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Head and Neck Oncology

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Abstract

Immunotherapy for Head and Neck Cancer

Background: Head and neck cancers (HNC) are malignant tumours that originate from the anatomical structures within the region such as oral cavity, oropharynx, hypopharynx, larynx, sinonasal tract, nasopharynx, salivary glands and thyroid with squamous cell cancer accounting for more than 90% of the histological types. Tobacco and alcohol traditionally have been associated with increased risk of developing HNSCC but more recently studies have implicated human papilloma viruses (HPV) especially type 16 in development of HNSCCs especially those of the oropharynx. Furthermore, patients with immune deficiencies as may be seen in diseases like HIV infection has been shown to be at higher risk of developing HNSCC as compared to others and these have lead to studies on the roles of immune system in development of HNC. There are different traditional treatment modalities for HNC ranging from surgery, chemotherapy, radiotherapy, a combination of any of the modalities sequentially or concurrently. These treatment modalities are associated with significant toxicity and low survivability thus directional change towards newer treatment modalities such as immunotherapy. The concept of immunotherapy in management of cancers was based on the assumption of tumours cells being recognized as foreign rather than as self thus they will be attacked by an activated immune system. The expression of microbial proteins, mutated proteins, and fusion proteins by the tumour cells makes them a target of the body immune defense systems. The body has immune surveillance system in which developing cancer cells are detected and eliminated before they mature. The immune surveillance includes the human leucocyte antigen (HLA) mediate T-lymphocytes and the natural killer cells (NK-cells). These cells with others are responsible for elimination of tumour cells thus halting cancer progression. However, head and neck cancers cells evade the body immune surveillance via their immunogenicity alterations, immune suppressor mediators' production and immune modulators cell types promotion. Squamous cell cancers of head and neck regions usually are immunosuppressive with patients having impaired natural killer (NK) –cell activity and tumor-infiltrating T lymphocytes as well as poor antigen-presenting function as compared to healthy individuals. They are also associated with Tregs cells which secrete suppressive cytokines such as TGF-β and IL-10, express cytotoxic T lymphocyte–associated protein 4 (CTLA-4).

Keywords: Transforming; Immunosuppressive mechanisms; Immunotherapies; T lymmphocytes

Introduction

Growth factor-β (TGF-β), interleukin (IL)-6, and IL-10, suppresses cell-mediated antitumor immunity. However, the presence of Tregs cells in HNSCC have also be associated with good prognosis as compared with other tumours such as lung and colon cancers thus suggesting that Tregs cells have dual purposes. Immunotherapy tends to target these cancer immunosuppressive mechanisms. Immunotherapies that have shown promising results in HNSCC include cancer vaccines using tumor peptide antigens, or viral, bacterial, and DNA based vectors as well as tumor antigen specific monoclonal antibodies (moAbs). HNSCC immunotherapy can be divided into 2: a) HPV+ve HNSCC immunotherapy and b) HPV-ve HNSCC immunotherapy.

Hpv+ve HNSCC Immunotherapy

Vaccines

Vaccines mediated immune treatment plan can either be prophylactic against primary infection with aiming of preventing carcinogenesis or therapeutic in already existing HPV-associated HNSCC targeting E6 and E7 oncoproteins. HPV preventive vaccines are based on virus-like particles generated from recombinant HPV protein and contain inactive L1 capsid proteins; they act by eliciting virus-neutralizing antibody responses that prevent initial infection, unfortunately the preventive vaccine is only effective for cervical cancer and not on HPV associated HNSCC [1]. Other vaccines are currently on trial such as DNA vaccines which induces non-living antigens able to induce CTL, Th and B cell immunity and these vaccines may turn up with positive results. In addition, others vaccines such as Dendritic cells (DC) vaccines which are produced by culturing ex vivo DCs that have been derived from patients with the HPV antigen; after maturation and activation the patient is re- injected with the DCs cells. Other vaccines on trials include the peptide vaccines which incorporate amino acid sequences synthesized to form an immunogenic peptide molecule representing the specific epitope of tumor-associated antigens (TTA) that binds onto human leukocyte antigen (HLA). After activation of CTLs by the peptide vaccine, cells can recognize peptide-major histo-compatibility complex proteins (MHC) I complex on tumor cells. Another immunotherapy strategy for HPV+ve HNSCC is the Adoptive T-cell transfer (ACT) which entails harvesting and ex vivo expansion of the patient's own tumor antigen specific T-cells. The T-cells are then re-introduced subsequently into the patient, with the view to enhance the immunity and improve anticancer immune response [2].

HPV-VE HNSCC Immunotherapy

Activation of patient's immune response to cancers cells with aim

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of wiping out the cancers cells or prolonged suppression of the cancers cells are the major objectives of immunotherapy. The immune system is specific, adaptable and has memories and these qualities that are utilized in immunotherapy [3].

Monoclonal Antibodies

Chimeric immunoglobulin G1 (IgG1) monoclonal antibody such Cetuximab that is used with radiotherapy or chemotherapy is example of monoclonal antibodies approved by FDA for HNSCC treatment. It functions through antibody-dependent cell mediated cytotoxicity (ADCC) which is a mechanism of cell-mediated immune defense whereby NK cells, actively lyse a target cell, whose membrane-surface antigen has been bound by cetuximab. NK cells are activated upon binding to surface receptor FCγRIIIa. It also functions by provoking CTL antitumor response through cross- priming of DCs and NKs. Other anti-EGFR monoclonal antibodies include panitumumab, nimotuzumab and zalutumumab.

Immune checkpoint blockers

Excessive inflammatory responses as well as development of autoimmunity can be prevented through immune checkpoint or inhibitory pathways [4]. They play an important role in the tumor microenvironment and can be a mechanism of tumor immune evasion when manipulated. These pathways are mediated by ligand and receptor interactions such as CTLA-4 and its ligands CD80 and CD84 and PD-1 and its ligands PD-L1 and PD-L2. Many of these checkpoints or pathways that are ligand-receptor interactions dependent are susceptible to blockage by antibodies or can be modulated by recombinant forms of ligands or receptors. Examples of immune checkpoint blockers include Ipilimumab and enoblituzumab. Furthermore, other checkpoint receptors such as LAG-3 or the killer-cell immunoglobulin-like receptors (KIRs) act by regulating immune response via interaction with MHC I molecules and they suppress cytotoxicity through turning off NK cells when HLA is expressed on tumor cells.

Dendrite cell vaccine and Adoptive T-cell transfer (ACT): These are also used in immune therapy of non HPV HNSCC and works as detailed above.

Combination Immunotherapy

This entails combination of 2 or more of the immune therapies with the view of targeting several immune response mechanisms thus enhancing anticancer immunity. Example includes use of two checkpoint inhibitors such as durvalumab and tremelimumab in patients with solid tumour HNSCC [5].

Conclusion

Immunotherapy utilization as a cancer treatment was based on the theories of immune- surveillance which was first floated in the 1800's but gained traction in the 1970's. It entails the detection and elimination of cancers cells. However, some cancers have been known to evade these defense system through different mechanisms such immune modulation or suppression. HNSCC is one of such cancers and is seen commonly in immune-compromised patients buttressing the role of immune surveillance in its etiology. The role of immunotherapy in HNC is thus aimed at eradication of cancers cells or their prolonged suppression with minimal or no side effects. There various immunotherapy modalities in treatment of cancer cells which include different vaccinations, monoclonal antibodies, immune checkpoint blockers and combination of any of these modalities either Concurrently or sequentially. Furthermore, many clinical trials are currently at different stages on the efficacies of these treatment modalities.

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