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Research Article

Immunotherapy: The Fourth Domain in Oral Cancer Therapeutics

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Abstract

Owing to high global prevalence, incidence and associated mortality, cancer of head and neck particularly oral cancer remains a cardinal domain for research and trials. Immune-modulatory therapies that employ patients own immune system for therapeutic benefits in oral cancer seems promising. The aim of this review is to gauge the potential of immunotherapy as fourth domain of Oral cancer therapeutics. Articles were searched using suitable search terms in MEDLINE and Google Scholar database to include clinical trials, meta-analyses, and research in humans / animals/ cell lines published in peer reviewed journals. A total of 97 articles were included in this review.

Literature has several studies and trials where different types of immune therapy has been attempted but it is crucial to identify precise biomarkers of genome based targeted agents and to find parameters to select patients who might benefit from immunotherapy. Also, further research is required to estimate predictive value of tumor mutational burden and mutational signatures so as to aid in personalized prediction of oral cancer therapeutic response.

Keywords: immunotherapy; pdl-1; pembrolizumab; oral cancer; head and neck cancer

Introduction:

The crux of cancer immunotherapy lies in the recognition of cancer cells as non-self / foreign and subsequent attack by an activated immune system.

In routine, immune surveillance actively destroys the suspected/altered cells (premalignant cells) before transformation into a tumor, but alterations in the transformed cells (allowing immune escape) or any derangements in the immune system enable cancer embodiment.

Owing to high global prevalence, incidence, and associated mortality, cancer of the head and neck particularly oral cancer remains a cardinal domain for research and trials.[1] The triple combination therapy comprising chemotherapy, radiotherapy, and surgery has been the routine line of treatment followed for decades, however poor outcomes in the form of a stunted 5-year survival rate make it imperative to find a more effective treatment. In the past two decades, research directed toward optimizing therapeutic regimes to improve the outcomes of cancer is persevering. This has resulted in new strategies based on an understanding of the pathology and molecular details of oral cancer. Immunotherapy has emerged as the most promising potential treatment of choice in oral cancer.

It is well known that the various physical, chemical, and biological carcinogenic factors that cause either genetic or epigenetic alterations, endow the cell to attain different peculiar carcinogenic traits (hallmarks of cancer) leading to the development of cancer.[2]

Out of all, the escape from immune surveillance plays a critical role bestowing, cancer cells capability to resist the host immune system either by developing an immunosuppressive state with lower absolute lymphocyte counts than those found in healthy subjects, impaired natural killer (NK) –cell activity, and poor antigen-presenting function or by inculcating a genetically modified immune resistant state.

Therefore, immune-modulatory therapies that overcome immune suppressive signals in oral cancer patients have therapeutic promise. These include various cancer immunotherapeutic methods such as immune checkpoint inhibitors (ICIs), cancer vaccines using tumor peptide antigens, or viral, bacterial, and DNA-based vectors as well as tumor

antigen–specific monoclonal antibodies (moAbs), cell-based therapies, and cytokines therapy. [3-7]

This review aims to gauge the potential of immunotherapy as the fourth domain of Oral cancer therapeutics. The initial section of this discussion provides an overview of role of immune system in oral carcinogenesis directing for various types of immunotherapeutic regimes for oral cancer. The later sections of describe the status of research in the field intending future directions for development of newer strategies based on individual cancer cells' characteristics determined by specific genes to obtain a "personalized treatment"

Method of data collection:

The MEDLINE and Google Scholar database search was done for scientific literature about immunotherapy in oral cancer. The search terms used were "Oral Cancer", "Oral Squamous Cell Carcinoma" OR "OSCC", "head and neck neoplasm" OR "HNSCC" AND "immunotherapy", "combination therapy", "immunotherapy". The final search encompassed articles published from 2012 to 2022 (10 years) and was limited to clinical trials, meta-analyses, and research in humans / animals/ cell lines published in peer reviewed journals having impact factor>1. The articles were screened to include only papers with clinically accurate and relevant information and to remove duplicate articles from independent searches. The bibliography was supplemented with additional articles that were found appropriate and necessary for a comprehensive literature review.

Results

The initial search resulted in the retrieval of nearly 491 manuscripts, which on further screening resulted in 123 manuscripts that were considered (Figure 1).

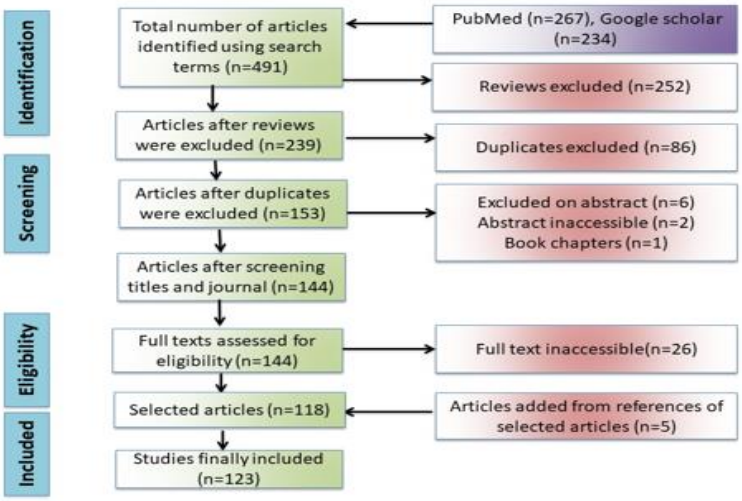

Figure 1: Flow chart of study selection adapted from PRISMA (Preferred Reporting Items for Systematic Reviews and meta-Analysis)

Discussion

The immune system plays a key role in almost all stages of oral carcinogenesis. A thorough know-how becomes essential to explore the potential of various types of immunotherapeutic regimes for oral cancer is described in Table 1.

S. No.	Studied by	Therapeutic regime	Type of cancer/lesion	Status/outcome
1	Padmanabhan et al 1987 [100]	Oral levamisole, at 150 mg daily doses for three consecutive days, once every two weeks.	Oral Squamous cells carcinoma stages T1N0M0 and T2N0M0	-Prolonged the disease-free interval of these patients by 44%. -No change in metastatic potential. -The restoration of leukopenia and lymphopenia observed after radiotherapy was faster in the levamisole group
2	Hadden et al 2003 [101]	Phase II trial perilymphatic injections of a natural cytokine mixture (NCM: IRX-2; 200 units IL-2 equivalence) for 10-20 days preceded by low dose cyclophosphamide (CY; 300 mg/m (2)) and followed by daily oral indomethacin (25 mg t.i.d.) and zinc (65 mg in a multivitamin preparation)	42 patients with squamous cell cancer of the head and neck	-42% patients had complete and partial clinical responses. -5 patients had minor responses. -90% had reduction in tumor area from 79% to 48% -Increased area of leukocyte infiltration from 9% to 32% with significant increases in Lymphocyte Count, CD3+, CD4+ and CD8+ T lymphocytes
3	Timar et al 2005 [102]	Phase II multicenter study Leukocyte Interleukin Injection (LI) 800 IU/d as interleukin-2 (IL-2), administered half peritumorally and half perilymphatically 5 times per week for 3 weeks	39 patients diagnosed with T2-3N0-2M0 OSCC	-2 pathologically complete, 2 major (> 50%), and 4 minor responses (> 30% but < 50%) resulted from LI treatment -Overall response rate, 42% -Markedly altered composition of tumor-infiltrating mononuclear cells, -Increased CD4+:CD8+ ratio, -Increased tumor stroma to epithelial ratio.
4	Yoshitake et al 2015 [103]	Phase II clinical trial of multiple peptide (cancer-testis antigens, including LY6K, CDCA1, and IMP3 vaccination	37 patients with advanced HNSCC	-Vaccine therapy was well tolerated. -Overall survival was statistically significantly with median survival time (MST) 4.9 months. -One of the patients exhibited a complete response.

5	Ferris at al 2018 [91]	Randomized controlled trial using nivolumab 3 mg/kg every 2 weeks	40 cases of recurrent or metastatic platinum-refractory SCC of the head and neck	-Nivolumab significantly improved Overall Survival. -Grade 3-4 treatment-related adverse event rates were 15.3% and 36.9% for nivolumab and Investigator's choice treatment, respectively.
6	Powell et al 2018 [104]	Single-arm, open-label, Phase Ib trial Pembrolizumab 200 mg iv 7 days before ChemoRadioTherapy (CRT) and every 3 weeks during CRT with 5 additional doses following CRT.	Stage III–IVB HNSCC	-Combination therapy was deemed safe and did not significantly limit radiation or chemotherapy dosing -Approximately 85% of patients (29/34) experienced complete response based on imaging and/or surgery and 97.1% (95% CI: 80.9–99.6) demonstrated progression-free survival at 1 year.
7	Dorta-Estremera et al 2019 [94]	α-PD-1 therapy with induction of IFN-α/β signaling via STING agonist and/or through CTLA-4 blockade	HNSCC not responding to α-PD-1 monotherapy.	-Sustained tumor regression in 71% of tumors
8	Cohen et al 2019105	Randomised, open-label, phase 3 study using pembrolizumab versus standard treatment (methotrexate, docetaxel or cetuximab)	495 recurrent or metastatic head and neck squamous cell cancer	-Status -Undergoing -Median overall survival was 8·4 months with pembrolizumab and 6·9 months with standard treatment. -Fewer patients treated with pembrolizumab than with standard of care had grade 3 or worse treatment-related adverse events (13% vs 36%).
9	Zandberg et al 2019 [79]	International, multi-institutional, single-arm, phase II study using durvalumab 10 mg/kg intravenously every 2 weeks for up to 12 months.	Recurrent/metastatic head and neck squamous cell carcinoma	-Durvalumab demonstrated antitumour activity with acceptable safety in PD-L1-high patients with R/M HNSCC
10	Burtness et al 20191 [06]	Pembrolizumab monotherapy, pembrolizumab plus chemotherapy (cisplatin or carboplatin plus 5-FU), or	882 untreated Recurrent/metastatic head and neck squamous cell carcinoma	-Overall Survival with pembrolizumab monotherapy was superior to EXTREME. -Responses were durable and the safety profile was favorable in both pembrolizumab arms.
		cetuximab plus chemotherapy (EXTREME)		-Neither pembrolizumab alone nor pembrolizumab with chemotherapy improved progression-free survival
11	Saba et al 2019107	Phase 3 trial, nivolumab 3 mg/kg every 2 weeks or Induction chemotherapy (IC) (methotrexate, docetaxel, or cetuximab) randomized, open-label,	361 histologically confirmed, recurrent/metastatic SCCHN of the oral cavity, oropharynx, hypo-pharynx, or larynx	-Nivolumab resulted in a higher median overall survival compared with IC in patients -OS benefit with nivolumab was maintained irrespective of tumor PD-L1 expression levels and HPV status -Nivolumab resulted in higher Overall Response Rate versus IC i.e. 12.8% Vs 6.6%
12	Xiong et al 2020108	Anti-PD-1 (nivolumab)	10 cases of Oral cavity squamous cell carcinoma	-Nivolumab causes opposing effects on CD4+ and CD8+ cell populations -CD4+ cell levels declining but increasing the proportion of Treg cells, -Unconventional CD8+ T-cell levels increasing with increased expression of immune mediators by CD8+ T-cell subpopulations.
13	Schoenfeld et al 2020109	Randomized phase 2 clinical trial using nivolumab, 3 mg/kg, weeks 1 and 3, or nivolumab and ipilimumab (ipilimumab, 1 mg/kg, given week 1 only)	29 patients with untreated squamous cell carcinoma of the oral cavity	-14 patients were randomized to nivolumab (N) and 15 patients to nivolumab/ipilimumab (N+I) -Evidence of response in both the N and N+I arm (volumetric response 50%, 53%; pathologic downstaging 53%, 69%; RECIST response 13%, 38%; and pathologic response 54%, 73%, respectively). -4 patients had major/complete pathologic response greater than 90% With 14.2 months median follow-up, 1-year progression-free survival was 85% and overall survival was 89%.
14	Rodriguez et al 2020110	Phase II clinical Trial of Pembrolizumab 200 mg given intravenous every 21 days, and vorinostat 400 mg given orally 5 days	Recurrent/metastatic squamous cell carcinomas of the head and neck, and salivary gland cancer	-Adverse events in all patients were: 27 (54%) with grade ≥ 1 and 18 (36%) with grade ≥ 3. -Median overall survival was 12.6 months

		on and 2 days off during each 21-day cycle		Median progression-free survival was 4.5 months
15	Machiels et al 2020 [111]	Randomized, double-blind, Phase III trial investigating pembrolizumab 200mg iv administered concurrently with chemoradiation therapy	780 previously untreated locally advanced HNSCC	-Status-Ongoing -Interim data revealed that the treatment regimen is tolerable and feasible.
16	Gurizzan et al 2021 [112]	Phase II, open-label, single-arm, multicentric trial of short course of immunotherapy with 4 administrations of avelumab	Oral Potentially Malignant Disorders (OPMD) that test positive for LOH	- Status-Ongoing -Interim data revealed that the treatment regimen is tolerable and feasible.
17	Liu et al 2021 [113]	A randomized phase II trial consisting of low dose (300 mg/m2) cyclophosphamide (day 1) followed by 10 days of regional perilymphatic IRX-2 cytokine injections and daily oral indomethacin, zinc and omeprazole	Untreated patients with Stage II-IV oral cavity carcinoma	-Consistent subtle, patient response after treatment with targeted neoadjuvant IRX-2 immunotherapy
18	Hwang et al 2021114	Open Label, Randomized, Two Arm Phase III Study Nivolumab in Combination with Ipilimumab Versus Extreme Study Regimen	947 Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck	-Status-Ongoing
19	Sacco et al 2021115	Open-label, non-randomised, multi-arm, phase 2 trial using pembrolizumab 200 mg intravenously every 3 weeks, combined with an initial loading dose of cetuximab 400 mg/m2 intravenously followed by 250 mg/m2 intravenously weekly (21-day cycle)	33 recurrent or metastatic HNSCC.	-By 6 months, the overall response rate was 45% (95% CI 28-62), with 15 of 33 participants achieving a partial response. -Pembrolizumab combined with cetuximab shows promising clinical activity for recurrent or metastatic HNSCC
20	Liu et al 2021116	Single-arm, investigator-initiated, single-institution phase II clinical trial using	12 high-risk, resectable oral cavity head and neck cancer	-33% overall response rate with reduction in tumor size
		3–4 biweekly doses of 3 mg/kg nivolumab		
21	Li et al 2021 [117]	Induction chemotherapy (IC) with sintilimab	163 patients with locally advanced head and neck squamous cell carcinoma	The addition of sintilimab to IC could provide longer progression-free survival (PFS) time than traditional chemotherapy regimen, without increasing the toxicity events.
22	Vos et a 2021 [118]	Non-randomized phase Ib/IIa trial using 2 doses (in weeks 1 and 3) of immune checkpoint blockade (ICB) using nivolumab (NIVO MONO) or nivolumab plus a single dose of ipilimumab (COMBO)	32 HNSCC patients	-Grade 3–4 immune-related adverse events were seen in 33% of NIVO MONO and 38% of total COMBO patients. -Major pathological response in 35% of patients after COMBO ICB
23	Poulose et al 2022 [119]	Phase 3 Randomized, Open-Label Clinical trial using pembrolizumab plus epacadostat, pembrolizumab monotherapy, and the EXTREME regimen (cetuximab + cisplatin or carboplatin + 5-fluorouracil) as first-line treatment	89 HNSCC Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma	-Trial is ongoing -Risk was least in pembrolizumab plus epacadostat (17.14%) followed by pembrolizumab monotherapy (21.05%), and the EXTREME regimen (28.57%)
24	Dzienis et al 2022 [120]	Phase 4, Single-arm, Open-label Clinical Study Pembrolizumab (MK-3475) Plus Carboplatin and Paclitaxel	100 Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma	Still recruiting
25	Wong et al 2019 [121]	Atezolizumab (Anti-PD-L1)	Squamous cell carcinoma of the head and neck	Still recruiting
26	Fuereder et al 2022 [122]	Prospective phase I/II trial. Docetaxel (DTX) 75 mg/m^2 plus pembrolizumab (P) 200 mg for up to six cycles followed by P maintenance therapy.	22 Platinum-resistant Recurrent /Metastatic HNSCC patients	-Overall response rate was 22% with 1 patient having complete response. -The median progression-free survival was 5.8 months. -1-year PFS and Overall Survival rates were 27.3% and 68.2%, respectively.
27	Gross et al 2019 [123]	Investigator-initiated, single-institution, pilot phase II study neoadjuvant PD-1 inhibition (cemiplimab) 350 mg every 3 weeks before surgical resection.	20 locoregionally advanced, resectable cutaneous squamous cell carcinoma of the head and neck	-12-month disease-free survival and overall survival rates were 95% 89.5% and 95% respectively.

Table: Description of the status of various Immunotherapeutic regimes for Head and Neck Cancer and Oral Cancer

1) Immunology of Oral Carcinogenesis

It is well understood that for attaining malignancy, phenotypically normal cells exploit the host tissue to facilitate growth.[8]

In a groundbreaking study, Scully (1983) addressed immunological anomalies in head and neck cancer patients as well as the data linking the immune system to carcinogenesis. Additionally, he provided an overview of the therapeutic approaches that use immune response modification (immunotherapy).[9]

There is ample evidence in the literature to demonstrate the close interaction between the immune system and tumours throughout the whole course of cancer genesis, progression, and metastasis. One significant and well-established characteristic of cancer is the tumor's

ability to evade the immune response's damaging components. Therefore, identifying prognostic indicators, lowering medication resistance, and creating novel treatments all depend on our ability to comprehend the interplay between the tumour and the host immune system.[10]

Both positive and negative effects might result from the intricate interactions or cross-talk between immune cells and cancer cells, i.e., tumour growth inhibition and enhancement. The final result is determined by the balance of these activities and can either be effective tumour elimination or tumour immune evasion.

The gradual development of an immune-suppressive environment within the tumour and the selection of tumour variations resistant to immune effectors, or "immunoediting," are necessary for immunoevasion.

T lymphocyte-mediated response, or cell-mediated immunity, is compromised in oral cancer. This is shown as a reduction in T lymphocyte counts and subpopulations, which lowers lymphokine production and impairs T lymphocyte lymphoproliferative responses to mitogens and antigens.[11]

When Boncinelli et al. (1978) examined the mononuclear cell infiltration linked to oral cancer, they found that a significant fraction of T lymphocytes (a cell-mediated immune response) was present, although negligible amounts of plasma cells were seen. [12,13]

While cell-mediated immune responses are not substantial in other carcinomas, they are in head and neck cancers, and this is the most visible immunologic shift linked to the disease. It is challenging to determine whether the immune abnormalities are primary or secondary to the carcinoma; however, since patients with oral carcinoma continue to have depressed cell-mediated immune responses following surgical treatment, while patients with other tumours recover, the defect may be primary in oral carcinoma patients. [14, 15] The dysplastic epithelial cells in oral cancer exhibit mononuclear cell infiltration in the connective tissue. [16] The more severe the dysplasia, the higher the density of the inflammatory cell infiltration. When there is a dense infiltration of mononuclear cells around the tumour, the prognosis of the illness is improved. Throughout the whole course of cancer's formation, progression, and metastasis, the immune system is seen to be involved.

Early-stage tumours release immunoinhibitory molecules [17], which suppresses both systemic and local immunity. In more advanced instances, however, there is a significant loss of immune effector cells. [18]

a) Role of immune response in formation/development of oral cancer

The interaction of cancer cells, healthy stromal cells, and host defense systems is a complicated process in the development of oral cancer.

It has been observed that initially acute inflammation tends to resolve tumors but when they fail, chronic inflammation sets in to promote tumor cell growth and angiogenesis as demonstrated in animal tumor models and human cancers.

Because of their ability to selectively recognize non-self-peptides from cellular compartments and to orchestrate a variety of immune responses that ultimately result in T cell-mediated tumour cell death, T cells have been a central focus of an antitumor response. Through the generation of cytotoxins and interferon (IFN)-γ, CD8 + cytotoxic T lymphocytes (CTL) and CD4 + helper T lymphocytes (Th)1 cells generally prevent the growth of cancer.[19]

Three phases may be used to summarise the T cell-mediated immune response: 1) Immune synapse, where tumour antigens attached to the MHC molecule on the surface of antigen-presenting cells are delivered to T cell receptor; 2) A confirmatory co-stimulatory signal, like the CD 28/B7 interaction, or an inhibitory signal is sent; 3) immune-activating cytokines, like interleukin 12 or type I interferon (IFN), confirm signal 2, which points the cell in the direction of stimulation or inhibition. [20-22] An immune response to an antigen can become stronger than to stimulatory receptors.

Normally, the inhibitory checkpoint receptors are present to prevent both an excessive immune response to non-self-antigens and autoimmunity to self-antigens. However, via a process known as "immune-editing," which involves the overexpression of inhibitory receptors, the recruitment of suppressive cells into the tumour Micro Environment (TME), and the inefficient presentation of antigen to T cells, tumour cells evolve a variety of strategies to evade immune detection and response. [23]

Whether malignant cells are able to withstand an activated antitumor T cell response depends on the final balance between effector cells, such as cytotoxic CD8-positive (CD81) T lymphocytes (CTL), and suppressive cells, such as Treg and myeloid-derived suppressor cells (MDSC). [24]

b) Role of immune response in the progression of oral cancer

There is enough data in the literature that shows tumours can occasionally go dormant in people for years before coming back. As far as is known, tumour cells take advantage of a number of variables to thwart the immune response. These variables include aberrant antigen presentation, tolerance and immunological deviation, the production of immune-suppressive cytokines, and regulatory cells, which can be produced by either cancerous or non-cancerous cells in the tumour microenvironment. When tumours down-regulate the antigen processing machinery that affects the major histocompatibility complex (MHC) I pathway, the proteosome components latent membrane protein (LMP) 2 and LMP7, and the transporter associated with antigen processing (TAP) protein, defective antigen presentation results. Tumour antigen expression is therefore down-regulated, which may increase the incidence and spread of tumours because cytotoxic T lymphocytes (CTL) are unable to identify target antigens on tumour cells. By interacting with the T cell receptor but not producing costimulatory molecules, tumour cells can cause tolerance in T cells. Furthermore, tumours elude immune response by tipping the scales from Th1 to Th2 (immune deviation), a process that is dependent on IL-10 and TGF-β. Additionally, there is evidence that both CTLs and natural killer (NK) cells are unable to kill tumour cells through death ligand-mediated inhibition of death receptors. According to studies, CTLs regulate the death of tumour cells via regulating the p53 tumour suppressor gene. Cancer immune evasion is therefore significantly influenced by variables that promote tolerance and immunological deviation. TGF-β, tumour necrosis factor (TNF)-α, IL-1, IL-6, colony stimulating factor (CSF)-1, IL-8, IL-10, and type I IFNs are examples of immune suppressive cytokines whose production plays a significant role in the growth of tumours. A variety of suppressive cell types, such as CD4 + CD25 + FoxP3 + regulatory T cells (Tregs), can mediate immune suppression within the tumour microenvironment. The generation of chemokines by tumour cells attracts tumor-derived Tregs, which are characterized by a greater suppressive activity than those found in normal tissues. [15]

Role of immune response in the prognosis of oral cancer

Oral cancer prognosis is well-established in connection to local immune responses, and when there is a substantial infiltration of mononuclear cells, the prognosis appears to be better [25]. When the local lymph nodes exhibit an enlarged inner cortex, a higher number of germinal centres, and a lymphocyte predominance pattern, they are also considered "active," which improves the prognosis. [26]

The heterogeneity of oral cancer is another significant aspect that influences the immune response and determines the prognosis. Genetic instability introduces heterogeneity in terms of both shape and physiology, which is manifested as a plurality of cell surface molecule expression and varying proliferative and angiogenic potential, even though tumours are known to start from a single altered cell. As a result, a large range of antigens, either tumor-specific or tumor-associated, are

expressed by the tumour cells. The discovery of possible targets, the effectiveness of treatment, and diagnosis are all significantly impacted by this variability. It is commonly known that a tiny percentage of cells within a primary tumour subpopulation develop the ability to spread to other locations by eluding immune clearance. The cancer cells' secretion of TGF-β plays a significant role in the spread of tumours.

Furthermore, in a way that is dependent on VEGF, inducible nitric oxide synthase (iNOS), and hypoxia in and around tumour vasculature, hypoxia also aids in the metastatic spread of cancer cells. Notably, hypoxia induces lysyl oxidase synthesis, which facilitates the establishment of pre-metastatic habitats. It also modifies pre-metastatic niches by drawing in MDSCs and inhibiting the activities of NK cells. [27]

In a comprehensive review published recently, Sievilainen et al. examined the prognostic significance of immune checkpoints in OSCC from 1985 to 2017. They found that seven immune checkpoints—PD-L1, FKBP51, B7-H4, B7-H6, ALHD1, IDO1, and B7-H3—had been linked to a lower chance of survival.28 Huang et al. conducted a meta-analysis to determine the prognostic value of TILs in OSCC. They discovered that whereas high infiltration of CD163+ and CD68+ macrophages was linked with a bad prognosis, high infiltration of CD8+ TILs, CD45RO+ TILs, and CD57+ TILs was related with favourable survival. [29]

Hadler-Olsen et al. discovered in another meta-analysis that there was a positive correlation between the outcome of patients with OSCC and CD163+ M2 and CD57+. [30]

2) IMMUNOTHERAPY: POTENTIAL IN ORAL CANCER THERAPY

Unquestionably effective against a few of cancer types, immunotherapeutic strategies hold up the prospect of even faster advancement when developed and paired with already available conventional treatments. Even though a great deal of information has been gathered about how tumours evade immune destruction, researchers and clinicians still face enormous challenges in their quest to find effective cancer medicines.

Immunotherapy can be said to as active based on its mechanism of action when the immune system targets and attacks the tumour cells directly. To combat the tumour cells, immune cells obtained from blood or biopsied cancer tissue are cultivated, collected, and grown in vitro before being reintroduced into the body. In active immunotherapy, dendritic cells, cytotoxic T cells, and natural killer cells were often used.

On the other hand, when immune cells' cell surface receptors are activated or increased, immunotherapy is regarded as passive. Thus, antibody-dependent cell-mediated (immunity) cytotoxicity is created, such as that caused by ipilimumab. [31]

Based on type of immunotherapy various sub categories have been identified. These can be studied as under-

a) Antibody based-

i. Immune checkpoint inhibitors (ICIs)-

The identification of inhibitory pathways that promote tumour development by reducing T-cell activity marked a significant turning point in the area of immunotherapy.

It is known that the use of so-called checkpoint inhibitors to disrupt these inhibitory pathways might cause a tumour to retreat. [32

Anti-CTLA-4 and anti-PD-1 antibodies are two checkpoint inhibitors that are often utilised therapeutically. Compared to anti-PD-1 antibodies, anti-CTLA-4 antibodies have a wider range of T cell activity, supporting the notion that anti-CTLA-4 has more adverse consequences than anti-PD-1. Membrane-bound PD-1 receptors represent immune cells such as T cells. When PD-L1, a ligand expressed by tumor cells, binds to PD-1, it can block cytolytic T cells from attacking and allow cancer cells to evade immune monitoring. Therefore, ICIs that can inhibit the PD1/PD-L1 interaction provide a viable course of treatment. [33]

Numerous clinical trials are testing immunotherapy that targets immunological checkpoints, either in isolation or in combination with chemotherapeutic or targeted therapeutic medications.

Other checkpoint inhibitor receptors, such as lymphocyte-activation gene 3 (LAG3) and T cell immunoglobulin mucin (Tim) 3, have shown therapeutic benefits in clinical studies when combined with PD-1 medicines, in addition to anti-PD-1 and anti-CTLA-4 antibodies. [34,35]

The most researched biomarker, according to a thorough study by Kujan et al. (2020), was PD-L1, followed by PD-1, CTLA-4, TIM-3, and LAG-3.

According to Ngamphaiboon et al., PD-L1 was expressed positively in 83.9% of OSCC samples in their cohort (n = 203). [36]

There is additional evidence linking elevated tumor-infiltrating lymphocytes (TILs) to PD-1/PD-L1 expression in OSCC. [37,38] Poor clinical outcome was linked to high expression of PD-L1. [39]

mbrolizumab and nivolumab, two immune checkpoint inhibitors (ICIs) that target programmed cell death -1 (PD-1) were authorised in 2016 as second-line treatments for recurrent and metastatic (R/M) head and neck cancer40. In 2019, pembrolizumab was approved as first-line treatment for advanced-stage HNC. [41]

Lately, anti-PD-L1 ligand has entered the final stages of commercial development under the trade name durvalumab for use in clinical settings. In the therapy of cancer, it has been demonstrated that PD-1 inhibition and radiation work well together. [42]

Checkpoint inhibitors frequently cause immunological side effects, particularly when used with anti-CTLA-4 antibodies since they function during the priming phase. Hepatitis, rash, hypothyroidism, adrenal insufficiency, colitis, and other autoimmune responses were among the symptoms. [43]

While maintaining long-term quality of life, it is critical to reevaluate these medicines due to the unfavourable responses and poor prognosis in locally-advanced oral malignancies.

Immunocheckpoint inhibitors (ICI) are recommended for the treatment of squamous cell carcinoma (SCC) of the head and neck based on the data that is currently available. The combination of neoadjuvant and adjuvant nivolumab as Immune Checkpoint inhibition in resectable locally-advanced oral cavity tumours was studied in a study conducted by Brooker et al. (2021). [44]

In order to determine the feasibility of targeting immune checkpoint molecules before to the advancement of oral potential malignant diseases (OPMDs) to OSCC, researchers have recently investigated the involvement of PD-1 and PD-L1. Actinic cheilitis patients had greater levels of PD-1/PD-L1 over-expression than healthy volunteers, but lower levels than those seen in OSCC. [45]

Inhibiting the PD-1/PD-L1 pathway can stop malignant transformation in OPMDs, and dysplastic lesions expressing PD-L1 on epithelium and subepithelial cells can elude the immune system. These findings are reported by Yagyuu et al. and Zhou et al. [46-48]

ii. Targeted monoclonal antibodies

Human or murine monoclonal antibodies with the capacity to attach to antigens linked to tumours can be produced.

Nivolumab, pembrolizumab, and cetuximab are the three monoclonal antibodies that the US FDA has authorised. However, additional signalling pathway inhibitors, such as temsirolimus and rapamycin, as well as monoclonal antibodies, such as cetuximab and bevacizumab, which target the EGFR and VEGFR, respectively, are also being evaluated for the treatment of head and neck squamous cell carcinoma (HNSCC).

Treatment options for unresectable recurrent or metastatic HNSCCs are limited. Because VEGF plays a crucial role in both cancer and immunosuppression, addressing it in both situations may be quite beneficial. A phase 2 study including R/M HNSCC indicated the potency

of axitinib as an inhibitor of VEGFR 1, 2, and 3, with therapy linked with a median overall survival of 9.8 months and a 6-month overall survival rate of 70% in patients substantially pretreated. [49]

In 95% of instances of HNSCC, there is a rise in EGFR expression, which inhibits invasion, metastasis, and apoptosis and causes the tumour to develop. [50, 51] Treating HNSCC using monoclonal antibodies that target EGFR, including cetuximab and panitumumab, has been shown to be successful whether used alone or in conjunction with radiation treatment. [52]

Similarly, Muc-1 levels are found to increase in HNSCC and antibodies against Muc-1 have shown regression in the tumor in advanced cancer. [53]

Immunoglobulins against mutated p [53] have demonstrated efficacy in treating HNSCC, especially in cases where node involvement is present. Gain-of-function activity of mutant p53, which inhibits both cell autonomous and non-cell autonomous surveillance mechanisms, is another factor that promotes the growth of cancer. [54, 55]

b) Adoptive cell transfer

The T cells obtained from blood or biopsied cancer tissue can be cultivated/harvested, grown in vitro, and then reintroduced back into the body to combat the tumour cells, as previously mentioned in the section. By genetically engineering certain antigen receptors into the cells, one can increase T cells' efficacy and improve their capacity to identify tumour antigen. [56]

Adoptive cell transfer (ACT) has shown promise in treating a variety of tumour types that were previously challenging to treat with traditional methods. ACT's success rate is driving improvements in the programme. [57]

Antigen receptors may be engineered by two methods: 1) enhanced MHC complex presentation, and 2) chimeric antigen receptor (CAR).

Viral vectors are used in the CAR T-cell immunotherapy process. The ability to tailor this technique to particular tumour antigens is by far its greatest benefit. [58-60]

c) Cancer vaccines

Cancer vaccines are created using the tumour cells from patients. They are engineered to contain the desired antigen, which can be a single antigen like RNA, DNA, or peptides, or multiple antigens like pulsed dendritic cells or whole cells that can teach T cells to identify and eliminate the cancer cells in the tumour. [61]
Vaccines can be used in conjunction with other immunotherapy methods to produce less harmful, long-lasting immunity. In addition to being costly, these vaccinations have other drawbacks, such as the inability to treat tumours that grow quickly and the potential for a lengthy immune response. [62]

Vaccines may be categorised as follows based on their nature and method of action: a) antigen vaccine; b) dendritic cell vaccine; c) DNA/RNA vaccine; and d) whole cell vaccination.

Certain antigens from tumour tissue, which have the ability to kill cancer cells, are the components of antigen vaccines. Future developments in genetic engineering make large-scale manufacturing possible.

Dendritic cell vaccines

Vaccines against tumour cells employ a dendritic cell's capacity to identify and target such cells. The vaccination that was created in the lab shows a lot of promise for tumour regression. It has been demonstrated that dendritic cell immunotherapy is a viable, safe, and successful treatment for a number of cancer types, including prostate cancer, glioblastoma, lung adenocarcinoma, lung adenocarcinoma, and oropharyngeal adenocarcinoma. [63-71]

On the other hand, there aren't many reports of DC-based immunotherapy for oral cancer yet.

Thus, DC vaccination offers cancer patients a fresh and bright future, either by itself or in conjunction with other medications such as immune checkpoint inhibitors. [72]

DNA or RNA vaccines are composed of RNA or DNA have shown to be great options for tumour regression. **Whole-cell vaccines** are created from whole cancer cells as opposed to particular antigens, DNA, or RNA. [31, 61]
Effectiveness challenges for T-cell-based immunotherapy, such as the existence of genetic changes in IFN response genes and antigen presentation machinery, may be addressed by natural killer (NK)-cell-based immunotherapy. Many solid tumour forms, including head and neck squamous cell carcinoma (HNSCC), have an immunosuppressive tumour microenvironment that can negate the effects of all immunotherapy treatments. In HNSCC, NK-cell activity is suppressed by myeloid-derived suppressor cells (MDSC). Significant amounts of CD14+monocytic-MDSC and CXCR1/2+ CD15+ PMN-MDSC are seen in tumour infiltrating and circulating in patients with HNSCC. Compared to circulation-source MDSC, tumour MDSC showed more immunosuppression. TGFβ and nitric oxide were two of the several, distinct, cell-specific pathways that mediated the immunosuppression of HNSCC tumour MDSCs. [63]

d) Cytokine immunotherapy

Cytokines are chemicals that help immune system cells interact with one another in order to produce a coordinated response to a target antigen, such as a cancer cell.

Immunotherapy based on cytokines activates immune cells via an intricate process, improving the synchronisation of stromal cells and tumour cells.

A number of cytokines have been created recently to treat cancer. At present, the FDA has authorised interferon α (IFN α) and interleukin 2 (IL-2) as two cytokines for clinical use.

Subcutaneous injections of **IFN α** cytokines have demonstrated remarkable outcomes in terms of tumour shrinkage. Nevertheless, IFN α exhibited a partial response and increased toxicity when paired with IL-2.73

IL-2 is a cytokine that has FDA approval that raises the number of TILs (tumor-infiltrating lymphocytes) and NK cells in the lesion. Patients with HNSCC who had monoclonal antibody treatment following surgery had a higher chance of survival when perilymphatic IL-2 injection boosted the number of tumor-reactive T cells in their bodies. [74]

Because of their greater degree of pleiotropism, cytokines present difficulties in their therapeutic use. They affect a wide variety of cell types in the body, which has a variety of opposing effects, including exhaustion, diarrhoea, pancytopenia, and weariness. [31,75]

Current Standing of Immunotherapy in Oral Cancer and Head And Neck Cancer Therapeutics

Literature has several studies and trials where different types of immunotherapies have been attempted. (Refer table)

Since the development of cancer immunotherapy, attention has been continually drawn to the treatment of head and neck cancer as well as oral cancer. Determining the specific indicators of genome-based targeted medicines and developing selection criteria for individuals who may benefit from this therapy approach become imperative. [76]

Patients with metastases from oral cancer or head and neck cancer are often not expected to recover, and few treatment strategies have been demonstrated to enhance overall survival (OS) or progression-free survival (PFS).77

Many prognostic indicators are used to evaluate the clinical outcome of chemotherapy; nevertheless, the most significant elements that might affect the response are the stage of the malignancy and previous treatments (chemo/radiation, surgery, or other). [58]

Additionally, a number of pharmaceutical substances, in particular monoclonal antibodies, have demonstrated significant promise in the management of HNSCC, and several of them are presently undergoing clinical trials. [78]

Immunotherapy was first authorised for recurring or metastatic instances of oral cancer, just as other head and neck malignancies. Recently, preoperative neoadjuvant immunotherapy has been offered for untreated oral cancer[79, 80]. Certain traditional anticancer medications, including lenalidomide, have immune-stimulating properties that can work in concert with other immune-based therapies. The idea that radiation treatment can strengthen the immune system's reaction to cancer is also thrilling. Even so, radiation dosage optimisation is still in its infancy.81, 82

To evaluate cancer response to immunotherapy, the gathered proof from systematic reviews and meta-analyses by Sievilainen et al83 (2019); Huang et al84 (2019), and Hadler-Olsen et al85 (2019) has been quite fruitful in disclosing the immune profile and their prognostic significance in tumors. Antibodies against both programmed cell death-1 (anti-PD-1) and programmed cell death ligand-1 (anti-PD-L1) are essential components of the presently authorised immunotherapy for head and neck cancer, which includes oral cancer. [86,87]

Using samples from patients receiving immunotherapy, several researchers have examined the two pertinent biomarkers (PD-1 and PD-L1) in order to determine which instances are more likely to benefit from such treatment. For instance, in recent head and neck cancer trials, expression of PD-L1 shown a substantial correlation with response to durvalumab, an anti-PD-L1 antibody. According to these investigations, a threshold of 25% for PD-L1-stained cancer cells can be used to assess a patient's reaction to durvalumab immunotherapy. [88]

In a different investigation on the anticancer efficacy of pembrolizumab-based immunotherapy, Chow et al. recommended that PD-L1 score be taken into consideration for both immune and cancer cells, with a 1% cutoff point. [89]

In a similar vein, Emancipator et al. reported that a "combined positive score," which calculates the impact of pembrolizumab on a cell's response by analysing the ratio of PD-L1-expressing cells (i.e., immune cells and cancer cells) to each viable cancer cell multiplied by 100 [90] .Such immunotherapy enhanced patient survival in a phase 3 study comprising 361 patients with recurrent HNSCC treated with nivolumab. PD-L1 expression, however, did not have a major impact on how well the therapy responded. [91-93]

Dorta-Estremera et al. (2019) tested methods for boosting anti-PD-1 therapeutic effectiveness using a preclinical HPV+ oral tumour model. While PD-1 blocking antibody monotherapy was shown to be ineffective against tumours implanted in the flank, it did cause regression in 54% of mice with orthotopic tongue tumours. A 100-day survival rate of 93.3% was seen when combination immunotherapy that targeted both CTLA-4 and PD-1 simultaneously was studied. In 71% of mice, systemic therapy with α-PD-1 and α-CTLA-4 antibodies together with the delivery of an agonist for Stimulator of Interferon Induced Genes (STING) into the flank tumours led to persistent tumour reduction. Thus, it was shown that α-PD-1 therapy in combination with CTLA-4 inhibition and/or STING agonist to induce IFN-α/β signalling may be a viable treatment option for patients with oral cancer, particularly those who do not react to α-PD-1 monotherapy. [94]

Other known parameters, such as tumour mutational load and mutational signatures, may also be linked to the response to immunotherapy, in addition to immune response and immunological biomarkers. [95]

The quantity of somatic mutations per coding region in a tumor's genome is referred to as the tumour mutational load. It has been demonstrated that, in addition to having a predictive value in many malignancies, tumour mutational load has a considerable value in predicting response to immunotherapy with pembrolizumab. [95-97]

Pembrolizumab has been advised for cases with a high tumour mutational burden (≥ 10 mutations/megabase), however some researchers have cautioned against applying this universal threshold and emphasised the fact that cytotoxic chemotherapy is frequently administered to cancer patients, which may result in a higher level of tumour mutational burden [98]. Therefore, in order to identify the subset of tumours that may benefit from immunotherapy, the ideal cutoff threshold for tumour mutational load in each kind of tumour still has to be determined.

Furthermore, it is imperative to acknowledge that the intricate tumour immunological milieu must be taken into account when evaluating the clinical outcome. Moreover, there is a correlation between comorbidities and hypercalcemia and poor clinical outcomes, higher recurrence rates, and shorter survival periods. [99]

This might draw attention to the challenge of comparing the results from several trials using PD-L1 as a prognostic marker in the event that the immunotherapeutic drugs were different. It is also crucial to remember that the results on PD-1and/or PD-L1 that were previously discussed were derived from investigations that encompassed several head and neck cancer subsites with well-known variations in their clinical behaviour. Furthermore, based on further research, it will be necessary to decide whether to assess PD-L1 expression in immune cells only or in both cancer cells and immune cells. Furthermore, as immunorelated signature has demonstrated a strong predictive value for immunotherapy in other tumour types, techniques other than immunohistochemistry for evaluating immunological biomarkers have to be explored in instances of OSCC receiving immunotherapy. [92, 93]

Conclusion

Immunotherapy has been a therapeutically useful treatment for oral cancer thanks to the incredibly successful use of immune response over the last three decades in grading, immunoscore identification, and biomarker discovery.

When it comes to both determining which patients would benefit from immunotherapy and monitoring the course of treatment, a clinically appropriate assessment of the immune response might be deemed essential. Validation studies are desperately needed in order to validate the results of biomarkers that take advantage of the immune response, making it easier to identify cases of oral cancer that can benefit from immunotherapy and to gauge the patient's response. We have hardly begun to learn how to apply these new medicines optimally, logically mix them, or combine them with proven treatments, despite significant recent advancements. The majority of immunotherapies have toxicity as a result of either a lack of significant effectiveness or specificity.

It is important that in order to accurately anticipate the response to immunotherapy, trials in the future should take into account particular research on oral cancer.

Additionally, research is still needed since the digital evaluation of immune biomarkers in oral cancer is still in its early stages.

Likewise, more investigation is needed to determine the predictive significance of tumour mutational load and mutational signatures in order to provide tailored prediction of oral cancer treatment outcome.

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