IMMUNOTHERAPY AND ORAL ONCOLOGY – A LITERATURE REVIEW

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Abstract

Cancer develops through a multi-step process that begins with genetic changes in healthy proliferation and differentiation.The goal of public health has made early detection of oral cancer a priority, and oral health professionals are playing a key part in this effort.(1–3).Humanity is cursed with cancer. Oral cancer is the most severe of them all since it has a negative emotional and physical impact on the sufferer. (4,5) Immune surveillance functions as a powerful tumour suppressor in a healthy environment because these changes cause the emergence of tumor-related antigens that the immune system can initially recognise. Nonetheless, it is thought that during this equilibrium phase, the immune system may lose its capacity to destroy cancer cells, or new mutations may cause tumour cells to become poorly immunogenic and resistant to removal by immune cells.(6)The main pillars of cancer treatment is surgery, chemotherapy, radiotherapy or combination of these. Recently, immunotherapy treatment has emerged as another modality, targeting cancer cells not by its anatomical location or disease process, but by inherent mechanisms which the immune system uses to distinguish between normal healthy tissue and unhealthy pathological tissue(7)

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1. Introduction.

A therapeutic strategy that targets or influences the immune system is known as immunotherapy.(8,9)The immune system of human body comprises of network of cells that act against agents foreign to human body including tumor cells. This tumor cells have the ability to invade host immune cells. These immune cells are found in the center or margins of tumor or in the adjacent lymphoid tissues or stroma. These cell location varies within a patient and between patients who have same histology of tumor. The immune cells that infiltrate tumor varies within patients and also between patients who have same histological features of tumor. The location, function of immune cells in tumor environment influence immune response and tumor outcome in patients with cancer. (10)The cancer cells escape from immune cells by secreting antigen that inactivates the cells of immune system and create a microenvironment that supress immune respone and promotes cancer formation. (11) Immunotherapy is a newer treatment modality that recognizes the tumor cells as foreign cells by the host immune system thereby paving a way for its eradication(12) This novel technology can be used as an adjunct treatment modality along with other treatment modalities like chemotherapy, radiation, cryoablation etc.Modulation of immune system refers to alteration of immune response that includes stimulation, amplification, expression or inactivation of the immune response. Immune responses takes place in three well defined phases: cognition, activation , and effector(13)

The evolution of our understanding of the immune system's function in cancer:

From ancient Egypt to the early 18th century in Europe, there are numerous accounts of tumorous growths regressing or disappearing after an infectious and/or high febrile episode. However, the scientific rationale for efforts to modulate the immune system to treat cancer can only be traced back to the second half of the 18th century, when histologic confirmation of a malignancy became possible.(14)After unintentional infections with erysipelas more than 135 years ago, the German doctors Busch observed a regression of tumours in cancer patients. Busch was the first to deliberately spread erysipelas to a cancer patient in 1868, and he noted a decrease in the size of the tumour.(15)Following his own independent discovery of a long-term regression of a sarcoma following an erysipelas infection, an American surgeon named William Coley of the Bone Tumor Service at Memorial Hospital in New York began a 43-year-old project involving the injection of heat-inactivated bacteria ("Coley's toxins") into patients with incurable cancers. In more than 1,000 patients, many or most of whom had sarcomas, he documented a considerable number of regressions and cures, and the approach began gaining widespread support.(16)Thomas and Burnet first proposed that lymphocytes might serve as sentinels to detect and potentially destroy somatic cells altered by mutations in 1957 (17)The first trial on a cancer vaccine was reported in 1959 by Ruth and John Graham. It involved 114 patients with gynecologic cancer who received adjuvanted tumour lysate treatment.(18) Strong evidence of T cell-mediated tumor-specific immune surveillance, genuine anticancer immunological responses, and tumour immune escape was reported by Schreiber and colleagues in 1998 and 2001. This study confirmed that IFN-mediated effector functions and lymphocytes act together to prevent the growth of carcinogen-induced malignancies and that immunological pressure on tumours gradually favours tumour cells with less immunogenicity. Consequently, while immunological pressure causes the selection of tumour cells that later manage to evade immune-mediated processes and continue to exist in the body, on the other hand, the immune response is effective as a tumor-suppressor.(18)(19) In 2001, V. Shankaran and his colleagues stated that lymphocytes are the building blocks of a "cancer immunosurveillance" mechanism that guards immunocompetent hosts against the development of primary tumours was largely disproved when it was discovered that athymic nude mice and syngeneic wild-type mice developed primary tumours indistinguishably. However, further discoveries that functional T cells are still present in naked mice and that the immune system's IFNgamma and perforin work together to help inhibit tumour development in mice have reignited interest in the immune system's potential to reduce tumour growth. Here, we demonstrate how lymphocytes and IFNgamma work together to both select for tumour cells with lower immunogenicity and to guard against the formation of carcinogen-induced sarcomas and spontaneous epithelial carcinomas. Thus, the immune system serves as a powerful extrinsic tumor-suppressor system.(20)

What is immunotherapy?

Immunotherapy is stimulation of specific components in the immune system to strengthen the immune system thereby it helps to counteract the unwanted signals that supress the immune system.(11). Immunotherapy, which can be widely split into passive (including adoptive and antibody-based) and active (including vaccine therapy and allergen-specific) techniques, tries to use the host's adaptive and innate immune response to achieve long-lasting eradication of sick cells. Active immunotherapy promotes the patient's immune response and leads to the formation of specific

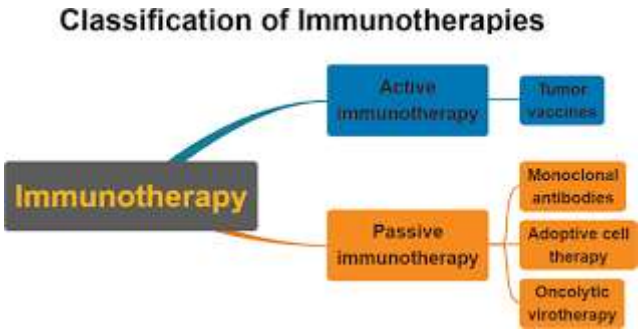
immune effectors, whereas passive-mediated immunotherapy includes the injection of ex vivo-generated immune elements (antibodies, immune cells) to patients.

Types of immunotherapy

Immunotherapy can be divided into active immunotherapy and passive immunotherapy.

Active immunotherapyisattacking tumor cells by immune cells present in our body in which tumor is target by the immune cells. These cells were derived from blood or tumor of the patient which is cultured in laboratory and injected back into the body, which in turn attack the tumor cells. In this treatment modality, Natural Killer cells, dendritic cells, cytotoxic T cells were used.(11)Active immunotherapy techniques, on the other hand, aim to promote effector functions in vivo. The immune system of the patient must be capable of responding to a challenge, being effectively activated, and mediating effector activities in order to administer active immunotherapeutics.The most significant active methods include vaccination tactics using tumour peptides or allogeneic entire cells, the use of autologous DCs as delivery systems for tumour antigen, and the intravenous administration of antibodies that specifically target key checkpoints of T cell activation.(8)

Passive immunotherapy involves enhancing the immune system by targeting the cell's surface receptors, which in turn can form antibody-dependent cell-mediated (immunity) cytotoxicity (ADCC), for example, ipilimumab.(11) Patients with cancer who have weakened, non-responsive, or poor immune systems are treated with passive immunotherapeutics. Ex vivo activated cells or molecules are used in passive protocols to replace missing or insufficient immune capabilities after being discovered inside the body. This group comprises, among other things, adoptive transfer of immune cells pre-activated to lyse tumours in vivo, systemic delivery of recombinant cytokines, and the infusion of tumor-specific antibodies.(8)



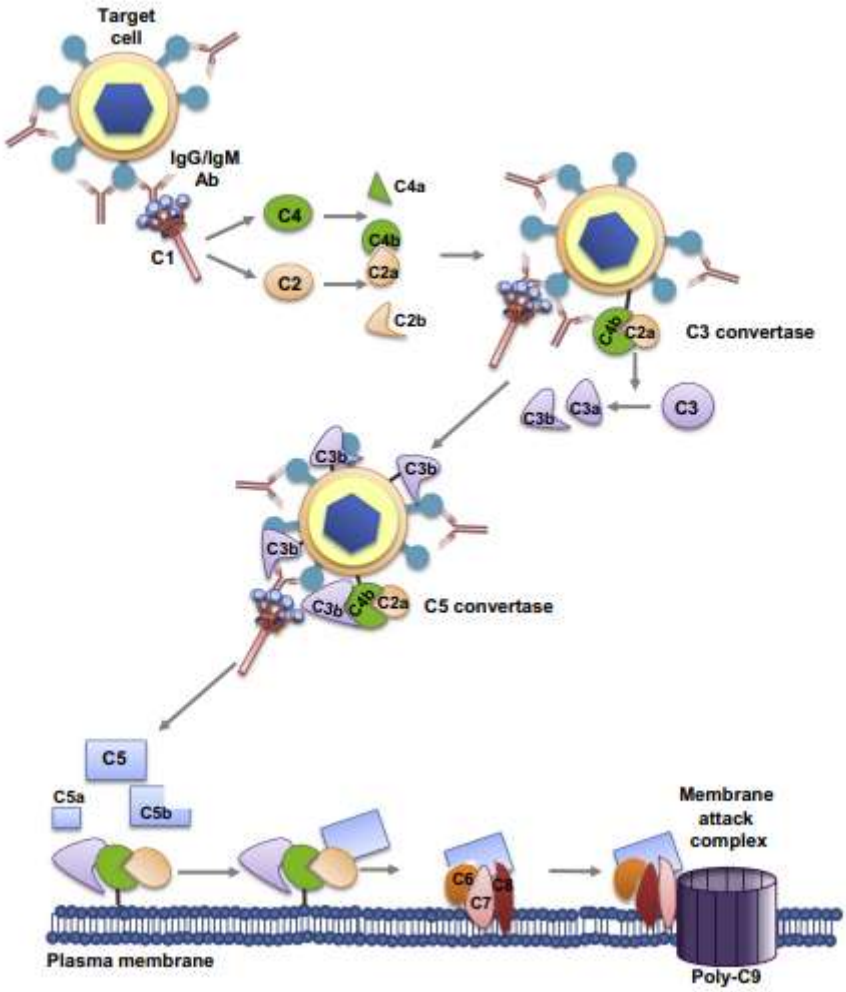
Immunotherapy can also be divided as **antibody based therapies, cellular immunotherapy, cytokine immunotherapy**

Antibody based immunotherapy

Since their discovery, antibodies have been viewed as ideal candidates or "magic bullets" for use in targeted therapy in the fields of cancer, autoimmunity, and chronic inflammatory disorders. (21)

Antibodies may target tumor cells by engaging surface antigens differentially expressed in cancers. By interacting with surface antigens that are differently expressed in malignancies, antibodies can engage tumour cells. For instance, Rituximab (1997), cetuximab (2004), and infliximab (2002) were examples of first-generation monoclonal antibodies utilised in cancer therapy. Infliximab was used to treat autoimmune illnesses. rituximab targets HER2 in breast cancer, cetuximab targets EGFR in colorectal cancer, and rituximab targets CD20 in non-Hodgkin B cell lymphoma. By obstructing the growth and survival pathways of ligand-receptors, the antibodies can cause tumour cell death. Innate immune effector mechanisms that interact with the Fc component of antibodies through Fc receptors (FcR) are also becoming recognised as being crucial. The processes include complement-mediated cytotoxicity (CMC) and antibody-dependent cellular phagocytosis (ADCP), as well as antibody-dependent cellular cytotoxicity (ADCC) (ADCP)(22)The area of cancer immunotherapy was revitalised by the discovery of antibodies that block checkpoint-mediated suppression of T cell responses. Unprecedented long-lasting remissions were brought on by these antibodies in individuals with advanced stage cancers who do not respond to traditional therapy, most notably melanoma and lung cancer.

Complement-mediated cytotoxicity



**Complement-dependent cytotoxicity is activated by the traditional complement system. When C1q identifies and binds to the Fc region of the immunoglobulin, the classical cascade is triggered (Ig). Then, a conformational shift in C1q activates C1r/C1s. C4 is split into C4a and C4b by C1s. The target cell's surface is immediately bound by C4b, and C1s then cleaves C2 into C2a and C2b. C3 convertase is created when C2a and C4b join forces. After C3 is split into two pieces by C3 convertase, C3b attaches to the C3 convertase complex to create C5 convertase. C5b then forms a loose association with the C5 convertase complex after C5 convertase splits C5 into two. C5b is subsequently bound by complement elements C6 and C7, which causes it to separate from the C5 convertase complex and bind inside the lipid bilayer. After C8 attaches to C5b-C7, the structure of the lipid bilayer is strengthened; C9 then binds to C8, activating it. C9 penetrates the lipid bilayer, polymerizes, and fully forms the membrane assault complex. This causes a pore to form on the target's surface, causing cell lysis.*(23)

Human IgG1 Fc-containing antibodies have the ability to initiate complement-mediated cell killing. One method they use to accomplish this is a process known as complement-dependent cytotoxicity, which involves the membrane assault complex directly killing tumour cells using complement.(24)The classical route (CP), which is strongly initiated by IgM/IgG clusters, is frequently referred to as being "antibody-dependent." On the other hand, the adaptable pattern recognition molecule (PRM) C1q activates complement by identifying specific structures either directly on microbial and apoptotic cells or via endogenous PRMs such immunoglobulins and pentraxins (e.g., Creactive protein; CRP). The proteases C1r and C1s are successively activated upon surface binding of C1q2,3 as a component of the C1 complex (i.e., C1qr2s2). After that, C1s splits C4 into C4a and C4b, revealing a previously concealed thioester and causing covalent deposition of C4b on surfaces close to the activation sites (i.e., opsonization).(25)Phagocytosis and proinflammatory signals are essential for complement-mediated defence against the majority of invading cells. The G-protein-coupled receptors known as the C3a receptor (C3aR) and the C5a receptor are constantly produced during activation and amplification and cause proinflammatory

signalling. Neutrophils, monocytes, and macrophages are drawn to areas of complement activation by the potent chemoattractants C3a and C5a Through the interaction of opsonins with complement receptors, they consequently encourage phagocytosis.

Cellular immunotherapy

Cellular immunotherapy is the practise of giving living cells to a patient; this type of immunotherapy can be active, like a dendritic cell (DC) vaccine, in which case the cells can prompt the patient's body to produce an anti-tumor response, or it can be passive, like the administration of antibodies.

Adoptive cell transfer (ACT), a form of passive therapy in which the cells have inherent antitumor activity, uses autologous or allogeneic lymphocytes that may or may not have undergone any modifications.(26)

Interactions between tumours and immune cells led to a new paradigm in cancer immunology, which is separated into three phases of cancer immunoediting: elimination, equilibrium, and escape. Immunity plays a dual role in the tumour microenvironment (TME). Malignant cells are eliminated in the first stage, or "elimination," by immune system cells. Once in a "equilibrium" state, the few tumour cells that escape immune death undergo molecular editing (mutations, gene rearrangements). Immune system cells and tumour cells coexist in the TME at this stage. Despite not being able to totally eradicate cancer, the immune system prevents it from spreading or metastasizing further.(27)

Cytokine immunotherapy

Soluble proteins called cytokines facilitate cell-to-cell communication. Clinical research resulted in the licencing of recombinant interferon-alpha and interleukin-2 for the treatment of numerous malignancies, even though efficacy was only moderate, on the basis of the finding of the potent anti-tumor activities of several pro-inflammatory cytokines in animal models.

On their cellular membrane, cytokine target cells express high-affinity receptors. The receptors then set off intracellular signalling after cytokine interaction, which changes gene transcription. Hence, cytokines affect cell division and proliferation as well as initiate or alter specific cellular processes. The information acquired from the concentration and timing of exposure to various cytokines is integrated by target cells that express the matching sets of receptors. As a result, high levels of complexity are a common hallmark of synergistic or antagonistic relationships between several cytokines.

Pro-inflammatory cytokines, which influence every stage of the cancer immune cycle, can support cancer immunotherapy. Consequently, cytokines can improve antigen priming, increase the number of effector immune cells in the TME and enhance their cytolytic activity. Yet, biotechnological methods must be used to modify the cytokines' pharmacological properties in order to create medications based on them.(28)

Role of immunotherapy in oral oncology

The microenvironment of head and neck squamous cell carcinoma is characterised by an aberrant cytokine profile that favours the release of immunosuppressive cytokines over activating cytokines. Dendritic cell function is inhibited by the inflammatory cytokine VEGF, which is generated by tumour cells and has been discovered in high concentrations in individuals with head and neck squamous cell carcinoma.(6)

In HNSCC/OSCC, tumor-induced immune evasion—which is partly mediated by T cell-suppressive immunological checkpoints—is the main cause of recurrence and metastasis. By blocking the inhibitory signals, immune check point inhibitors such atezolizumab, durvalumab, avelumab, and CTLA-4 ipilimumab and tremelimumab increase T cell activation and promote endogenous anticancer action.(29)

HNSCC patients typically have immune system abnormalities, including decreased natural killer cell activity, poor antigen presentation, low absolute lymphocyte counts, and alterations in genes that control inflammation. Programmed death-1 (PD-1) receptor, an immunological checkpoint in a healthy immune system, is largely expressed on the surface of activated CD4+ and CD8+ T cells. When PD-1 is activated by any of its ligands, programmed death-ligand 1 or 2 (PD-L1 or PD-L2), T-cell activation is inhibited, which reduces the inflammatory response. Tumor-infiltrating lymphocytes, particularly T helper 1 cells, stimulate interferon-mediated signalling and promote the expression of PD-L1 on cells in the tumour environment in HNSCC and other solid tumours.(30)

Immune checkpoint inhibitors

The duration and intensity of immune responses are controlled by coinhibitory pathways (also known as "immune checkpoints") that prevent excessive autoimmunity. Costimulatory molecules alter T-cell activation. Tumor immune evasion can be accomplished by manipulating immunological checkpoints.PD-1 and its ligands PD-L1 and PD-L2 are two examples, as are CTLA-4 and its ligands CD80 and CD86. Syngeneic murine tumours are rejected when anti-CTLA-4 MoAb treatment is blocked.Ipilimumab, an anti-CTLA-4 MoAb, showed clinical promise and received FDA approval in 2011 for use in patients with metastatic melanoma.Tremelimumab, which is being studied in individuals with HNSCC, also targets CTLA-4. Anti-PD-1 or PD-LMoAbs have more recently

shown clinical benefit, whether used alone9–11 or in combination with ipilimumab12, especially in patients with HNSCC.(31)

Elimination, equilibrium, and escape phases make up the three stages of cancer immunoediting. The immunological escape phase develops as a result of prolonged antigen stimulation that culminates in a phenotype of worn-out T cells. During T-cell activation, inhibitory receptors (IRs), also known as immunological checkpoints, are produced. This signalling causes the immune response to be suppressed as the antigen is removed from the body. CTL4 is a cytotoxic T cell antigen. T-cell activation is controlled by CTLA4, a competitive antagonist of the CD28-B7 interaction. In addition to promoting immune system activation, CTLA4 is constitutively expressed on regulatory T cells (Tregs), a group of cells that prevents antitumor immunity in healthy people while maintaining self-tolerance.(32)

Conclusion

Individuals who react to IT have a long-lasting and durable response; however, unlike cytotoxic therapy, response to IT may not be noticed right away. Pseudo-progression, or early tumour progression prior to response, is hypothesised to be caused by an increase in tumour immune cell infiltration.

Because to this issue, researchers have started using alternate clinical endpoints and radiologic criteria to assess the clinical response of IT.The rise of IT agents has caused the field of oncology to change quickly. With the help of these agents, there is hope that patients will soon have another therapeutic alternative after trying out a variety of other techniques. Intelligent combinatorial trials, as well as assessments of these medications in the first-line scenario and in early-stage disease, will be the foundation of IT in the future.(32)

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