IMMUNOTHERAPY IN HEAD AND NECK CANCER

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ABSTRACT

Introduction: Head and neck cancer is the 8th with the highest mortality rate and a low 5-year survival rate of 40-50 %. In patients who experience recurrence or metastases, especially in nasopharyngeal cancer and are HPV-positive, first-line immunotherapy can be performed through immune checkpoint inhibition using antibodies against program med death (PD-1) inhibitors. **Objective:** To know the action of immunotherapy against head and neck cancer cells. **Conclusion:** The programmed death (PD-1) inhibitor is an immunotherapy technique widely used today in head and neck cancer. As with other therapy modalities in general, it is necessary to pay attention to the side effects of im munotherapy that affect the body in the form of toxicity.

Keywords: malignancy, malignancy in the head and neck

Introduction

Head and neck cancer, mainly Squamous Cell Carcin oma (SCC), is a common and deadly type of cancer. It is often caused by smoking and alcohol consumption. The symptoms can be non-specific, making early detection d ifficult. Treatment options include surgery, radiotherapy, and chemotherapy, but they often fail due to the comple x nature of the cancer. Immunotherapy, particularly PD-1 inhibitors, has emerged as a promising treatment for h ead and neck cancer. However, it is important to conside r and manage the potential side effects of immunothera py.[1]

Squamous Cell Carcinoma

Definition

Cancer or malignancy is a group of diseases due to u ncontrolled cell growth that can infiltrate normal body tis sues.[4] Cancer cells also can migrate from the primary m ass through the blood and lymphatic system to other org ans. This process is called metastasis. [7] Head and neck c ancer can grow from different sources or origins, from th e lips to the cervical oesophagus. [1,2,4]

Squamous cell carcinoma, which arises from the muc osal epithelium located in the oral cavity, pharynx, and la rynx, represents the predominant form of malignancy ob served in cases of head and neck cancer. This specific t ype of cancer originates from the thin, flat cells that line these regions, known as squamous cells. The developme nt of squamous cell carcinoma in these areas is particul arly noteworthy due to its high prevalence and incidence rates. [3,4]

Epidemiology

Head and neck cancer, specifically Head and Neck S CC (HNSCC), ranks 8th in global cancer occurrence and mortality rates. The 5-year survival rate is low, ranging fr om 40% to 50%. Age and gender contribute to the develo pment and prognosis of HNSCC, with males being more commonly affected. These factors are important conside rations in diagnosis, prognosis, and treatment.[5]

Risk Factor

Head and neck cancer can be influenced by factors such as:[1]

a. Smoking and alcohol consumption

Cigarettes contain carcinogenic substances like nit rosamines and polycyclic aromatic hydrocarbons (P AHs) that can cause head and neck cancer by dam aging DNA and activating oncogenes. Alcohol cons umption also increases the risk and growth of canc er cells by facilitating the entry of carcinogens, inhi

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biting cell differentiation, and disrupting DNA repair and immune system functions.[6-9]

. HPV Infection

HPV-16 infection is an independent risk factor for head and neck cancer, particularly HNSCC of the oropharynx. It is found in 25% of HNSCC cases. Sexual contact is associated with an increased risk of HPV-related cancer. HPV infection leads to increased PD-1 expression, decreased COX-2 expression, and the release of proinflammatory cytokines. This combination contributes to tumor cell resistance to the immune system, resulting in a poorer prognosis.[11]

b. Diet

Diet plays a significant role in head and neck cancer risk. Regular consumption of non-starchy foods like fruits, vegetables, and carotenoid-rich foods lowers the risk, while frequent consumption of red meat increases the risk. Including more fruits and vegetables in your diet and reducing red meat intake can help lower the chances of developing head and neck cancer[1]

c. Family History

Family history suggests a genetic component in head and neck cancer development. Genetic polymorphisms in enzymes involved in carcinogen processing and genes related to DNA repair and apoptosis increase the risk of HNSCC.[9]

d. Poor oral hygiene and dental health are potential risk factors for head and neck cancer. Accumulated dental plaque and toxins in the oral cavity can increase the risk. Chronic irritation from tobacco and alcohol use further contributes to metabolic disorders and cancer development[1]

Diagnosis

Diagnosing head and neck cancer involves a comprehensive evaluation, including patient history, physical examination, and supporting tests. Symptoms vary depending on the cancer location, leading to challenges in early detection. Histopathological examination through biopsies confirms the presence of cancer. Proper biopsy selection is crucial for accurate diagnosis. HNSCC is characterized by atypical cells and squamous cell differentiation. Staging and HPV infection status are important prognostic factors, determined using the TNM system[5]

Treatment

Head and neck cancer is typically managed through a variety of therapeutic approaches, including surgical intervention, radiotherapy, and chemotherapy. Surgery, as one of the primary treatment options for head and neck cancer, involves the removal of the malignant tumor and potentially affected adjacent tissues. The extent of surgical intervention varies depending on the size and location of the tumor, and can range from minimally invasive procedures, such as endoscopic resections, to more extensive operations involving the removal of lymph nodes or even partial or total removal of affected structures, such as the tongue, jaw, or larynx. Surgical interventions aim to eliminate the tumor while preserving vital functions and maintaining the patient's quality of life. Surgery is commonly used for oral cancer, while radiation therapy is primarily employed for pharynx and larynx cancer. Single interventions like surgery or radiation can achieve high cure rates for small tumors without nodal involvement.[5]

For cases with extra-nodal spread, narrow surgical margins, or perineural invasion, recurrence risk is higher. High doses of cisplatin and radiation can extend disease-free time in such cases. Chemoradiation is the preferred treatment for T3 staging with multiple node involvement and function preservation. In cases of recurrence or metastases, options include resection, re-irradiation (especially for nasopharyngeal cancer), or metastasectomy (especially for HPV-positive patients). First-line therapy involves immune checkpoint inhibitors like pembrolizumab or PD1-targeting antibodies. Patients ineligible for first-line therapy can receive a combination of cetuximab and chemotherapy.[5]

Prognosis

Many patients are diagnosed at a late stage, leading to lower chances of successful treatment. Delayed treatment is also linked to an increased risk of local failure and higher mortality rates.[3,12]

Immunotherapy

History

Immunotherapy has a long history, dating back to the late 19th century when Dr. William Coley observed tumor regression in a patient after developing an infectio

n. However, due to the advent of radiotherapy and limite d success rates, the idea was abandoned. It wasn't until the 1980s that the role of T cells in cancer prevention w as recognized, leading to the development of modern im munotherapy drugs.[6]

Class of Immunotherapy

Immunotherapy has several classes of agents t hat can be given, which in the immunotherapeutic appro ach are divided based on their mechanism of action, incl uding checkpoint inhibitors, cytokines, monoclonal antib odies, vaccines, and adoptive cell transfer.[6,7]

Checkpoint Inhibitors

Within the HNSCC tissue, there is a notable dec rease in the population of lymphocytes, which are a criti cal component of the immune system responsible for rec ognizing and eliminating abnormal cells. This diminished presence of lymphocytes can impair the body's immune r esponse against the cancer cells, limiting the ability to m ount an effective antitumor immune defense. This tissue is called a cold tumour. Its caused by the presence of im mune checkpoints, namely molecules whose job is to ma intain T cell tolerance to host cells and protect surroundi ng cells by suppressing the immune response. [2] Drugs s uch as ipilimumab have become standard therapy for me lanoma with metastases.[2,12]

Cytokine (Interferon)

The use of interferon in cancer immunotherapy began with a study conducted in 2000. This study stated an increased risk of cancer in rats with lower interferon-gamma (IFN-γ) levels, IFN-γ receptors and cells that pro duce IFN-γ. Research conducted in 2006 reported a goo d response in patients with melanoma who were injecte d with interferon alfa-2b. This drug, PegIntron, was appr oved by the FDA as a treatment for melanoma with meta stases in 2011.[6,7,8]

Monoclonal Antibody

The dysregulation of EGFR signaling can lead to uncontrolled cell growth and the development of tumors in the head and neck region. To specifically target the ab errant EGFR signaling and impede tumor growth, a mono clonal antibody called cetuximab has been developed. C etuximab is designed to bind to EGFR with high specifici ty, effectively inhibiting its activity and downstream sign aling cascades. By binding to EGFR, cetuximab blocks th e binding of natural ligands that would typically activate the receptor, thereby preventing the subsequent cellular responses that promote tumor growth and progression. One of the primary mechanisms by which cetuximab exe rts its anticancer effects is through the inhibition of EGF R-mediated cell proliferation. By blocking EGFR signalin g, cetuximab interferes with the intracellular pathways t hat drive cell division and replication. This impediment t o cell growth can lead to the suppression of tumor growt h and potentially induce cancer cell death.[7,14]

Vaccines

The HPV vaccine Gardasil was approved by the FDA in 2006 to prevent HPV-related cancers. In 2014, a multicenter trial showed improved survival in pancreatic cancer patients with allogeneic pancreatic tumor cell GM CSF treatment. In 2015, the FDA approved talimogene la herparepvec (Imlygic) as an intralesional injection for m elanoma. Ongoing research focuses on brain tumor patie nts.[6,7,13]

Adoptive cell therapy

During the early 2000s, research focus ed on T cells for cancer treatment, including adoptive T c ell therapy and chimeric antigen receptor (CAR) T cells. I nterleukin-2 (IL-2) was explored to enhance cell transfer . Genetically engineered T cells showed promising respo nses in lymphoma and leukemia patients, suggesting the ir potential for cancer treatment. This research laid the f oundation for further studies on adoptive T cell therapy a nd genetically modified T cells in cancer treatment.[6,7]

Immunotherapy in Head and Neck Cancer

Immune Response to Head and Neck Cancer Cells

Within the context of head and neck cancer, genetic mut ations affecting the human leukocyte antigen (HLA) and antigen processing machinery (APM) genes can significa ntly impede the ability of cytotoxic T cells (CTL) to ident ify and eliminate cancer cells. These mutations have a n egative impact on the prognosis of patients. Identifying t hese mutations is crucial for developing effective treatm ent strategies. Restoring the function of HLA and APM g enes may enhance CTL-mediated immune responses an d improve patient outcomes. CTL activation and regulati on are influenced by signals mediated by T cell receptor s (TCR), B7 molecules, CD28, and immune checkpoint re

ceptor CTLA-4. CTLA-4 can suppress T cell function and cause immune suppression. Understanding these mecha nisms can help develop targeted therapies for head and neck cancer.[2,13,14]

In head and neck cancer, increased PD-L1 expression co ntributes to immunosuppression and poor prognosis. TI M-3 expression is associated with metastasis and recurr ence. Targeting the TIM-3/Galectin-9 axis and inhibiting immune checkpoint signals can be potential therapeutic strategies. LAG-3 and PD-1 co-expression leads to decr eased CD8+ function. Tumors induce immune suppressi on through regulatory T cells and cytokine production, b oth locally and systemically. Understanding and address ing these mechanisms can help develop effective treatm ents for head and neck cancer [13,14,,15]

Tumor cells employ various mechanisms to eva de the immune system, including loss of antigen express ion, secretion of immunosuppressive cytokines, recruitm ent of immunosuppressive cells, and exploiting immune checkpoint pathways like PD-1. The interplay between i mmunostimulatory and immunosuppressive events withi n the tumor environment is crucial to consider, especiall y in the context of immunotherapy. Pro-inflammatory cyt okines and cytotoxic T cells play significant roles in com bating tumor cells[13,14]

Use of Immunotherapy in Head and Neck Cancer

Immunotherapy aims to inhibit the evasion of ca ncer cells from the immune system. It can be achieved t hrough various techniques such as targeting EBV, kinase inhibitors, PD-1 inhibitors, dendritic cell therapy, CAR-T therapy, and cancer vaccines to generate anti-cancer im mune responses.[7,14, 15]

Immunotherapy Targeted with Epstein-Barr Virus

In EBV-targeted immunotherapy, the goal is to manipulate cytotoxic T lymphocytes to attack the infecte d cancer cells by targeting specific epitopes.[7,8]

Kinase Inhibitor Therapy

Kinase inhibitor therapy, exemplified by drugs s uch as erlotinib, can bolster the antitumor immune respo nse through two mechanisms: immunogenic modulation and heightened susceptibility of tumor cells to immune-mediated destruction. Erlotinib, specifically a tyrosine ki nase inhibitor, impedes the proliferative impact of EGFR by inhibiting its phosphorylation and disrupting intracellu lar signaling. As a result, erlotinib induces apoptosis and impedes the growth of tumor cells[7]

Therapy Programmed Death (PD-1) Inhibitors

PD-1 inhibitors are important immunotherapy te chniques used to prevent immune suppression by tumor cells. Drugs like nivolumab and pembrolizumab target P D-1 and have shown promising results in clinical trials fo r various cancers, including head and neck cancer.[12]

Nivolumab and pembrolizumab are PD-1 immun e checkpoint inhibitors that have shown effectiveness in treating head and neck cancer. [14, 15]

Dendritic Cell Therapy

Dendritic cells, derived from CD34+ stem cells, are antigen-presenting cells that can be activated to enh ance the immune response against tumors. Immunother apy utilizing dendritic cells involves delivering antigens d irectly to specific dendritic cells or using dendritic cell ag onists to stimulate immune responses, Further research is needed to optimize dendritic cell-based immunothera py for clinical use[7]

Therapy Chimeric Antigen Receptors (CAR-T)

CAR-T, a synthetic receptor, boosts T cell funct ion against cancer cells, with the third generation exhibit ing superior efficacy compared to earlier versions. This m ethod holds promise for enhancing patient outcomes an d minimizing side effects linked to conventional cancer t herapies[7,9]

Cancer Vaccine

Cancer vaccines stimulate strong immune respo nses against specific antigens and cells to overcome can cer cell immunity. One type of vaccine involves the use o f p53 peptide mutations, which form neo-antigens on tu mor cells and increase immune cell responses. Another s tudy focuses on the overexpressed FJX1 antigen in naso pharyngeal carcinoma, showing immunogenicity and pot ential as a vaccine-based therapy. These vaccines have the potential to be effective treatments for cancer patien ts.[13,15]

Toxicity

Adoptive cell transfer therapy is a personalized t reatment method utilizing modified T cells to precisely ta rget tumor-associated antigens. This therapy shows pro

mise in effectively eliminating cancer cells while minimiz ing side effects. However, toxicity related to anti-CTLA-4 therapy can occur, with symptoms including enterocoli tis, autoimmune hepatitis, dermatitis, and other less com mon disorders. Patients experiencing these symptoms s hould seek medical attention promptly[15]

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