Review Article

Immune checkpoint inhibitors: Utilizing patient's own immunity to treat oral cancer

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Abstract

Head and Neck squamous cell carcinoma is an immunosuppressive state. HNSCC evades immune responses through multiple resistance mechanisms. Because of better understanding of interaction between tumour microenvironment and immune regulators, there is increasing interest in role of immunotherapy as a treatment modality of HNSCC. Many clinical trials have been performed using checkpoint inhibitors, as monotherapies and combination therapies. Immune checkpoint molecule, programmed cell death 1 (PD-1) has shown promising results as a treatment of Recurrent and Metastatic HNSCC. This review discusses immune checkpoint molecules, their functional mechanisms, role of immunotherapy as a monotherapies and combination therapy for better treatment and prognosis of HNSCC patients.

Keywords: Head and neck squamous cell carcinoma, immune checkpoint inhibitors, immunotherapy, oral cancer

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INTRODUCTION

Cancer has become deadly and hazardous term for whole world as it leads to a compromised life style and high mortality rate. In India, lip and oral cancer had second highest incidence (comprises of 10.3% of all new cancer cases) and 3rd highest mortality rate accounting for 8.8% of all cancer associated mortality in 2020, as per the data of Globocan 2020.[1] In India, tobacco consumption (smoked and smokeless) is the major cause for oral cancer.[2]

Till date, surgery, chemotherapy and radiation therapy have been the modes of general treatment for oral cancer. All of these treatment approaches have their own side effects. Due to clinical manifestations of oral cancer and various side effects of cancer therapy often leads to negative influence on quality of cancer patient's life.[3] Long-term surgical complications in oral cancer patients include difficulty in speech, mastication and swallowing along with risk of injury to cranial nerves.[4] Normal cells also get damaged by chemotherapy along with cancerous cells. Blood forming cells in bone marrow, hair follicles, cells in oral cavity, digestive tract and reproductive system are most likely to get damaged during the treatment which leads to fatigue, hair loss,[5] easy bruising and bleeding, gastrointestinal distress,[6] anaemia,[7] nausea, vomiting[8] and infertility.[9] Radiation therapy causes acute response in head and neck causing erythema, inflammation and desquamation of dry and moist surfaces, which usually

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manifests as mucositis, pruritis, hypersensitivity, pain, ulceration in mucosa.[10]

At present, to overcome these side effects various clinical trials have been done to indicate the use of *immunotherapy* in cancer patients. Immunotherapy implies the utilization of person's own immunity against cancer cells. Prevention, control and elimination of cancer can be possible with the help of body's own immune system. Immunotherapy has shown successful results in non-small-cell lung cancer, small cell lung cancer, urothelial carcinoma, renal cell carcinoma, hepatocellular cancer, localized or metastatic prostate cancer, primary brain tumour.[11]

Oral cancer lends itself to immunotherapy.[12] Oral cancer frequently engages with immune cells within its local microenvironment, presenting opportunities for targeted immunotherapy. Furthermore, oral cancer can affect systemic immune responses, enabling therapies to activate the immune system on a wider scale.[13] Infiltrating immune cells like T- cells, B-cells, natural killer cells, dendritic cells, macrophages are part of microenvironment of tumour. T-cells have ability to recognize antigenic peptides present on cancer cell surface by HLA Class-I molecules and kill target cancer cells. Loss of HLA-1 expression is an important escape mechanism for tumours. The decreased HLA-1 expression built the base for the need of immunotherapy. In case of cancer, multiple cell-surface inhibitory receptors present on T-cells are overexpressed like *Programmed cell death protein-1(PD-1), Lymphocyte activation gene-3(LAG-3), T-cell immunoglobulin domain and mucin domain-3(TIM-3)* and *T- cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (TIGIT)*. It leads to decreased immunity to fight against cancer cells. Immunotherapy can modulate body's response in various manner. Among them, Immune checkpoint inhibitors are important mode of treatment for cancer. Immune checkpoint inhibitors work by blocking these receptors so that T-cells can differentiate cancer cells from healthy cells.

This review discusses immune checkpoint receptors and provides an update on immune checkpoint inhibitors as an aid in oral cancer treatment.

IMMUNOTHERAPY

Immunotherapy is also known as biological therapy.[14] The drugs used for immunotherapy are known as Biologic Response Modifiers. They act by activation or suppression of immune system.[15]

According to its function, immunotherapy can be of 2 types:

(1) Activation immunotherapies
- It is designed to elicit or amplify an immune response.
- Various approaches for activation immunotherapies include *Dendritic cell-based pump-priming or vaccination,*[16] *T-cell adoptive transfer,*[17] *checkpoint inhibitors*[18] and *immune enhancement therapy.*[19]
- It can be used as an immunotherapy in Head and Neck cancer as well as other cancer treatment.

(2) Suppression immunotherapies[20]
- It reduces or suppress an immune response.
- Immunosuppressive drugs are used.

History of immunotherapy

The first scientific attempt to modify patient's immune system, to cure cancer was done by two German physicians, *Fehleisen and Busch*. Significant tumour regression after erysipelas infection was noticed by them.

William Bradley Coley first harnessed immune system in bone cancer patient in 1891. He is known as *father of immunotherapy*. He injected different mixtures of live and inactivated *Streptococcus pyogenes* and *Serratia marcescens* into tumours for experiment. He achieved success but the mechanism of action was not known. It was known as "Coley's toxin".[21]

James, Allison and *Tasuku Honjo* worked on checkpoint molecules as potential therapeutic targets. They received the Noble prize award for the same in 2018.[22]

IMMUNE CHECKPOINT INHIBITORS (ICIS)

Introduction of T cell targeted biologic response modifiers blocking the immune checkpoint has been one of the greatest achievements during the last decade in cancer management.[23] Immune suppression by cancer cells aids in cancer growth and progression. Cancer cell activate different immune pathways that harbour immunosuppressive functions.[24] ICI therapy is associated with *tumour infiltrating lymphocytes (TILs)* and other immune cells in *tumour micro environment (TME)*.[25]

Emergence of ICIs

In 1950, Burnet and his colleagues gave the idea of "immunosurveillance that is the process by which cells of immune system look for and recognise foreign pathogens, pre-cancerous and cancerous cells in the body" and by escaping those surveillance mechanism, the tumour can grow. In 2002, Dunn and his colleagues named this escape from immunosurveillance as '*cancer immunoediting*'.[26] There are three sequential phases of immunoediting: Elimination, Equilibrium and Escape. Initially, immune system tries to eliminate cancer cells. However, with

weaker immunogenicity, it leads to proliferation of cancer cells. After proliferation of these cancer cells, it become impossible to prevent tumour formation.[27]

Idea of "Tumour evasion" was proposed in 2000s.[28] The cancer cells' aggressive suppression of host's immune system leads to creation of a favourable environment for sustained cancer growth.[29]

Regulatory T cells, macrophages, inhibitory cytokines, and immune checkpoint receptors such as CTLA-4, PD-1/PD-L1, TIM3, LAG-3, TIGIT, *Glucocorticoid induced TNFR family related gene (GITR), V-domain Ig suppressor of T cell activation (VISTA)* play a major role in this process.[11,27] Using *immunohistochemistry (IHC)* and flow cytometric detection method, several researchers have studied immune checkpoint molecules. LAG-3 was first discovered in 1990. In 1996, Leach and his colleagues demonstrated anti-tumour effects of CTLA-4 inhibitors antibodies.[30] TIM-3 was first reported in 2002.[31]

In 2011, Ipilimumab gained approval as first immune checkpoint inhibitors of CTLA-4 receptor. It was rapidly followed by development of monoclonal anti-bodies targeting PD1 (pembrolizumab and Nivolumab) and PDL1(atezolizumab and druvalumab).[32]

How ICIs work?

Immune system is network of biological process that protects body from disease. It detects and responds to variety of pathogens, cancer cells and foreign bodies to distinguish them from body's own healthy tissue. Immune system consists of mainly two types of immune cells: *Innate immune cells* and *Adaptive immune cells*.

Innate immune cells like basophils, dendritic cells, eosinophils, langerhans cells, mast cells, monocytes, macrophages, neutrophils and natural killer cells are the first line of defence, targeting invaders at first sign of an infection or inflammation. It provides a predefined reaction to broad group of situations and stimuli.[33]

Adaptive immune cells (T lymphocytes) are specialized, systemic cells that attack specific antigens. Adaptive immune system provides a specific reaction to each stimulus by learning to recognize molecules it has previously encountered.[33]

Immunological checkpoints are immunosuppressive molecules that can maintain self-tolerance by modulating T cell function and protecting surrounding tissues by suppressing immune responses. Tumour cells take advantage of this feature to evade attack by immune cells. Cancer is called "cold tumour" as cancer cells can escape immune surveillance because they are body's own mutated cells which the immune system of body is not able to recognise and cannot distinguish them from body's own healthy cells. Oral cancer tissues in immunosuppressive state have lesser number of lymphocytes, NK cells as compared to normal healthy tissue. In addition, tumour cells secrete immunosuppressive and pro-apoptotic factors, as well as upregulate inhibitory cell surface molecules that can lead to evasion of immune response.

To eliminate HNSCC using immunotherapy, specific identification of tumour cells and lysis by CTLs are required. ICIs work by blocking immune checkpoint receptors (CTLA-4, PD-1, TIM-3, LAG-3, TIGIT, GITR, VISTA). T-cells can differentiate a cancer cell from healthy cell, when these receptors are blocked.[11]

Mechanism of immune escape in HNSCC is shown in Flowchart 1.

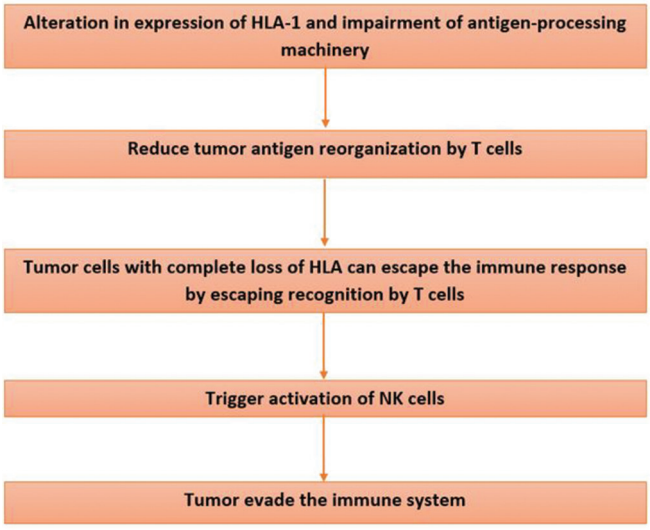
T cell activation

Dual-signalling is required for T-cell activation[11]:

First signal is induced when T-cell receptor recognizes MHC-antigen and second signal is mediated by B7 molecule on surface of APC and CD28 molecule on surface of T cells, which are also known as Co-stimulating factor.

IMMUNE CHECKPOINT RECEPTORS

An immune checkpoint is a regulatory signal that affects immune activation and self- tolerance. Immune checkpoint signalling is critical for preventing autoimmunity and



Flowchart 1: Flowchart shows Mechanism of immune escape in Head and Neck Squamous cell carcinoma

protecting host tissues from immune-mediated indirect damage. Immune checkpoint receptors (PD-1, CTLA-4, TIM-3, LAG-3, TIGIT, GITR and VISTA) are present on T cells.

Cytotoxic T lymphocyte antigen-4 (CTLA-4)

CTLA-4 is a key inhibitory receptor.[34] 90% of CTLA-4 is present in intracellular compartment of resting T cells.[35] CTLA-4 is less expressed in active B cells, monocytes, granulocytes and dendritic cells.[36] CTLA-4 is also expressed on regulatory T cells. When it gets activated with CD28, it produces transforming growth factor-β (TGF-β).[37] CTLA-4 and CD28 both are transmembrane receptors. When CTLA-4 binds to B7 protein (Present on antigen-presenting cells), it induces T cell dysfunction. Without damaging the normal tissues, CTLA-4 can stimulate the immune response. Whereas, cancer cells can stimulate expression of CTLA-4 by secreting TGF-β, which leads to T cell exhaustion.[38]

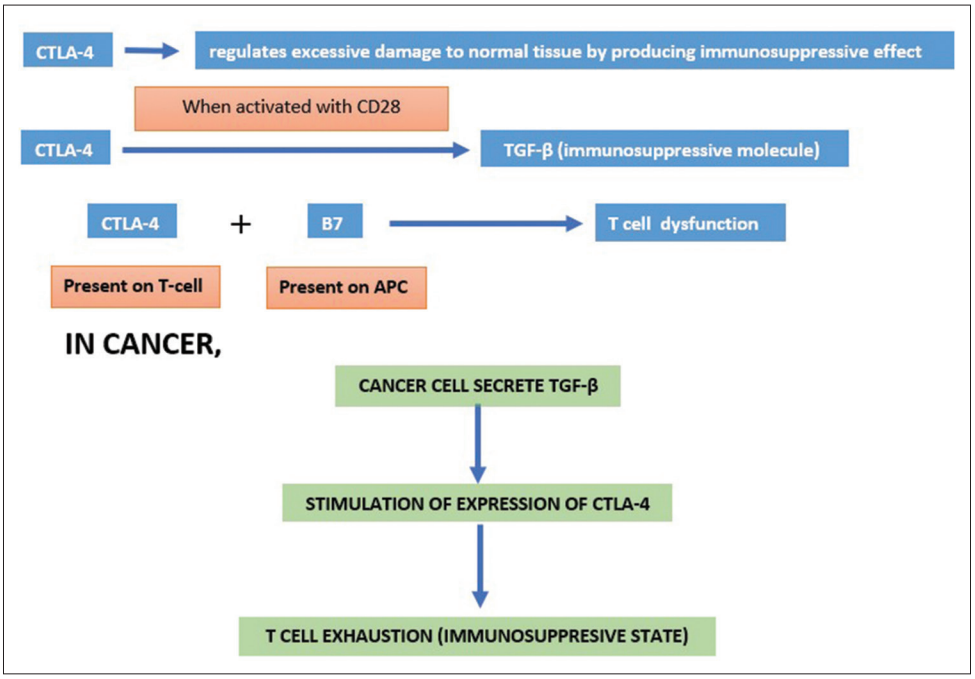
Proliferation of T cells and production of interlukin-2 can occur, if the interaction between B7 and co-stimulatory molecule CD28 occur. Since CTLA-4 prevents this interaction by binding with B7.[39] So, blocking CTLA-4 can abolish inhibition of T cells that leads to antitumour immune response in the body.[11]

Ipilimumab and Tremelimumab are used in phase-III trials as human anti-CTLA-4 antibodies. In phase-I/II trials it is proven that both antibodies are safe and show some activity as monotherapy and combined with IL-2 or conventional therapy.[40,41] Ipilimumab increases overall progression free survival (PFS) and immune-mediated PFS, but do not increase overall survival (OS).[42] Ipilimumab is more effective after chemotherapy.[43] Ipilimumab may be promising for oral cancer. Tremeimumab can be used in patients with relapsed malignancy.[11] Mechanism of CTLA-4 is shown in Flowchart 2.

Programmed cell death protein-1/programmed death-ligand 1 (PD-1/PD-L1)

PD-1 is cell surface receptors and is expressed on T cells and pro-B cells.[44] Overexpression of PD-1/PD-L1 is reported in oral cancer. Maruse *et al.*[45] has shown that nodal metastasis and poor prognosis in oral cancer is associated with PD-1/PD- L1 expression. PD-1 belongs to extended CD-28/CTLA-4 family of T cell regulators.[46] PD-1 has two ligands (PD-L1 and PD-L2) which are members of B7 family. PD-1 prevents autoimmune diseases by promoting apoptosis of antigen- specific T cells in lymph nodes and/or by reducing apoptosis in Tregs (regulatory T cells, suppressive T cells).[47] Because of this same mechanism, it also prevents immune system from detecting and destroying cancer cells.

Oral cancer tissues produce PD-L1 through abnormal PD-1 signalling pathway, which leads tumour suppression. PD-1/PD-L1 signalling pathway can be activated in chronic inflammatory environment. HPV^+ oral cancer tissues have more lymphocytes and higher levels of PD-L1 than HPV^- oral cancer tissues. Infiltrated CTLs express more PD-1. PD-1/



Flowchart 2: Flowchart shows Mechanism of CTLA-4

PD-L1 axis can be blocked at different levels: Targeting PD-1 or targeting PD-L1. Approved monoclonal antibodies Nivolumab and Pembrolizumab are anti-PD-1 antibodies and Avelumab and Atezolizumab are anti- PD-L1 antibodies. Nivolumab and Pembrolizumab have been approved by FDA for recurrent-metastatic HNSCC which are resistant to Cisplatin. Patients treated with Nivolumab have longer OS than patient receiving standard treatment. With the help of IHC, researchers evaluated PD-L2 expression in tumour tissue. PD-L2 can be detected in tumour with no PD-L1 expression. Longer PFS and OS was observed in patients with PD-L2^{+} tumour than PD-L2^{-} tumours.[11]

Combination of PD-L1 and CTLA-4 antibodies have shown better results than either antibody alone.[48] PD-1 antibody reactivate CD8^{+} T cells ability to lyse cancer cells, whereas CTLA-4 antibody enhances antigen specific T cell dependent immune reaction.

T-cell immunoglobulin domain and mucin domain-3(TIM-3)

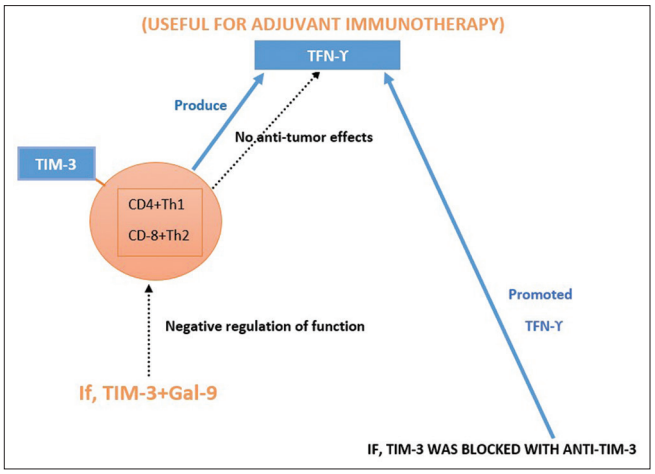
TIM-3 is a regulator of immune response. It is also known as Hepatitis A virus cellular receptor-2 (HAVCR2) which is encoded by HAVCR2 (TIM-3) gene. First described in 2002 0n cell surface of CD4+Th1 and CD8+Tc1 cells which produce IFN-ϒ (it has anti-tumour effects) Its expression was also detected in Th17 cells, regulatory T cells and innate immune cells like dendritic cells, NK cells and monocytes.

It acts as a negative regulator of Th1/Tc1 function by triggering cell death upon interaction with its ligand, Galectin-9. TIM-3 pathway may interact with PD-1 pathway. It leads to dysfunction of CD8+T cells and regulatory T cells in cancer. TIM-3 is mainly expressed on activated CD8+T cells and suppresses macrophage activation following PD-1 inhibition. Upregulation was observed in tumour progressing after anti-PD-1 therapy. It is a form of adaptive resistance to immunotherapy.[49] TIM-3 expression shows a positive relation between metastasis of lymph nodes and recurrence.

When TIM-3 was blocked with anti-TIM-3 monoclonal antibody, antitumor response of T cells mediated IFN- ϒ was promoted. Multiple clinical trials with anti- TIM-3 monoclonal antibodies and in combination with anti-PD-1 or anti-PD-L1 therapies are going on.[11] Mechanism of TIM-3 is shown in Flowchart 3.

Lymphocyte activation gene-3 (LAG-3)

LAG-3 protein, belongs to immunoglobulin superfamily. LAG-3 is expressed on activated T cells, natural killer cells, B cells and plasmacytoid dendritic cells. LAG-3 negatively regulates cellular proliferation, activation and homeostasis of T cells. It also plays role in Treg suppressive function. MHC-Class II with higher affinity than CD4. Fibrinogen-like protein-1 (FGL-1) is a new ligand for LAG-3 found by Wang and his colleagues in 2019. FGL-I functions independently of MGL-II. FGL-1 inhibited the activation of antigen-specific T cells. Blocking FGL-1-LAG-3 interaction enhances T cell response and promotes anti-tumour immunity. In mast human cancers, FGL-1 is upregulated.[11,50]



Flowchart 3: Flowchart shows Mechanism of TIM-3

Relatimab, monoclonal anti-LAG-3 antibody is currently in phase-2 clinical testing. Combination therapies involving LAG-3 antibodies and CTLA-4 or PD-1 antibodies are going on.

T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (TIGIT)

TIGIT is a member of poliovirus receptor (PVR)/Nectin family. It is also known as Washington university cell adhesion molecule (WUCAM)/V-set and immunoglobulin domain-containing 9(VSIG9). TIGIT regulates T-cell mediated immunity via CD226/TIGIT-PVR pathway. TIGIT is expressed in effector and regulatory CD4+T cells, follicular helper CD4+ T cells, effective CD8+ T cells and NK cells. CD155 is a high- affinity ligand of TIGIT that is highly expressed on endothelial cells, fibroblasts, DCs and tumour cells.

It increases IL-10 secretion, reduces the secretion of pro-inflammatory cytokines and inhibits anti-tumour immune response, when CD155 present on surface of tumour binds to TIGIT on surface of NK and T cells. CD112 and CD113 also bind with TIGIT, but CD155 has higher affinity for TIGIT than CD112 and CD113.

CD155, CD112 and CD113 also share a ligand with CD226. So, inhibition of TIGIT can lead to activation of co-stimulatory molecule CD226 and TIGIT/CD226 forms a network that regulates human T cell function. TIGIT-targeting therapy is still in early stages of clinical development.[11]

Glucocorticoid induced TNFR family related gene (GITR)

GITR belongs to tumour necrosis factor receptor (TNFR) superfamily. It is expressed on surface of CD25+ CD4+ Tregs, effector T cells and NK cells. Binding of GITR and its ligand GITRL can reduce recruitment of Tregs, weaken their inhibitory function, promoting secretion of pro-inflammatory cytokines and enhancing anti-tumour function.[11]

AMG 228 is an agonistic human IgG1 monoclonal antibody that binds to human GITR. Tran B *et al.*[51] conducted a study with AMG 228, the result showed that drug was well tolerated. Patient did not show dose-limiting toxicity. There was no evidence of T cell activation or anti-tumour activity with a single application of AMG 228 therapy.

V-domain Ig suppressor of T cell activation (VISTA)

VISTA is a type 1 transmembrane protein that functions as immune checkpoint. It belongs to immunoglobulin superfamily and is part of B7 family. VISTA is primarily expressed in WBCs. VISTA is produced at high levels in TILs, such as myeloid- derived suppressor cells and regulatory T cells. VISTA helps created an immunosuppressed TME by enhancing Treg maturation and inhibiting T cell activation.[11,52]

V-set and immunoglobulin domain- containing 3 (VSIG3) is a novel ligand for VISTA. The interaction of VSIG3 and VISTA on activated T cell inhibits T cell proliferation and production of T cells and inhibiting T cell activation.

Preliminary results of Phase-I clinical trial of monoclonal antibody targeting VISTA in advanced cancer show good safety tolerance and anti-cancer activity in patients with advanced tumours.[11,52]

COMBINATION IUMMNE CHECKPOINT INHIBITORS

Immune checkpoint inhibitor monotherapy clinical trials have shown trigger activation of compensatory T cell associated checkpoints.[53] Inhibition of PD-1/PD-L1 proved effective treatment of many types of cancer. But in process of inhibiting PD-1/PD-L1 axis, the expression of other immune checkpoints, such as TIM-3 get upregulated, which may be related to adaptive resistance and it decreases anti-tumour response.[11] Preclinical evidence supports a rationale of combination therapy as, by blocking more than one of these pathways, including PD-1, LAG-3 and CTLA-4 may reduce tumour growth. It improves tumour immune response and survival.[47] Combination of checkpoint inhibitors can target many co-stimulatory and co- suppressive interactions.[11] Combination therapy is considered as rational and feasible approach to achieve treatment effects.

PD-1/CTLA-4

In a clinical case report by Schwab K.S. *et al.*,[54] patients with head and neck squamous cell carcinoma were administered a combination of nivolumab (3 mg/kg body weight every 2 weeks) and ipilimumab (1 mg/kg body weight every 6 weeks). A follow up CT scan after 4 months of the surgery showed a cancer response. However, MRI showed local recurrence after 7 months.

PD-1/GITR

In 2017, Siu L.L. *et al.*[55] conducted a phase I/II study of BMS-986156 (GITR-antagonist) alone and in combination with nivolumab in patients with advanced solid tumours. The result showed that combination of ICIs of PD-1 and GITR was well tolerated. There was no obvious dose-limiting toxicity. Anti-PD-1 and anti-GITR antibody combination therapy can be beneficial by enhancing anti-tumour activity of T cells.[11]

PG-1/LAG-3

Woo SR suggested that PG-1/LAG-3 combination therapy may promote tumour-specific responses relative to nonspecific or self-antigen-specific immune responses. It is less toxic than CTLA-4 blockade.[56]

Combination of ICIs with radiotherapy

Radiation leads to increased release of cytokines which promotes T cell trafficking and priming. This is initiated through detection of DNA damage by cyclic guanine monophosphate (GMP)- adenosine monophosphate (AMP) synthase (cGAS).

To determine whether immune checkpoint blockade can enhance response to radiation, Demaria *et al.*[57] utilized 4T1 mouse mammary model and treated mice either a monoclonal antibody against CTLA-4 (qH10) alone, RT (24 Gy in 1 or 2 fractions) to primary tumour alone or with combination of both. Combination therapy showed significantly improved OS and resulted in fewer lung metastases.

Combination of ICIs with chemotherapy

Chemotherapy modifies tumour microenvironment and retards tumour growth. It arrests cell cycle, inhibits

Table 1: Various clinical trials of immunotherapy in oral cancer patients

Year, Author and Country	Type of Cancer	Sample size and type	Checkpoint targeted	Intervention	Outcome and Conclusion
Kiyota N, *et al*.[58] Japan, Taiwan, Hong Kong and Korea. Clinical trial registration NCT02105636. 2017	Recurrent Squamous cell carcinoma of head and neck	As a part of global trail *n*=361. *n*=23 Nivolumab 3 mg/kg every 2 weeks. *n*=11 3 mg/kg Investigator's choice	PD-1	Administration 3 mg/kg Nivolumab until intolerable toxicity or disease progression. The primary endpoint was overall survival.	Nivolumab demonstrated a survival advantage compared with conventional treatments in Asian patients with platinum- refractory recurrent or metastatic SCCHN, and was well tolerated.
Ferris RL, *et al*.[59] Japan, Taiwan, Hong Kong and Korea. Clinical trial registration NCT02105636. 2018	R/M SCCHN with tumour progression/ recurrence within 6 months of older platinum therapy	*n*=361. Randomized, open label, phase 3 trail. Age: 18 years or. Randomized to 2:1.	PD-1	Randomized 2:1 to nivolumab 3 mg/kg every 2 weeks or investigator's choice. Primary endpoint: Overall survival.	Nivolumab significantly improved OS at primary analysis and demonstrated prolonged OS benefit. OS benefit was observed with nivolumab irrespective of PD-L1 expression and HPV status.
Ferris RL, Licitra L, *et al*.[60] Japan, Taiwan, Hong Kong and Korea. 2019	R/M SCCHN	*n*=361. Randomized, open label, phase 3 trail. Age: 18 years or older. Randomized to 2:1.	PD-1	In the randomized, open-label, phase III CheckMate 141 trial, patients were randomized 2:1 to nivolumab 3 mg/kg every 2 weeks or investigator's choice (IC) of single-agent chemotherapy, with stratification by prior cetuximab exposure. Primary endpoint: OS Additional endpoint: PFS, Objective response rate and safety.	OS benefit with Nivolumab was maintained across patient baseline subgroups.
Saba NF, *et al*.[61] Japan, Taiwan, Hong Kong and Korea. ClinicalTrials.gov: NCT02105636. 2019	R/M SCCHN	*n*=361. Randomized, open label, phase 3 trail. Age: 18 years or older. Randomized to 2:1.	PD-1	Analysed by age <65 year and ≥65 year for efficacy and safety.	Nivolumab resulted in a higher survival in patients <65 and ≥65 year with a manageable safety profile in both age groups.
Oliva M.[62] America. 2021.	Newly diagnosed T2-4a, N0-2 or T1 >1 cm- N2 oral cavity carcinoma.	*n*=10.	Synergistic anti-tumour activity in combination with anti-PD-1.	All patients received sitravatinib 120 mg daily from day 1 upto 48 hours pre-surgery and one dose of nivolumab 240 mg on day 15. Surgery was planned between day 23 and 30. Standard of care adjuvant radiotherapy was given based on clinical stage.	Sitravatinib plus nivolumab is safe and leads to deep clinical and pathological responses in oral cavity carcinoma.
Jie HB, Schuler PJ, *et al*.[37] America. 2015.	Untreated stage III/IV Head and Neck Cancer.	*n*=22 patients treated with Cetuximab plus cisplatin/ paclitaxel/radiotherapy followed by 6 months of maintenance single agent Cetuximab *n*=18 patients receiving single-agent Cetuximab	CTLA-4^{+}	Peripheral venous blood samples were obtained from both the groups.	Cetuximab treated shows improved clinical response by adding Ipilimumab or other strategies of Treg ablation to promote anti-tumour immunity.

Contd...

Table 1: Contd...

Year, Author and Country	Type of Cancer	Sample size and type	Checkpoint targeted	Intervention	Outcome and Conclusion
Schoenfeld JD, *et al*.[63] America. ClinicalTrials. gov Identifier: NCT02919683. 2020.	Untreated squamous cell carcinoma of oral cavity (≥T2 or clinically positive mode)	*n*=29	PD-1 CLTA-4+	Treatment was administered with nivolumab 3 mg/kg, week 1 and 3, or nivolumab and ipilimumab (ipilimumab, 1 mg/kg, given week 1 only). Patient had surgery 3 to 7 days following Cycle 2.	Treatment with *N* and *N*+I was feasible prior to surgical resection.
Vos JL, Elbers JBW.[64] Netherlands. ClinicalTrails. gov Identifier: NCT03003637 2021.	T2-T4, N0-N3b, M0 primary or recurrent HNSCC, planned for surgery. Age: 18 years or older.	*n*=32.	PD-1 CLTA-4+	Patients are treated with 2 doses (in weeks 1 and 3) of immune checkpoint blockade (ICB) using nivolumab or nivolumab plus a single dose of ipilimumab prior to surgery.	Data indicate that neoadjuvant COMBO ICB is feasible and encouraging efficacious in HNSCC.

DNA replication, disturbs cell metabolism or suppresses microtubule assembly. Some cytotoxic chemotherapeutic drugs can induce immunogenic cell death and stimulate anti-tumour immune response.

Based on immunomodulatory effect of chemotherapeutic agents, chemotherapy might be given with anti-PD-1/ anti-PD-L1 to achieve both rapid and long-term cancer control.[54]

CLINICAL TRAILS OF ICIS IN ORAL CANCER PATIENTS

Various clinical trials on immunotherapy for oral cancer patients is listed in Table 1 with conclusion. Nivolumab as a monotherapy and in combination with other immunotherapy drug has shown improved overall survival in Recurrent or Metastatic Head and Neck squamous cell carcinoma.

CANCER VACCINE

Cancer vaccines are a type of immunotherapy aimed at activating the immune system to recognize and attack cancer cells by identifying specific antigens unique to tumors. Unlike traditional vaccines, which prevent disease, most cancer vaccines are therapeutic and target existing cancers. They stimulate immune cells, especially T-cells, to identify and eliminate tumor cells. Examples include preventive vaccines, such as the HPV vaccine, and therapeutic vaccines that can be tailored to individual cancers, promising targeted, less invasive treatments.[65]

LIMITATIONS OF IMMUNOTHERAPY

Immunotherapy in oral cancer treatment has limitations, such as the tumor's capacity to evade immune detection, leading to reduced effectiveness. Not all patients respond, and some experience autoimmune side effects due to heightened immune activity. The immunosuppressive tumor microenvironment further limits therapeutic impact, and tumors can develop resistance, reducing long-term benefits. Additionally, the high cost of immunotherapies affects accessibility, emphasizing the need for further research.[66]

CONCLUSION

Immune checkpoint inhibitors use patient's own immune system, which can be suppressed by cancer cells. As immunotherapy can increase anti-tumour response, it is an emerging promising treatment for oral cancer patients. Reduced mortality and increased overall survival/ progression free survival are seen in patients of oral cancer treated with monotherapy or combination therapy. For better prognosis, changes in dosage, timing and combination with pre-existing treatment modali ties are needed.

In India, clinical trials of immune checkpoint inhibitors as a treatment of oral cancer are still in early stage. Owning to the current scenario in Indian subcontinent where the number of oral cancer patient cases are very high with high mortality rate, more clinical trials are required for better prognosis and survival.

Key messages

(Provide appropriate messages of about 35-50 words to be printed in centre box):

Immunotherapy is bringing new era in cancer treatment. Immune checkpoint inhibitors have shown promising results in various cancers. ICIs in oral cancer can give better results with good prognosis by utilizing patient's

own immunity against oral cancer cells. ICIs can be used as monotherapy or as combination therapy.

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Conflicts of interest

There are no conflicts of interest.

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