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Immunotherapy in oral diseases

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Abstract

Immunotherapy is one of the newer entities which is promising, at least can be very much helpful as an adjuvant therapy. This newer modality of the treatment in the field of cancer treatment may be the fourth pillar supporting surgery, chemotherapy, and radiotherapy. Careful selection of patient is the key for success of immunotherapy, which is based on patient's immunological contexture.

Immunotherapies are disease management strategies that target or manipulate components of the immune system. Infectious diseases pose a significant threat to human health as evidenced by countries continuing to grapple with several emerging and re-emerging diseases

Novel and innovative therapeutic strategies are necessary to overcome the challenges typically faced by existing infectious disease prevention and control methods such as lack of adequate efficacy, drug toxicity, and the emergence of drug resistance.

As evidenced by recent developments and success of pharmaceuticals such as monoclonal antibodies (mAbs), immunotherapies already show abundant promise to overcome such limitations while also advancing the frontiers of medicine.

This review aimed to present the fundamental aspects of tumor immunity and immunotherapy, focused on various oral diseases.

Keywords: Immunotherapy, Vaccine, Checkpoint Inhibition, T-cells

Introduction

Immunotherapy or biological therapy is the treatment of disease by activating or suppressing the immune system. Immunotherapies designed to elicit or amplify an immune response are classified as activation immunotherapies, while immunotherapies that reduce or suppress are classified as suppression immunotherapies.

In recent years, immunotherapy has become of great interest to researchers, clinicians and pharmaceutical companies, particularly in its promise to treat various forms of cancer.[1,2,3] As a result, the standard of care for cancer is changing, as well as gaining complexity for managing patient care.[4-9]

Immunomodulatory drugs currently have unknown effects on the body.[10]

Cell- based immunotherapies are effective for some cancers. Immune effector cells such as lymphocytes, macrophages, dendritic cells, natural killer cells (NK Cell), cytotoxic T lymphocytes (CTL), etc., work

together to defend the body against cancer by targeting abnormal antigens expressed on the surface of tumor cells. Vaccine-induced immunity to Covid-19 relies mostly on an immunomodulatory T cell response.[11]

Therapies such as granulocyte colony-stimulating factor (G-CSF), interferons, imiquimod and cellular membrane fractions from bacteria are licensed for medical use. Others including IL-2, IL-7, IL-12, various chemokines, synthetic cytosine phosphate-guanosine (CpG) oligodeoxynucleotides and glucans are involved in clinical and preclinical studies.

Immune system is the guardian of our body; it detects and destroys abnormal cells that are found in milieu. Abnormal cells may be foreign bodies, microorganisms, and even cancer cells. Ehrlich proposed that the immune system can search and attack transformed cells before any clinical presentation. Though cancer cells originate in the body, their genetic heterogeneity and components make them noticeable to the immune system. William Coley in 1891 found regression in cancer when he injected inactivated bacterial toxin (Coley's toxin). The immune system mainly comprises two arms, namely, innate and adaptive immunity.

The innate immunity encompasses macrophages, natural killer (NK) cells, dendritic cells, and eosinophils, and the adaptive immunity includes B and T lymphocytes, commonly known as B and T cells. B cells produce antibodies and T cells generate CD4+ and CD8+ cells. Cancer cells escape immune system by decreased expression of cell surface antigen, by secreting antigen that inactivates immune system, and by inducing microenvironment to secrete substances suppressing immune responses, thereby promoting tumor growth.[1,2]

Immunotherapy involves the stimulation of specific components of immune system, thereby strengthening it to counteract the signals that suppress the immune system.

Immune surveillance and Immune Editing

The concept of immune surveillance was later discovered when the tumor-associated antigen was discovered in transplanted animal model.[11] The immune modulators such as levamisole were used for adjuvant therapy in colorectal cancers but had guarded results. Bacillus Calmette-Guérin (BCG), a well-known tuberculosis vaccine, has shown tumor regression in bladder cancer when injected intravesically.[12]

The immune surveillance has evolved into immune editing (a new concept put forward by Schreiber *et al*., which comprises three phases. The immunosurveillance or elimination phase is the first phase, in which the tumor growth is controlled by destruction of nascent cancer cells by T-cell activation via antigen presentation.

Equilibrium phase is the second phase, which is characterized by tumor heterogeneity due to genetic instability of cells. In this phase, the tumor growth is in a steady state, either by growth enhancement or by inhibition. The escape phase is the final phase in which tumor cells escape or suppress immune system, thereby leading to tumor progression.[13,14]

Immunotherapy in oral diseases

Lichen planus

Pembrolizumab is a humanized antibody to programmed death receptor 1 (PD-1) that inhibits the interaction between PD-1 and its ligand, programmed death ligand 1 (PD-L1). While immunotherapies with anti-PD-1 antibodies have shown significant clinical efficacy in the treatment of advanced-stage melanoma, non-small-cell lung carcinoma, and several other malignant diseases, they can induce T-cell activation that causes various immune-related adverse effects (irAEs)

including maculopapular rash, vitiligo, pruritis, thyroiditis, hepatitis, diabetes mellitus, hypophysitis, and myasthenia gravis.[15]

In addition, recent studies reported that lichen planus (LP) is also a common cutaneous irAE associated with anti-PD-1 therapies. LP is a T-cell-mediated inflammatory keratinizing disease that develops in skin and mucosa, and LP involving the scalp has rarely been described. We herein present an unusual case of pembrolizumab-induced LP that occurred on the scalp of a patient with lung adenocarcinoma.

Immunotherapy with pembrolizumab, an anti-PD-1 antibody, can induce T-cell activation that results in various immune-related adverse effects such as lichenoid tissue reaction. However, lichen planus is generally found on the extremities and/or oral mucosa, and unlike in this case, the scalp is rarely affected.[16]

Several studies are listed in the literature concerning the topical use of tacrolimus, a drug with immunosuppressive activity and structurally related to sirolimus, in the symptomatic therapy of lichen planus of the oral mucous membranes, a disease which presents analogies with types of alterations that are precancerous. In general, the results of the experiments conducted were encouraging but we want to emphasize that the topical use on oral precancerous lesions has not yet been approved.[17]

Oral submucosal fibrosis

Oral Submucous Fibrosis has been defined as an insidious chronic disease of unknown etiology, reported mainly in Indians, and affecting the entire oral cavity.

The basic change is a fibro-elastotic transformation of the connective tissue in the lamina propria preceded by vesicle formation. In its later stages the oral mucous membrane becomes stiff and the patient suffers from trismus and resultant difficulty in eating[18]

The most widely accepted theory of the etiopathogenesis of Oral Submucous Fibrosis. is that of an autoimmune response. By opposing the actions of soluble factors released by sensitized lymphocytes following activation by specific antigens, hyaluronidase is known to decrease collagen formation by virtue of its specific action on hyaluronic acid, which plays an important role in the formation of collagen.

These effects of steroids and hyaluronidase may be responsible for the better results obtained in respect of trismus and fibrotic bands in the group receiving a combination of hyaluronidase and dexamethasone[19]

Fibrosis should be given a course of local injections of hyaluronidase bi-weekly for the first three weeks, followed by a combination of dexamethasone and hyaluronidase locally for the next seven weeks, to achieve quicker and maximal improvement

Leukoplakia

Oral potentially malignant disorders (OPMDs) comprise a range of clinical-pathological alterations that are frequently characterized by an architectural and cytological derangements upon histological analysis. Among them, oral leukoplakia is the most common type of these disorders. Currently, the definition of leukoplakia is a “white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer”. In addition, leukoplakia is primarily a clinical term and has no specific histology[20]

Going beyond the specific role of cluster cells or cytokines, the data of this brief analysis describe the existence of a relationship between the activity of the immune system, sometimes also of an inhibitory type, and the evolution of precancerous lesions of the oral cavity.

There are several lines of evidence that many cancer chemoprevention agents, such as aspirin, COX-2 inhibitors, aromatase inhibitors, and bisphosphonates, act by enhancing immunosurveillance and/or inverting the immune evasive processes that potentially malignant disorders induce.

The use of PD-1 inhibitors appears interesting in patients with advanced disease of the head and neck area; several experimental studies also seem to suggest the possible use of PD-1 inhibitors as drugs for prevention. [21]

Four administrations of Pembrolizumab are given to patients affected by oral IEN and characterized by molecular high-risk profile of LOH, such as 3p14 and/or 9p21 and other chromosomic alterations. However, the route of administration, the elevated cost of PD-1 antibodies, and the high risk of toxicities might limit the clinical efficacy of this treatment[22].

Emerging evidence shows that inhibition of mTOR could influence the anti-tumor immune response. Even though the PI3K/mTOR pathway is the most frequently started up, these new results show that the combination of immune oncology agents and mTOR inhibitors could provide novel precision therapeutic options for HNSCC[23].

Oral cancer

According to the Global Cancer Report in 2018, head and neck squamous cell carcinoma (HNSCC) was the eighth most frequent cancer in the world, and the mortality rate ranked eighth among all cancers.1 Despite the trend of improved survival rates for patients with cancer over the past 20 years, local and distant failure after treatment of advanced HNSCC occur in up to 40% and 30% of patients, respectively.

Immunotherapy can be broadly divided into active and passive.

Active immunotherapy involves attack of tumor cells by directing immune system (tumor as target). The immune cells were derived from blood or tumor of the patient, cultured in laboratory, and put back into the body, which in turn attack the tumor cells. In active immunotherapy, NK cells, dendritic cells, and cytotoxic T cells were commonly used.

Passive immunotherapy involves enhancement of immune system by targeting cell surface receptors, which in turn can form antibody-dependent cell-mediated (immunity) cytotoxicity (ADCC), for example, ipilimumab[24].

Checkpoint inhibitors

The discovery of inhibitory pathways, which suppress T-cell activity leading to tumor growth, made a big revolution in the field of immunotherapy. Blocking these inhibitory pathways via monoclonal antibodies, which are otherwise called checkpoint inhibitors, has proved to be one of the best ways to regress tumor.[25]

Checkpoint inhibition has a variety of applications in immune oncology ranging from lung cancer to oral cancer.

Among checkpoint inhibitors, anti-CTLA-4 and anti-PD-1 antibodies are commonly used for therapeutic purposes. Anti-CTLA-4 antibodies have broader T cell function compared to anti-PD-1 antibodies, which reinstates that anti-CTLA-4 has more side effects than anti-PD-1. Recently, anti-PD-L1 ligand is in the late phase of commercial development for clinical practice with name durvalumab.

Ipilimumab was approved by the European Organisation for Research and Treatment of Cancer (EORTC) for the adjuvant therapy in patients with high-risk melanoma.[26,27]

The combination of nivolumab and ipilimumab was approved in the United States for the treatment of BRAF-negative melanoma Apart from anti-PD-1 and anti-CTLA-4 antibodies, other checkpoint inhibitor receptors such as lymphocyte-activation gene 3 (LAG3), mucin domain 3 (TIM-3), and T-cell immunoglobulin have demonstrated therapeutic effects in clinical trials in combination with PD-1 agents. The combination of radiation and PD-1 blockade was proved to be synergistic in the treatment of cancer.[28]

Immune-related adverse reactions are common with checkpoint inhibitors, especially with anti-CTLA-4 antibodies, as these act in the priming phase. The autoimmune reactions manifested were hepatitis, rash, hypothyroidism, adrenal insufficiency, colitis, and so on. Pembrolizumab was approved by the FDA for treating patients with recurrent head and neck squamous cell carcinoma (HNSCC).

Targeted monoclonal antibodies

Monoclonal antibodies are made from either human or murine antibody components that bound to tumor-associated antigen leading to ADCC. The best example in this group which is used therapeutically is antibody against epidermal growth factor (EGFR). Deregulation of EGFR leads to the inhibition of apoptosis, invasion, metastasis, and angiogenic potential.

Compared to normal mucosa, EGFR level is increased in 95% of HNSCC. In HNSCC, the expression of EGFR is increased, which correlates with aggression of the cancer. EGFR is responsible for tumor progression in many solid tumors, especially in HNSCC.[29]

Monoclonal antibodies such as cetuximab and panitumumab are EGFR targeted therapies; they are proven to be effective against HNSCC either alone or in combination with radiotherapy. Muc-1 levels are found to increase in HNSCC; antibodies against it have shown regression in the tumor in advanced cancer. p53 is normally mutated in HNSCC; antibodies to mutated p53 proved to be useful in treating HNSCC with node involvement.[30]

Cancer vaccine

Cancer vaccines are made from patients' tumor cells, which strengthen defense mechanism. These educate T cells to recognize and kill the cancer cells in the tumor. Cancer vaccine is designed in such way that it contains a desired antigen, may be single antigen such as RNA, DNA, or peptides, or multiple antigens such as pulsed dendritic cells or whole cells. Vaccines can generate long-lived immunity with minimal toxicity and also can be combined with other immunotherapy techniques. However, these vaccines have some disadvantages such as they are expensive, cannot be used for fast-growing tumors, and take long time to get immune response.[31,32]

Cancer vaccine types

Antigen vaccines: They are made up of specific antigens from patients' tumor, which in turn can destroy cancer cells. With advancements in genetic engineering, large-scale production is feasible in future.

Dendritic cell vaccines: The role of dendritic cell to recognize and attack tumor cells is well understood. This vaccine, developed in laboratory, has a great potential in tumor regression.

DNA or RNA vaccines: These vaccines made of either DNA or RNA material proved to be excellent candidates for tumor regression.

Whole cell vaccines: Instead of specific antigens, DNA, or RNA, these vaccines are developed from entire cancer cells.[33,34]

Cytokine immunotherapy

Cytokines are molecular messengers that allow the cells of our immune system to communicate with each other to generate a coordinated response to a target antigen (cancer cell). This immunotherapy stimulates immune cells through a complicated pathway, thereby increasing coordination between tumor cells and stromal cells. In recent years, a number of cytokines have been developed for the treatment of cancer.

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

IFN α: These cytokines when injected subcutaneously in renal cell carcinoma have shown tumor regression. These have shown excellent results in stage 3 melanoma. The combination of IFN α and IL-2 showed partial response and higher toxicity.[35]

IL-2: It is an FDA-approved cytokine for metastatic melanoma. These cytokines increase level of NK cells and tumor-infiltrating lymphocytes (TILs) in the lesion. Peri lymphatic IL-2 administration has increased the survival rate of patients with HNSCC; increased tumor reactive T cells were found in patients who underwent monoclonal antibody therapy after surgery. The therapeutic application of cytokines is challenging because of their higher degree of pleiotropism. They act on many cell types in the body, which leads to many opposing effects such as diarrhea, fatigue, pancytopenia, and tiredness.[36,37]

Conclusion

Cancer treatment is one of the challenging aspects in the medical field; the treatment modalities ranging from surgery to chemotherapy and radiation are yielding mixed results. To overcome this hurdle, newer innovative approaches are needed to reduce the morbidity and mortality of the patients. Immunotherapy is one of the newer entities that is promising, at least can be very much helpful as an adjuvant therapy.

The disadvantages of surgery such as recurrence of tumor or non-resect able lesion and toxicity of radiotherapy or chemotherapy can be substantially reduced by immunotherapy when used in combination with these treatment modalities. Scientists and clinicians are involved in more number of researches and preclinical and clinical trials in the field of immunotherapy.

This newer modality of the treatment in the field of cancer treatment may become the fourth pillar supporting surgery, chemotherapy, and radiotherapy. Careful selection of patient is the key for success rate of immunotherapy, which is based on patient's immunological contexture.

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