Immunotherapy: The future of cancer treatment

Manisha Sahu, Hemakumari Suryawanshi

Department of Oral Pathology and Microbiology, Chhattisgarh Dental College and Research Institute, Rajnandgaon, Chhattisgarh, India

Abstract

Head and neck squamous cell carcinomas (HNSCCs) are one of the most common cancers worldwide. A large number of patients are diagnosed with locally advanced disease and require multimodal treatment approaches. Standard treatment modalities ranging from surgery to chemotherapy and radiation are yielding mixed results. To overcome this hurdle, newer innovative approaches are required to reduce the morbidity and mortality of the patients. In the last few decades, immunotherapy has become an important part of treating some types of cancer. The immune system plays a key role in the development, establishment and progression of HNSCC. A greater understanding of the dysregulation and evasion of the immune system in the evolution and progression of HNSCC provides the basis for improved therapies and outcomes for patients. Newer types of immune treatments are now being studied, and they will impact how we treat cancer in the future. This article provides a brief overview of the current immunotherapeutic strategies for cancer with emphasis on HNSCC.

Keywords: Adoptive cell transfer, head-and-neck squamous cell carcinoma, immune checkpoint inhibitors, immunotherapy, monoclonal antibody, oncolytic viruses, tumor vaccine

INTRODUCTION

Head-and-neck squamous cell cancers (HNSCCs) are one of the most common cancers worldwide.[1] The treatment of HNSCC varies by tumor site and stage, however the standard treatment include surgery, radiation and cytotoxic chemotherapy.[2] Despite advances in treatment, more than half of all cancers recur locoregionally or distantly.[3] Cancer immunotherapy is emerging as a beneficial tool for cancer treatment by activating the immune system to produce antitumor effects. In 1891, Dr. William Coley, the father of immunotherapy, made the first attempt to stimulate the immune system for improving a cancer patient's condition by intratumoral injections of inactivated bacterial toxin.[4]

All cancers arise as a result of somatic genomic alterations. These alterations arise sequentially and give rise to the progressively more aggressive and invasive phenotypes during tumorigenesis. Such genomic variations could give rise to tumor antigens, which could be recognized by the immune system as nonself and elicit cellular immunwponses.[5] However, avoiding immune destruction is one of the hallmarks of cancer. HNSCCs are highly immunosuppressive malignancy with high mutational burden. Cancer cells have evolved multiple mechanisms, such as defects in antigen presentation machinery, the upregulation of negative regulatory pathways and the recruitment of immunosuppressive cell populations to escape immune surveillance. There has been extensive

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research on the complex and dynamic interaction between tumor cells and host immune cells which has led to the development of currently approved immunotherapies. Immunotherapy is designed to either actively target a specific antigen on the tumor or enhance the host's immune system.[1,5]

Cancer immunotherapy was voted "breakthrough of the year" by Science in 2013 and has revolutionized the field of oncology.[6] The cancer immunotherapy aims at harnessing the specificity and killing mechanisms of the immune system to target and eradicate malignant cells. The Society for Immunotherapy of Cancer established the Cancer Immunotherapy Guideline-Head and Neck Cancer subcommittee to provide evidence-based recommendations on how best to incorporate immunotherapies into practice for the treatment of patients with HNSCC.[7] The present article provides a brief overview of the current immunotherapeutic strategies for cancer with emphasis on HNSCC.

TUMOR IMMUNOLOGY

Immune system
The immune system is comprised of the innate and adaptive immune system. The innate immune system includes dendritic cells (DCs), natural killer cells (NK), macrophages, neutrophils, eosinophils, basophils and mast cells. Innate immune cells do not require prior stimulation by antigens and act as a first line of defense against foreign antigens. The adaptive immune system includes B lymphocytes, CD4+ helper T lymphocytes and CD8+ cytotoxic T lymphocytes, and requires formal presentation by antigen-presenting cells (APCs) for its activation. The adaptive immune system generates antigen-specific T- and B-cell lymphocytes.[8]

Immunoediting
Each cell is estimated to experience over 20,000 DNA damaging events each day which are normally repaired. Cells which are not repaired and which acquire malignant or potentially malignant changes are then usually recognized and killed by the tumor immunosurveillance system. However, tumor cells develop mechanisms to thwart immune recognition and response, a dynamic process termed immunoediting that leads to immune escape.[8]

There is now an improved understanding of the complex interaction between immune system and tumor cells. The theory of Immune Editing was put forth by Schreiber *et al.* where they hypothesize that the body's immune system interacts with the tumor in three distinct phases namely elimination, equilibrium and escape.[9,10] The cancer

immunosurveillance hypothesis developed by Burnet and Thomas is now considered a component of cancer immunoediting.

The elimination phase refers to the initial damage and possible destruction of tumor cells by the innate immune system, followed by presentation of the tumor antigens in the cellular debris to DCs which then present them to T-cells and thereby create tumor-specific CD4+ and CD8+ T-cells. These help destroy the remaining tumor cells if elimination is complete. The equilibrium phase occurs when any tumor cells survive the initial elimination attempt but are not able to progress, being maintained in a state of equilibrium with the immune cells. In the escape phase, cancer cells grow and metastasize due to loss of control by the immune system.[8]

Escape mechanisms of HNSCC
HNSCC is one of the most immunosuppressive human tumors.[11] Tumor is able to evade immune destruction not only by modulating its own cellular characteristics but also by creating its own "tumor microenvironment (TME)." Many signaling molecules and cell types play a role in tumor-driven immune tolerance, from cytokines to both the innate and adaptive arms of the cellular immune system.[12]

MOLECULAR ESCAPE MECHANISMS

Tumor-derived factors
The production of immunosuppressive cytokines, including transforming growth factor (TGF)-b, interleukin (IL)-6 and IL-10 inhibit T cell proliferation and effector functions. Tumor cells also deplete local micronutrients and overexpress indoleamine 2,3-dioxygenase, an enzyme responsible for depletion of tryptophan, which hinders T cell proliferation and activation. It has also been shown that exosomes secreted by HNSCC are enriched for suppressive compounds (including cyclooxygenase-2, TGF-b, programmed death 1 [Programmed cell death receptor 1] and cytotoxic T lymphocyte antigen 4 [Cytotoxic T lymphocyte associated molecule 4]) that promote CD8+ T cell apoptosis, inhibit CD4+ T cell proliferation, upregulate (regulatory T cells) Tregs and impair NK cell function.[12]

Beyond secreted cytokines and metabolites, HNSCCs have developed mechanisms of human leukocyte antigen (HLA) modulation for immune escape. HNSCC provoke genetic alterations in key genes associated with processing and presentation of neoantigens, including signal transducer and activator of signal 1 deficiency and downregulated

transporter for antigen processing, without significantly affecting HLA expression itself.[12]

Suppressive cellular tumor infiltrate
HNSCC regulate and recruit immune populations capable of modulating T and NK cell responses, including Tregs, myeloid-derived suppressor cells, tumor-associated macrophages and cancer-associated fibroblasts. Immunomodulation enacted by these various cell populations contributes to a tumor-promoted microenvironment.[12]

IMMUNE CHECKPOINTS

In the healthy state, effector functions of the immune system must be held in check to prevent damage to self (autoimmunity) or prolonged activation. Checkpoint molecules are generally thought of as primarily immunosuppressive and the key inhibitory checkpoint receptors are PD-1, CTLA4, lymphocyte activating gene 3 and T cell immunoglobulin (IgG) and mucin domain-containing 3.[12]

Immunotherapy can be broadly divided into active and passive.[4]

Active immunotherapy
The active approach involves directing the host immune system to tumor-associated antigens on the surface of tumors. These antigens can be specific proteins or carbohydrates that are exclusively expressed or overly expressed in tumor cells.

Passive immunotherapy
Passive immunotherapy involves enhancing the standard anticancer response by the immune system using monoclonal antibodies (MoAbs), lymphocytes and cytokines.

TYPES OF IMMUNOTHERAPY

Adoptive cell therapy (ACT)
The central premise in ACT is that T cells are crucial for eliminating cancer cells and hence transfer of T cells in expanded numbers can augment anti-tumor immunity.[13] Adoptive cell therapy (ACT) utilizing either tumor-infiltrating lymphocyte (TIL)-derived T cells or T cells genetically engineered to express tumor recognizing receptors has emerged as a powerful and potentially curative therapy for several cancers.[14]

TYPES OF ADOPTIVE CELL THERAPY

Tumor-infiltrating lymphocyte therapy (unmodified cells)
ACT involves isolating TILs from cancers, growing them in culture and then reintroducing them to the patient who has undergone a lymphocyte depleting preparatory regimen. There is now a greater number of activated cells available, enhancing the body's anti-tumor immune response.

Engineered T-cell receptor therapy (modified cells)
With modern genetic engineering technology, specific antigen receptors can be introduced into T cells allowing them to recognize tumor specific antigens. These lymphocytes can then be produced on a large scale and used in patients. T-cell receptor (TCR)-modified T cells exert antigen recognition in a major histocompatibility complex-dependent manner.

The first evidence of the feasibility and clinical potency of TCR gene therapy targeting the melanoma differentiation antigen MART-1, present in approximately 80%–95% of melanomas was demonstrated in 17 patients with progressive metastatic melanoma.[15]

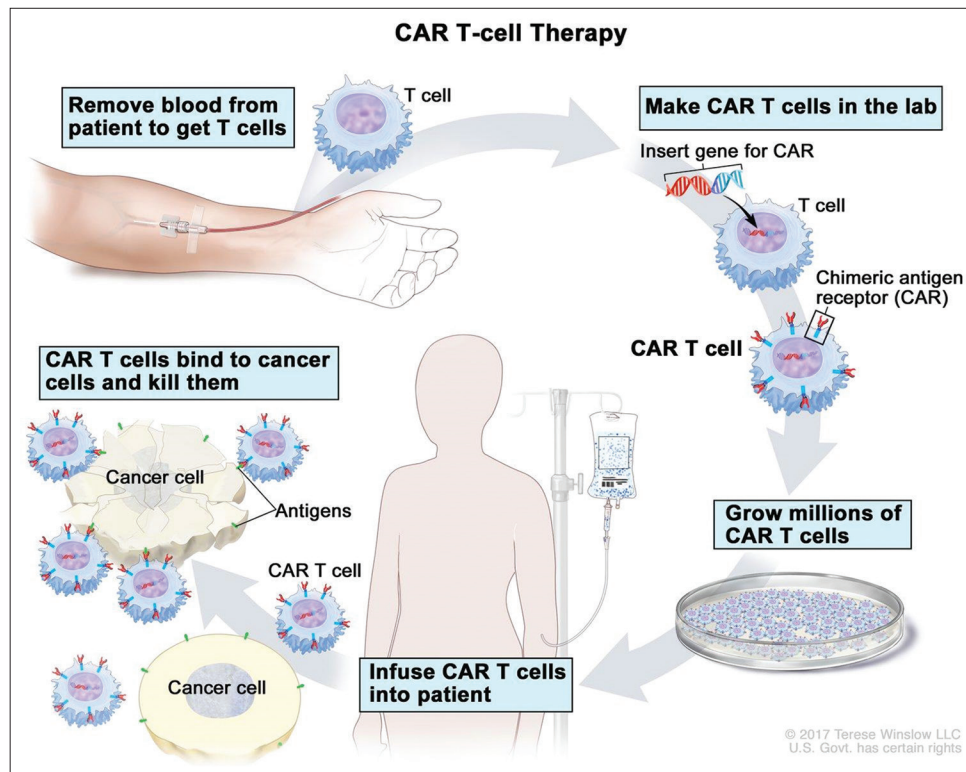### Chimeric antigen receptor T-cell therapy (modified cells)
Chimeric antigen receptor (CAR) is introduced to the T lymphocyte surface with help of a viral vector [Figure 1]. CARs are specialized structures with both antigen binding as well as intracellular signaling apparatus such that they can recognize antigens independent of APCs and can also drive cellular activation.[13]

IMMUNE CHECKPOINT INHIBITORS

Immune checkpoints are the normal components of immune system. T-cell activation is functionally determined by antigen presentation along with many co-stimulatory and co-inhibitory signals. In the presence of these co-inhibitory signals, the stimulatory signal will fail, leading to the induction of T-cell anergy or apoptosis, weakening the immune response due to failure to induce cytotoxicity.[16,17] Co-inhibitory molecules called checkpoints prevent exaggerated immune response and maintains immune tolerance in normal physiological conditions. These inhibitory checkpoints are overexpressed in the TME, contributing to tumor-promoting immunosuppression. These checkpoints are blocked by checkpoint inhibitors which are MoAbs.[18]

The most widely used targets for immune checkpoint inhibitors are

- CTLA4 – Cytotoxic T lymphocyte-associated molecule 4
- PD1 – Programmed cell death receptor 1
- Programmed cell death ligand 1.

Figure 1: Chimeric antigen receptor T-cell therapy is a type of treatment in which a patient's T cells (a type of immune cell) are changed in the laboratory so they will bind to cancer cells and kill them. Credit: National Cancer Institute US

The two major classes of checkpoint inhibitors currently used are anti CTLA-4 antibodies (e.g., Ipilimumab) and anti PD-1 [Figure 2] (Nivolumab and Pembrolizumab) antibodies.[18]

TARGETED MONOCLONAL ANTIBODIES

It is a form of active immunity was MoAbs target specific antigen present on cancer cells. MoAbs can either be unconjugated or be conjugated with therapeutic drugs that would produce a cytotoxic effect on cancer cells. Overexpression of epidermal growth factor receptor (EGFR) has been noted in up to 90% of HNSCC and upon binding of EGF promotes tumor cell proliferation, angiogenesis and metastasis. MoAbs such as cetuximab and panitumumab are EGFR targeted therapies; they are proven to be effective against HNSCC either alone or in combination with radiotherapy. Cetuximab is a mouse–human chimeric IgG1 Ab targeting EGFR whereas Panitumumab is a fully human IgG2 antibody.[19-21]

Other promising antigens of HNSCC which can be targeted.

Vascular endothelial growth factor (VEGF) AND VEGFR, insulin-like growth factor receptor which are overexpressed in HNSCC.

ONCOLYTIC VIRUS THERAPY

Oncolytic virus therapy originated from the finding that virus-infected tumor cells are destroyed by the cytopathic effects of viruses.

Viruses are infectious agents that are capable of infecting living cells, hijacking their genetic machinery, which allows the viruses to replicate inside them.In this therapy genetically modified viruses are used to infect tumor cells. The virus-infected tumor cells are destroyed by the cytopathic effects of viruses which stimulate a pro inflammatory environment to augment systemic antitumor immunity. Cell death induced by viral infections in tumor tissues also promotes inherent tumor immunity in cancer patients. Several DNA and RNA viruses have been proposed as candidates for this treatment through *in vitro* and *in vivo* studies as well as clinical trials. They are termed "oncolytic viruses" as they are designed to target tumor cell specifically.[5,22]

The first oncolytic virus therapy was approved by the US Food and Drug Administration (FDA) in 2015 – talimogene laherparepvec (T-VEC) for the treatment of melanoma. T-Vec, also known as Imlygic, a genetically modified herpes simplex virus, demonstrates impressive clinical benefits for patients with advanced
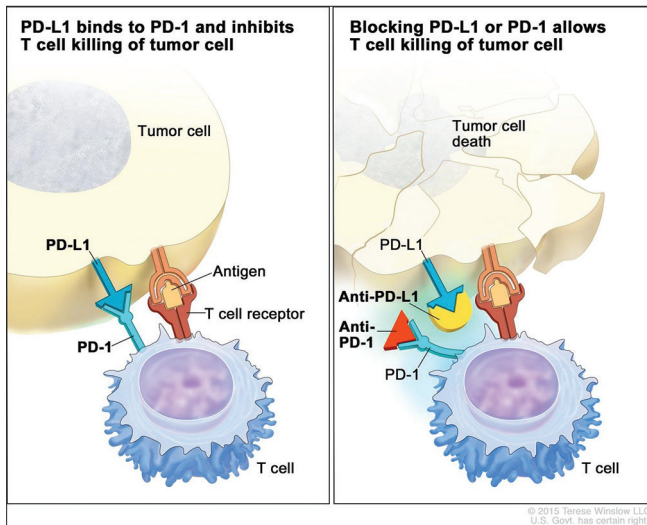
Figure 2: Checkpoint proteins, such as PD-L1 on tumor cells and PD-1 on T cells, help keep immune responses in check. The binding of PD-L1 to PD-1 keeps T cells from killing tumor cells in the body (left panel). Blocking the binding of PD-L1 to PD-1 with an immune checkpoint inhibitor (anti-PD-L1 or anti-PD-1) allows the T cells to kill tumor cells (right panel). Credit: National Cancer Institute US

melanoma and has been approved for the treatment of unresectable metastatic melanoma.

CANCER VACCINES

Cancer vaccines are sub classified as
- Prophylactic vaccines
- Therapeutic cancer vaccines.

Prophylactic vaccines are used for the prevention of primary and secondary cancer which is aimed at reducing cancer incidence, morbidity and mortality.

They are designed to alert the immune system to a specific virus so that it can recognize and attack the virus before it is able to cause an infection. This type of vaccine is administered to healthy individuals.[23]

The U. S. FDA have approved two prophylactic vaccines, including one for hepatitis B virus that can cause hepatocellular carcinoma and another for human papillomavirus (Gardasil) accounting for about 70% of cervical cancer.[24]

Therapeutic cancer vaccines are administrated to cancer patients and designed to eradicate cancer cells through strengthening patient's own immune responses. Based on their content, they may be classified into several major categories, which include cell vaccines (tumor or immune cell), protein/peptide vaccines and genetic (DNA, RNA) vaccines.

Bacillus Calmette–Guérin (BCG) and sipuleucel-T (Provenge®) are two examples of therapeutic cancer vaccines. The BCG vaccine is approved for patients with early-stage bladder cancer and sipuleucel-T (Provenge®) are approved for asymptomatic metastatic castrate-resistant prostate cancer. Sipuleucel-T works by inducing an immune response, targeting the prostatic acid phosphatase antigen, which is overexpressed in the majority prostate cancers.[23,24]

CYTOKINES

Cytokines are molecular messengers that allow the cells of the immune system to communicate with one another to generate a coordinated, robust, but self-limited response to a target antigen. Cytokines are secreted or membrane-bound proteins that act as mediators of intercellular signaling to regulate homeostasis of the immune system. They are produced by cells of innate and adaptive immunity in response to microbes and tumor antigens.[25,26]

Two cytokines currently approved by the FDA for clinical purposes are interferon α (IFN α) and IL-2.

Interferon α
These cytokines when injected subcutaneously in renal cell carcinoma have shown tumor regression.[27] These have shown excellent results in stage 3 melanoma. The combination of IFN α and IL-2 showed partial response and higher toxicity. IFN α plays multifaceted roles in tumor control, including directly eradicating tumor cells through inducing senescence and apoptosis and boosting effective antitumor immune responses through the stimulation of DC maturation and the enhancement of T-cell cytotoxicity.

Interleukin-2
It is an US FDA-approved cytokine for metastatic melanoma.[27] These cytokines increase level of NK cells and TILs in the lesion. Perilymphatic IL-2 administration has increased the survival rate of patients with HNSCC; increased tumor reactive T cells were found in patients who underwent MoAb therapy after surgery.

CONCLUSION

Cancer immunology is a rapidly evolving field. Understanding the behavior of cancer cells, identifying target antigens and detailing immune system pathways have allowed scientists to explore new approaches in immunotherapies. Despite impressive advances in immunotherapies there are few challenges including limited response rates, the inability to predict clinical efficacy and potential side effects such as autoimmune

reactions or cytokine storm. In order to augment responses, rational combinations of immunotherapeutic agents and new immunotherapy technologies are being vigorously investigated.

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