembrolizumab alone in patients with PD-L1–positive tumors (CPS $\geq$ 1), leading to FDA approval of pembrolizumab as first-line therapy in 2019. The final analysis showed response and survival rates that were better with pembrolizumab/chemotherapy versus cetuximab/chemotherapy (EXTREME), regardless of PD-L1 status.[77] Based on these results from KEYNOTE-048, the current standard of care for recurrent/metastatic HNSCC is pembrolizumab alone for patients with PD-L1–positive tumors (CPS $\geq$ 1) and pembrolizumab plus chemotherapy for tumors with low expression of PD-L1 (CPS < 1). According to this scoring system, most patients with R/M disease are eligible for first-line pembrolizumab, which is far better tolerated than cytotoxic chemotherapy.

Because PD-1 inhibitors pair well with radiation and with chemotherapy, a logical next step was to combine all three modalities as a potential way of improving survival rates in patients with high-risk disease. In one study, pembrolizumab was added to radiation and low-dose, weekly cisplatin. This regimen was well tolerated and feasible, with most patients receiving the intended total doses of radiation and cisplatin.[78] In RTOG 3504, the addition of nivolumab to radiation with or without cisplatin or cetuximab was also safe and feasible.[79] However, these studies have not provided much information about efficacy of these regimens compared with chemoradiation alone. In the phase III JAVELIN head and neck 100 study, the addition of avelumab (anti–PD-L1) during and after cisplatin chemoradiation showed no added benefit versus chemoradiation plus placebo.[80] Although the reasons for this negative result are under debate, preclinical studies suggest that radiation is more likely to enhance the antitumor immune response when given in fewer, larger doses.[72,73] In contrast, cisplatin enhances the immune response when used in small weekly doses.[65] Thus, the standard radiation fractionation (2 Gy daily for 35 fractions) and high-dose cisplatin that are typically used for HNSCC may not be the optimal regimen for pairing with anti–PD-1/PD-L1 therapy.

Another way to enhance response rates to PD-1 checkpoint inhibitors is to administer them before surgery (neoadjuvant). Preclinical studies suggest neoadjuvant is more effective than adjuvant administration, likely because of the presence of anti–PD-1–responsive tumor infiltrating lymphocytes.[81] Response rates to neoadjuvant immune checkpoint blockade seem to be much higher than those seen in patients with R/M HNSCC.[82,83] Phase II studies using pembrolizumab or nivolumab in the neoadjuvant setting for high-risk HNSCC have shown acceptable toxicity, and delay in the timing of surgery has been uncommon. Pathologic responses were seen in more than 40% of surgical specimens, and some complete pathologic responses have

been noted.[82–84] A phase III study of neoadjuvant and adjuvant pembrolizumab for patients with high-risk, surgically resectable HNSCC (KEYNOTE-689) is currently enrolling at multiple centers.[85]

CLINICS CARE POINTS

- Head and neck cancers may respond well to immunotherapy based on a high number of mutations and, in the case of HPV-positive disease, the presence of viral antigens.
- Patients with recurrent or metastatic HNSCC can be treated with PD-1 checkpoint inhibitors, which have fewer side effects than cytotoxic chemotherapy.
- Patients with recurrent/metastatic head and neck cancers that do not express PD-L1 are treated with PD-1 inhibition in addition to cytotoxic chemotherapy.
- In addition to immune checkpoint inhibitors, several other immunotherapeutic strategies are under rigorous investigation in numerous clinical trials.
- PD-1 immune checkpoint inhibitors can enhance the activity of chemotherapy and radiation, but the combination of all three modalities has been disappointing thus far.
- The use of neoadjuvant (presurgical) PD-1 immune checkpoint inhibitors seems to be a promising strategy for high-risk HNSCC.

DISCLOSURE

N.C. Schmitt: advisory board for Checkpoint Surgical; book royalties from Plural Publishing.

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