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Immunotherapy in Oral Cancer: Review

SUMMARY

Squamous cell carcinoma of the head and neck (HNSCC) is the sixth most prevalent malignant entity with a significant fatality rate. The International Agency for Research on Cancer reported in 2018 that there are approximately 350,000 newly diagnosed instances of oral cancer per year, amounting to a cumulative incidence of 4.0 per 100,000 people. The aim of this review was to investigate the biomarkers associated with immunotherapy in head and neck cancer, and in particular oral cancer, as well as their respective immunotherapeutic agents. An extensive review of the literature was carried through. Relevant articles were searched in Medline Pubmed, Web of Science and Google scholar. The inclusion criterion was that the article should be written in English, whereas the exclusion criterion was the opposite. The current standard of care (SOC) for disease that recurs locally and/or metastatic disease was, until recently, platinum-based chemotherapy plus cetuximab. A potential treatment option is the monoclonal antibody cetuximab, which extends median progression-free survival (PFS) as it targets the epidermal growth factor (EGFR). Last decade, research has shown that there are two mechanisms of tumor's microenvironment (the immune escape and the T-cell exhaustion) which are related to total survival from cancer. Consequently, scientists focused on immunotherapy, a new therapeutic approach that activates a patient's immune system to fight tumor cells. Immune checkpoint inhibitors (ICIs) are a category of immunotherapies that are extremely effective at reactivating the immune system's defence against cancer. Oral cancer immunotherapy could target two significant immune checkpoints, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed death-1 (PD-1).

Keywords: Immunotherapy, Oral Cancer, CTLA-4, PD-1

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Introduction

One of the six most common types of cancer worldwide is cancer of the head and neck. Specifically, it accounts for 4% of all cancers this type of cancer is a group of diseases that develop in the paranasal sinuses, the oral cavity, the pharynx, the larynx, the lips, and the nasal cavities [1]. It accounts for 4% of all cancers. The most prevalent subtype of this disease is oral cancer, which is cancer of the oral cavity. Squamous cell carcinoma is the most common type of cancer among these conditions (oral squamous cell carcinoma (OSCC) or head and neck squamous cell carcinoma (HNSCC). The complex process of oral carcinogenesis is carried on by the accumulation of several genetic and epigenetic changes carried on by oral carcinogens (such as alcohol, cigarettes, betel nut, and/or human papillomavirus) (HPV). Nearly 700,000 new cases and 380,000 deaths from head and neck cancer occur each year worldwide, and over 10,000 of these deaths occur in the United States alone [2]. Patients with head and neck epithelial tissue cancer who have returned or metastasized require better prognoses (HNSCC) [3]. The majority of

HNSCC patients have diseases that are locally advanced and have a high likelihood of recurrence, with just about 10% of patients having metastatic disease. The primary definitive simultaneous chemoradiation or surgical excision of the following risk-adapted adjuvant radiation with or without platinum-based chemotherapy, the principal tumor and draining lymphatic system, continue to be the main treatments for locally formed HNSCC. It is significant to emphasize that the quality of life (QOL) of patients is frequently severely impacted by multimodality treatment. Patients with recurrent/metastatic (R/M) disease typically have an overall survival (OS) of 10 to 13 months [1].

In response to the aforementioned rates, the Society for Immunotherapy of Cancer (SITC) established an expert committee tasked with emerging consensus guidelines for new immunotherapies, including accurate patient selection, therapy sequencing, response monitoring, management of adverse events and biomarker screening These recommendations for consensus provide a framework to assist clinicians to recognize how immunotherapies fit into the context of this disease and standardizing application throughout the sector for the benefit of patients. Due to regional variations in approvals, accessibility, and rules concerning the specified medicines, this panel primarily concentrated on FDA-approved medications in order to treat patients in the United States [2].

Immunotherapies aim to raise immune system activity to destroy cancerous cells. Immune checkpoint inhibitors (ICIs) are a type of immunotherapies that have proven to be highly effective in reactivating the immune system's defence against cancer. In the past ten years, advances in next-generation genome-wide sequencing and immunotherapies have changed cancer research, biomarker identification, and patient care. The theories behind immunotherapy are immunoediting and immunosurveillance [4].

Three phases constitute immunoediting: the elimination phase, the equilibrium phase, and the escape or evasion phase. The emergence, growth, and development of HNSCC are significantly influenced by the immune system [5]. Tumor cells supress the immune system and escape from its attack using many mechanisms. During cancer development, there is a lack of oxygen, so VEGF and chemokines are produced, and monocytes are attracted. Monocytes differentiate in tumor-associated macrophages (TAM) which also produce VEGF [5]. An abnormal neo-vasculature is encouraged by an overabundance of these pro-angiogenic substances, which also cause fluid leakiness and raises interstitial fluid pressure (IFP). Effector T cells (Teff) cannot proliferate in this hypoxic, low pH environment, and PD-L1 is increased. Additionally, the accumulation of T regulatory cells (Treg), myeloid-derived suppressor cells (MDSC), and inhibition of dendritic cell maturation are caused by cytokines produced by tumors such as VEGF, prostaglandin E2, interleukin-10 (IL-10), and transforming growth factor-b (TGF-b). Further, these cytokines cause the endothelium to change toward immunosuppression [5].

First of all, the kinetics of ICI response differs among patients and agents/combinations. Monitoring strategies used for responders to cytotoxic chemotherapy may not apply to immunotherapy [6]. Thus, immunotherapy response is evaluated with different criteria from other therapeutical approaches. In solid tumors, immune-related response criteria (irRC) and immune-related Response Evaluation Criteria are used (irRE-CIST) to provide a more detailed observation [6]. Due to the potential for the delayed response from immunotherapy, these approaches evaluate the initial assessment of disease progression. In addition, new lesions are not always considered as disease progression, but they may be added to the total tumour burden. In this way, it is possible to avoid premature therapy termination and obvious consequences for the patient from a trial [6].

For example, hyperprogression and pseudoprogression are usual conditions that clinicians have to face [6]. The first one is an initial increase in lesion diameter on imaging that may be caused by inflammation (perhaps indicative of tumor progression), followed by cancer shrinkage, which is thought to be an uncommon but potential occurrence in solid tumors. The second one shows a very quick tumor progression following immunotherapy, which may indicate that some patients were negatively impacted by the treatment [6].

The aim of this review was to investigate the biomarkers associated with immunotherapy in head and neck cancer, and in particular oral cancer, as well as their respective immunotherapeutic agents.

Material and Methods

An electronic search of the literature was performed to identify articles investigating head and neck cancer, oral cancer, immunotherapy, immunotherapeutic agents and biomarkers. The literature search was conducted using MEDLINE (National Library of Medicine)-PubMed, Web of Science and Google scholar without restrictions concerning the date of publication. The following keywords were used (connecting different keywords with AND, OR): head and neck cancer, oral cancer, immunotherapy, immunotherapeutic agents and biomarkers. This was followed by a manual search and references were used to identify relevant articles. The articles identified from the electronic and manual search were screened to eliminate those that failed to meet the respective inclusion and exclusion criteria as listed below. The sole inclusion criterion was that the article should be written in English, whereas the exclusion criterion was the opposite.

Results

Biomarkers

Checkpoint blockade immunotherapy is not efficient in all tumour types and patients [7]. There are many different types of tumours, result of different mutations. The tumour microenvironment also plays a significant role in tumour growth. The most important molecules with a critical role in these procedures are:

PD-1/PD-L1 *(programmed death-1, programmed cell death ligand 1)*

The CD28 receptor family includes PD-1, which is mainly expressed in activated T cells and B cells [8]. Monocytes and a small percentage of thymocytes also contain it. PD-L1 and PD-L2 are ligands for PD-1. Both ligands are expressed on activated lymphocytes as well as endothelial and epithelial antigen-presenting cells. PD-L1 is induced and constitutively expressed in a range of solid and hematological malignancies, even though it is only weakly expressed in normal tissues. The development of malignancies can be facilitated by the overexpression of PD-L1 in tumor cells [5,8,9].

A few PD-1 antibodies have received FDA approval to treat HNSCC that has spread to other organs. Although several experi-mental therapies are still in research, response rates to anti-PD-1 immunotherapy are just 20% in HNSCC patients. The PD-1/PD-L1 pathway generally aims to prevent collateral tissue damage by inhibiting T-cell activation and decreased expression of the immune system. It has been shown that when its two ligands, PD-L1 (B7-H1) and PD-L2, are activated, PD-1 inhibits both the innate and adaptive immune response (B7-DC) [10,11].

Reduced T cell receptor (TCR) signaling, decreased cytokine production, decreased target cell lysis, modified lymphocyte motility, altered metabolic programming, and apoptosis are all consequences of PD-1 engagement with its ligands. The PD-1/PD-L1 axis is disrupted, which reactivates anti-tumor T-cell responses [12,13].

CTLA-4 *(cytotoxic T-lymphocyte-associated protein 4)*

The first inhibitory checkpoint identified was CTLA-4. Transmembrane receptors CTLA-4 and CD28, which are expressed by CD4 and CD8 cells, mediate conflicting roles in T-cell activation. A pair of ligands (CTLA-4—>CD86, CD28—>CD80) both receptors express on the outside of cells that present antigensCo-stimulatory and co-inhibitory significant applications of the activation of T cells, respectively. The B7-1 or B7-2 molecules on APC, which bind to CD28, are the primary costimulatory signals from T cell activation (on T cells) [14]. The effect is that the T cells are activated, and cytokines are produced. Conversely, CTLA-4 transmits an inhibitory signal, has a higher affinity for the B7 molecule than CD28, and as a result competes with B7 for binding, inhibiting CD28-mediated T cell co-stimulation and activation. Transforming growth factor (TGF), an immunosuppressive molecule, is produced when CD28 is used to activate it. By preventing T-cell attenuation during the priming phase, blocking CTLA-4 can eliminate the inhibition of T cells, allowing the development of effector T cells and activating an antitumor immune response in the host. When combined with IL-2 or conventional chemotherapy, anti-CTLA-4 antigens have a selective inhibitory impact on Tregs and promote the priming and development of antitumor T-effector cells [15]. Malignancy risk is increased by inflammation carried on by chemical and physical agents [2,8].

CTLA-4/PD-1

The PD-1/PD-L1 and CTLA-4 pathways are regarded as non-redundant. Anti-CTLA4 and anti-PD1/PD-L1 antibodies have already been shown to interact combined synergistically in advanced melanoma to inhibit these two immune inhibitors [16,17]. Because PD-1 and T lymphocytes are significantly inhibited by CTLA-4 receptors in different ways, they have a synergistic effect [14,18].

CXCL8 *(C-X-C motif chemokine ligand 8)*

Macrophages, epithelial cells, smooth muscle cells in the airways, and endothelial cells all produce CXCL8 (IL8). Through its CXCR1 and CXCR2 receptors, it can stimulate neutrophils, DCs, mast cells, endothelial cells, and keratinocytes. Many cancer types, including breast, colon, ovarian, pancreatic, prostate, and hematological malignancies, exhibit increased CXCL8 expression. The up-regulated CXCL8 is indicative of a poor prognosis, a high tumor burden, metastasis, and reduced survival [2].

Interleukin-8 receptors are known as CXCR1 and CXCR2. CXCL8- CXCR1/2 axis contributes to tumor immuno-suppression in a variety of cancer types. More particular, preclinical animal models have demonstrated that CXCL8, which is a key regulator of growth and angiogenesis, correlates with a poor prognostic factor in melanoma [2,19]. CXCR2 dramatically increases the angiogenesis, invasion, and migration of human melanoma cells that are conducted by CXCL8 whereas CXCR1 alone is associated with CXCL8-mediated chemotaxis [2]. Chemokines targeting CXCR1/2, including CXCL1, 5, 7, and 8, are produced and expressed by several cancer cell types in a way that encourages autocrine cancer cell proliferation and migration. Based on an oncoming analysis, CXCL8 expression is much higher in cancerous tissues than in healthy ones in cases of oesophageal, pancreatic, head and neck, and colon cancers. In human tumors, chemokine expression also relates to tumor grade and metastatic potential [20].

LAG-3 *(lymphocyte activation gene 3)*

Due to negative inhibition of T cells and potential to mediate exhaustion when combined with PD1, Lymphocyte Activation Gene-3 (LAG3; CD223) is

a potential target for cancer immunotherapy. Major Histocompatibility Complex Class II (MHC II) is more appropriately bound by LAG-3 than CD4+. The C-type lectin receptor superfamily member LSECtin is another ligand for LAG-3. The interaction between LAG-3 and LSECtin, which is expressed on tumor cells, limits CD8+ T cell signaling in melanoma. Human T and NK cells with activation markers express LAG3. LAG3 is an activation marker for CD4+ and CD8+ T lymphocytes in physiological settings [20,21]. LAG3 has been discovered to be significantly expressed on Tregs that are entering tumors in human cancer patients as opposed to the peripheral in many tumor subtypes. A concentration of these immunosuppressive cells during the development of the tumor may reduce the T cells' response and encourage the growth of the tumor.

Tregs express LAG-3, hence blocking LAG-3 could prevent them from operating normally. However, more research is required to determine whether blocking LAG-3 can affect the immunosuppressive cells in HNSCC and reactivate the antitumor response of T cells. The third IR to be clinically addressed with an antagonistic monoclonal antibody (mAb) began phase I clinical trials with anti-LAG3 (BMS-986016) in 2013 [2,20,21].

STAT3 *(signal transducer and activator of transcription 3)*

An integral part of the immunosuppressive tumor microenvironment is STAT3, a transcription factor. Inhibiting STAT3 has been demonstrated to increase radiosensitivity in preclinical studies. In a phase, IB/II trial, the interaction between durvalumab and either danvatirsen (AZD9150, a STAT3 inhibitor) or AZD5069, a CXC chemokine receptor 2 (CXCR2) inhibitor, was assessed [9,20]. In Part A of this trial, danvatirsen separately or in conjunction with the STAT3 inhibitor durvalumab was investigated, as well as the CXCR2 inhibitor, in dose escalation in solid tumors (either by itself or in conjunction with AZD5069) PD-L1 pretreated/naive patients were studied in Part B for the effects of durvalumab combined with either danvatirsen (a STAT3 inhibitor) or AZD5069 (a CXCR2 inhibitor), as well as durvalumab as a monotherapy, on the primary-endpoint overall response rate (ORR) and disease-control rate (DCR) [9,20]. At the 2017 ESMO Annual Meeting, findings from the dose escalation in solid tumors were reported, and they suggested that the combination of danvatirsen with durval-umab improved antitumor effectiveness. Preliminary results from the dose-expansion cohort, which consisted of 38 patients with PD-L1 treatment-naive/pretreated R/M HNSCC, were presented at the 2018 ESMO Annual Meeting. With four full responses and six partial responses, the ORR was 26%. Responses could be observed regardless of PD-L1 expression or HPV status. The most significant AEs—an increase in thrombocytopenia and liver enzymes—were controlled and reversible, confirming the medication's safety and tolerability. These findings call for additional research since they point to anti-PD-L1 and STAT3 inhibitor combinations having anticancer effects [9,20,22].

CXCR2 *(C-X-C motif chemokine receptor 2)*

CXCR2 provides cytokine receptor functions. By interleukine-8 signaling, it is associated to the development of the condition and is overexpressed in HNSCC. Durvalumab was tested in conjunction with the CXCR2 inhibitor AZD5069 in the SCORES study [20]. The dose expansion cohort's preliminary findings, which involved 20 patients with PD-L1 treatment nave/pretreated R/M Durvalumab and AZD5069-treated HNSCC were released at the 2018 ESMO Annual Meeting. Regrettably, in contrast to the STAT3 inhibitor, the addition of AZD5069 did not seem to improve outcomes, as evidenced by the ORR of 10% and the causally associated adverse events suffered by 76% of patients [20]

IDO1 *(Indoleamine 2,3-Dioxygenase 1)*

IDO1 is a catabolizing enzyme that decreases T cells by kynurenin accumulation and tryptophan depletion in the vicinity of the tumor microenvironment. This causes immune resistance to develop and is linked to a bad outcome in laryngeal SCC. There are numerous IDO1 inhibitors under clinical development [20,22].

Epacadostat is a very effective and targeted oral inhibitor of the IDO1 enzyme. In the phase I portion of the ECHO-202/KEYNOTE-037 trial, which included the medications epaca-dostat and pem-brolizumab for patients with advanced solid tumors, only two of the 62 patients had R/M HNSCC. At the 2017 ASCO annual meeting, preliminary findings from the HNSCC cohort of this phase I/II study were presented. Patients were considered eligible if they had received at least one line of platinum-based therapy and had PD-1/PD-L1 naive R/M HNSCC [20,22]. Two patients with R/M HNSCC were among the 38 patients enrolled. Patients who had received one or two lines of therapy had ORRs of 34% (2 CR and 8 PR) and 62%, respectively (eight stable diseases). Patients who had had at least three previous lines of therapy had ORR and DCR of 14% (1 PR) and 43% (2 SD), respectively. Regardless of the HPV status, the response was appropriate. Analysis of PFS and biomarkers has not yet been provided. With 11% of patients reporting grade 3 treatment-related adverse events, the combination was well tolerated [20,22].

Other Targets

Future studies on the treatment of HNSCC with additional antibody-based medicines for solid tumors may be conducted. For instance, antibodies against T-cell immunoglobulin and mucin domain 3 (TIM-3), killer cell immunoglobulin-like receptor, and T-cell immunoreceptor with Ig and ITIM domains (killer cell immunoglobulin-like receptor (KIR)) [21,23].

Immunotherapeutic agents

CETUXIMAB

Over 90% of HNSCC cases have elevated EGFR expression as seen by immunohistochemistry (IHC). Cetuximab is an IgG1-based chimeric antibody that targets an extracellular epitope in the EGFR ligand-binding region and is composed of 65% human and 35% murine components [20]. The inclusion of cetuximab resulted in a significant improvement, according to a phase III multicenter experiment. It was the first case of statistically significant evidence of a survival advantage for EGFR-directed therapy when combined with cytotoxic therapy [24].

NIVOLUMAB

A completely human IgG4 anti-PD-1 monoclonal antibody called nivolumab has demonstrated anti-tumor activity in a variety of tumor types [25]. Patients with recurrent head and neck squamous cell carcinoma who had disease progression despite platinum-based chemotherapy improved to life noticeably longer on nivolumab than on conventional therapy. According to Checkmate 141, patients who received nivolumab treatment experienced considerably longer overall survival [17,18,26].

DURVALUMAB

Durvalumab, a human IgG1 monoclonal antibody (mAb), prevents PD-L1 from binding to PD-1 and CD80, enabling T cells to recognize and eliminate tumour cells (TC). Durvalumab monotherapy was studied in the single-arm, phase II HAWK trial (NCT02207530 in patients with R/M HNSCC that is platinum-resistant who had PD-L1 high levels [27]. In patients with HNSCC who had progressed after receiving first-line platinum-based treatment in the R/M scenario and had PD-L1-high expression (TC 25%), durvalumab showed clinically significant anti-tumour efficacy [28]. In a phase III research titled “Durvalumab with or without tremelimumab in patients with recurrent or metastatic head and neck squamous cell carcinoma: EAGLE, a randomized, open-label phase III investigation» the effectiveness of durvalumab and tremelimumab (an anti-CTLA-4 monoclonal antibody) in comparison to standard of care (SoC) for HNSCC patients was also assessed [28]. Tremelimumab was introduced to durvalumab, but this did not improve durvalumab activity. However, higher response rates and survival rates at 12 to 24 months indicate that durvalumab is therapeutically active [29].

According to a study of 62 patients with HNSCC (40.3% were HPV-positive,32.3% had tumor cell PD-L1 expression>25%, and 62.9% were current/former smokers), durvalumab demonstrated a manageable safety profile, comparable to other anti-PD-L1 and anti-PD-1 clinical studies and encouraging anti-tumour activity, observed as early as 1.2 months [30].

PEMBROLIZUMAB

An anti-PD-1 antibody named pembrolizumab prevents PD-1 from interacting with its ligands. In a series of KEYNOTE studies, pembrolizumab has been evaluated for its clinical efficacy in 12 different malignancies (bladder cancer, breast cancer, colorectal cancer, esophageal cancer, gastric cancer, head and neck cancer, hematological cancer, lung cancer, melanoma, ovarian cancer, pediatric cancer, and other cancers). In a study with 60 patients who had PDL1-expressed HNSCC, pembrolizumab treatment produced a 20% ORR. Interestingly, tumors that expressed PDL1 more intensively had a higher ORR of 50% [31,32].

Pembrolizumab showed clinically substantial anticancer activity as well as an acceptable safety profile in patients with HNSCC, according to the results of the *Results from a Single-Arm, Phase II Study on Pembrolizumab for Platinum-and Cetuximab-Refractory Head and Neck Cancer* [33–35]. The main goal of KEYNOTE-048 was to evaluate the response of patients with previously untreated metastatic or recurrent HNSCC to cetuximab plus chemotherapy to pembrolizumab, either as a monotherapy or in combination with chemotherapy. Participants in the study had to have untreated locally incurable recurrent or metastatic HNSCC. In a series of KEYNOTE studies, pembrolizumab has been evaluated for its clinical efficacy in 12 different malignancies (bladder, breast, colorectal, esophageal, gastric, head and neck, hematological, lung, melanoma, ovarian, pediatric, and other solid tumors). In a study with 60 patients who had PDL1-expressed HNSCC, pembrolizumab treatment produced a 20% ORR. Interestingly, tumors that expressed PDL1 more intensively had a higher ORR of 50% [31,32].

AVELUMAB

A completely human anti-PD-L1 IgG1 monoclonal antibody named avelumab only binds to PD-L1 and separates it from PD-1 [36]. Avelumab stimulates the innate immune system and produces antibody-dependent cell-mediated cytotoxicity. Studies have generally indicated that it has a tolerable safety profile in a variety of solid tumors and long-lasting antitumor efficacy [37]. The overall response to avelumab in the second line of recurrent/metastatic HNSCC was similar to that of pembrolizumab or nivolumab, according to the results of the safety phase of the randomized phase III trial GORTEC 2017-01 (REACH) [38–40].

Patients in this study were randomly assigned in a 1:1 ratio to either arm A (cisplatin-RT), B (avelumabe-cetuximabe-RT) in cohort 1 (fit for high dose (HD) cisplatin), or C (avelumabe-cetuximabe-RT) or D (cetuximabe-RT) in cohort 2. (unfit for HD cisplatin). Five patients experienced acute AEs of grade IV, or a rate of 12%, which was comparable to historical rates

observed in SOC arms. The combination of Avelumabe and cetuximab RT was well tolerated and did not produce grade IV AE [41,42].

ATEZOLIZUMAB

Atezolizumab is an anti-PD-L1 humanized monoclonal antibody of IgG1. It has been studied in a phase I trial that enrolled 32 patients with R/M HNSCC (including four with nasopharyngeal cancer). According to this study, the response to atezolizumab was not dependent on PD-L1 expression nor HPV status and has a promising clinical activity with a reliable safety profile [43]. In patients with high-risk locally advanced squamous cell carcinoma of the head and neck, a phase III study is currently being conducted with atezolizumab as adjuvant therapy following definitive local therapy. i- PD-L1 [37].

TREMELIMUMAB

A completely human monoclonal antibody against CTLA-4 is tremelimumab. The CheckRad-CD8 trial's findings suggest that durvalumab/tremelimumab and cisplatin/docetaxel initial therapy can be administered in a single cycle, and the adverse effects of the therapy were tolerable [44]. Tremelimumab plus durvalumab has been shown to have a higher rate of disease control in HNSCC than tremelimumab alone. When it comes to immune-related side effects, durvalumab and tremelimumab have often demonstrated equal risks of any grade adverse events. In HNSCC, there was a decreased risk of adverse treatment-related events of any grade [45].

Tremelimumab improves T-cell priming in the initial stages, so combining it with another PD-(L)1 agent that only releases the already immune reaction, like durvalumab, may not be effective. However, combining tremelimumab with other cell death-inducing treatments like chemotherapy or radiation therapy may maximize its effectiveness [44].

IPILIMUMAB

The combination of an CTLA4 inhibitor such as ipilimumab with cetuximab, an EGFR-specific monoclonal antibody that enhances the cytotoxic function of effector T and NK cells and promotes the expansion of CTLA4+ Treg, might promote the ablation of Tregs, and lead to a better clinical response. According to Marie-Nicole Theodoraki et al. (2019) of the 18 HNSCC patients treated with combination therapy, only five (28%) experienced tumour recurrence during the first 24 months of follow-up [36,46]. The phase III clinical study, Checkmate-067, demonstrated that the combination of both CTLA4 and PD-1/PD-L1 inhibition could have an advanced therapeutic outcome in HNC patients [47]. According to the IMCISION clinical trial NCT03003637, neoadjuvant ipilimumab + nivolumab can safely be administered to advanced HNSCC patients prior to major surgery, and the efficacy of this combination is promising [48].

RELATLIMAB

The first LAG-3-blocking antibody to show a therapeutic advantage in patients with Phase 3 data is relatalimab. In a phase III trial, the LAG-3 antibody relatlimab in combination with nivolumab led to a considerably longer PFS than nivolumab alone, and the combination exceeded nivolumab monotherapy in terms of progression-free survival [49]. In phase, I/IIa research for PD(L)-1 pretreated individuals, nivolumab + relatlimab demonstrated an ORR of 11.5% in all patients and 18% in those with LAG-3 expression >1% [50].

NAVOXIMOD

Navoximod is an experimental IDO1 small molecule blocker with a cell-based potency of 75-90 nM for IDO1 (GDC-0919; previously NLG919). In preclinical models, navoximod and anti-PD-L1 therapy combine more efficiently than either medication own to activate intratumoral CD8+ T cells and slow tumor growth [51]. During a phase IB investigation of advanced solid tumors. Although activity was detected in this study, there was no definite evidence of any advantages to using navoximod and atezolizumab together to treat unselected patients.

Discussion

Immunotherapies known as immune checkpoint inhibitors (ICIs) are incredibly effective at reactivating the immune system's defenses against cancer. CTLA-4 (cytotoxic T-lymphocyte-associated protein) and PD-1 (programmed death-1) have been identified as potential targets for oral cancer immunotherapy and they are two significant immune checkpoints that were examined, among others.

Infection with the human papillomavirus (HPV) is thought to contribute to around 25% of all HNSCCs worldwide [52]. HPV-related (HPV+) HNSCC are mainly found in the oropharynx, differ from their non-viral-related counterparts clinically and physiologically, and have a reasonably good prognosis. Standard medicines successfully manage the disease locally in > 90% of cases, while the likelihood of distant metastasis is around 8–10% [53,54]. Immunotherapy with anti-PD1 checkpoint inhibitors has shown promising results for patients with advanced HNSCC, irrespective of HPV status [55]. Strategies that target various immunological checkpoints alone or in conjunction with therapeutic vaccines and/or targeted treatments have emerged with encouraging outcomes [13,56–58].

Surprisingly, tumors with HPV positivity presented significant infiltration by PD-1-positive cells or the total number of PD-1+CD4 and PD-1+CD8 T cells were linked to considerably longer life for HNSCC patients [4]. Patients who had tumor-infiltrating T cells that were PD-1-positive

greater than 15 PD-1 cells/fields, the median value, had a 60-month overall survival rate of 93.9%, compared to patients who had low levels of PD-1-positive cell infiltration, who had a 60-month overall survival rate of 63.6% [57]. According to Badoual *et al*., tumor-infiltrating T cells that express the PD-1 gene are a good indicator of prognosis in HPV-related head and neck cancer [57].

There are significantly positive associations between the expression of PD-L1, PD-1, and human papillomavirus infection (P16 positive) in HNSCC [57]. According to Chen et al., HNSCC patients who have strong PD-L1/PD-1 expression typically experience higher total survival and a reduced risk of recurrence [3].

Even though multimodality treatments [such as radiotherapy (RT) provided following surgery, chemoradiotherapy (CRT), or permanent CRT] are frequently used for locally advanced HNSCC, the prognosis is still poor, and the risk of recurrence is significant. To increase the response rate and reduce the risk of recurrence, it is currently being investigated to combine immunotherapy with radiotherapy or CRT. Numerous experiments are still being conducted, and the outcomes are encouraging.

Infected areas that have already been exposed to radiation as well as distant, non-irradiated locations may respond better when combined with immune checkpoint inhibitors [59]. This synergistic effect can also enhance the efficacy of immunotherapy through stimulating the surface expression of the major histocompatibility complex (MHSC) class 1, calreticulin, and the release of high mobility group box protein 1, (HMGB1) [60]. Since they are less effective when used individually, all tumor-related antibodies are currently utilized in combination with chemotherapeutic medicines, without any overlap in side effects.

By releasing neoantigens, modifying the tumor microenvironment by eliminating Tregs and MDSCs, decreasing the expression of PD-L2 on tumor cells and DCs, maturing APCs, enhancing tumor visibility, and lowering MHC-I expression, chemotherapy can support immune checkpoint inhibitor therapy. Conversely, chemotherapy could lead to lymphopenia and neutropenia, which could inhibit the clonal expansion of effector cells, hence interacting with the function of checkpoint inhibitors. Chemotherapy must therefore be carefully thought out [61].

Results from immunotherapy and chemoradiation combinations have been reported to be positive. Irradiation can have a synergistic impact with ICIs, and concomitant platinum-based chemotherapy may have added advantages, according to Plavc *et al.* [62]. However, more research is required to substantiate the effectiveness of this combination [61,63].

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 module, the head and neck-specific module, or the European Quality of Life-5 Dimensions criteria can all be used to assess patients with head and neck cancer. According to the findings of the Check-Mate 141 study, cancer patients who get immunotherapy had a higher quality of life than those who undergo cytotoxic therapy, with advantages for a social function, exhaustion, and cognitive ability. This is consistent with numerous other studies that have supported the positive effects of ICI on these patients' quality of life [53,64,65].

Several recent studies have found that immunotherapies significantly improved patients' quality of life compared to standard of care (SOC) [2]. Although, HNSCC patients commonly struggle with pain, cognitive impairment, social impairment, and discomfort caused by vascular, aesthetic, and airway problems, all of which have an adverse effect on daily life and quality of life. The subcommittee on head and neck cancer of the Cancer Immunotherapy Guideline, which was developed by the Society for Immunotherapy of Cancer (SITC), reached the conclusion that treatment with ICIs may maintain or improve quality of life compared to SOC because there were reduced high-grade side effects [2]. The subcommittee emphasized the impact of head and neck tumors on nutrition as eating, drinking, and breathing could become more complicated. Patients frequently need specialized care, thus it is essential to check on patients' quality of life every three months. Additionally, patients' emotional health should be regularly examined during general appointments because HNSCC is related to an increased risk of depression [2].

In reality, patients with autoimmune diseases, metastases in the brain or lungs, cases of active infections requiring treatment (such as HIV, hepatitis B, and C), patients receiving immunosuppressive or systemic steroid therapy, and patients with other comorbidities were excluded from the initial clinical trials. The increasing body of evidence suggests that these potential treatments could be given to these patients without risk [66].

A wide range of distinct immune-related adverse effects (irAEs) that reflect auto-immune reactions is related to immunotherapy. The irAEs related to ICIs differ from chemotherapy-related irAEs both clinically and pathophysiological. Immunotherapy, for instance, does not directly affect the bone marrow or induce hair loss, though the fundamental processes of these immune-related adverse outcomes are not precisely understood. Nevertheless, Immune checkpoint inhibitor drugs have a very large spectrum of side effects that can be classified as general or organ specific [18,53].

In particular, a number of immune-related adverse effects have been associated to the administration of CTLA-4, PD1, and its ligand PDL-1 inhibitors, either individually or in combination. The most frequent side effects are dermatologic toxicities [67]. Indeed, Das et al., found that 43% of patients with metastatic HNSCC treated with anti-PD-1 antibodies experienced irAEs. Cutaneous

irAEs were the most common (33.9%), followed by musculoskeletal (25.4%) and endocrine (23.7%) side effects [68]. Oral toxicity has been sporadically reported for both PD-L1 and PD-1 (nivolumab, pembrolizumab) inhibitors, but no grade≥3 adverse events have been ever reported [69].

Side effects are significantly more controllable when they are immediately detected and treated. When performed for restaging, surveillance, or FDG-PET/CT, side effects frequently produce abnormalities that are visible on CT, MR, or these imaging techniques. Immune-related adverse effects may cause observations and metabolic changes before the onset of clinical symptoms, enabling early treatment modification [17,70].

So far, research has shown that immunotherapy is a durable cure for many types of tumors, including neck and head cancers. One of the main issues is that not all patients respond to these therapies. The future of immunotherapy research lies in finding ways to increase that response rate. Additional biomarker analyses are being conducted to comprehend the clinical activity of immune checkpoint inhibition and, as a result, boost the response rate of all patients. A combination of current PD-1 inhibitors with other immunotherapies and targeted agents may increase response rates.

Immunotherapy is associated with a variety of diverse immune-related side effects that resemble autoimmune reactions. Even though the majority of studies have indicated that these irAEs are well tolerated, more data should be gathered to determine the presence of any genetic risk factors (such as the HLA-DR alleles associated with autoimmune diseases) or whether the CTLA-4 blockade itself is the cause of in order to treat patients [64].

Future research is necessary to determine if immunotherapy could be personalized and whether it could be indicated in earlier cancer stages. Finally, the cost of immunotherapy should be reduced to be widely used, even as a standard of care therapy.

Conclusions

Renewing interest in immunotherapy as a potential treatment for HNSCC is the understanding of the mechanisms of the patient's immune system, which can be blocked by cancer cells. Current results from the trials have shown improved response rate and overall survival when patients are treated with nivolumab, durvalumab, pembrolizumab, etc. Biomarkers such as PD-L1 expression, a pre-existing CD8+ T cell infiltrated tumor microenvironment and tumor mutational variations can indicate the success of this type of therapy. In addition, the combination of immunotherapy agents or the additional use of radiation or chemotherapy is under investigation to increase the response rate. Many of these studies indicate the improved quality of life in these patients in contrast with those who were treated with SOC because of the lower toxicity levels. In terms of drug development and clinical trials, this field is developing extremely quickly and is incredibly active. The growing armamentarium of anticancer Immuno-oncology medications may not ultimately include many of these agents but given the variety of the mechanisms currently investigated and the promising initial results, it is likely that several truly effective new treatment strategies will emerge.

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