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 programmed 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 immunotherapy 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 Carcinoma (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 difficult. Treatment options include surgery, radiotherapy, and chemotherapy, but they often fail due to the complex nature of the cancer. Immunotherapy, particularly PD-1 inhibitors, has emerged as a promising treatment for head and neck cancer. However, it is important to consider and manage the potential side effects of immunotherapy.

Squamous Cell Carcinoma

Definition

Cancer or malignancy is a group of diseases due to uncontrolled cell growth that can infiltrate normal body tissues. Cancer cells also can migrate from the primary mass through the blood and lymphatic system to other organs. This process is called metastasis. Head and neck cancer can grow from different sources or origins, from the lips to the cervical oesophagus.

Squamous cell carcinoma, which arises from the mucosal epithelium located in the oral cavity, pharynx, and larynx, represents the predominant form of malignancy observed in cases of head and neck cancer. This specific type of cancer originates from the thin, flat cells that line these regions, known as squamous cells. The development of squamous cell carcinoma in these areas is particularly noteworthy due to its high prevalence and incidence rates.

Epidemiology

Head and neck cancer, specifically Head and Neck SCC (HNSCC), ranks 8th in global cancer occurrence and mortality rates. The 5-year survival rate is low, ranging from 40% to 50%. Age and gender contribute to the development and prognosis of HNSCC, with males being more commonly affected. These factors are important considerations in diagnosis, prognosis, and treatment.

Risk Factor

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

1. Smoking and alcohol consumption
   Cigarettes contain carcinogenic substances like nitrosamines and polycyclic aromatic hydrocarbons (PAHs) that can cause head and neck cancer by damaging DNA and activating oncogenes. Alcohol consumption also increases the risk and growth of cancer cells by facilitating the entry of carcinogens, inhibiting the repair of DNA, and promoting cell proliferation.

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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 cancer1.

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 development1.

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 system5.

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 radiotherapy 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 infection...
n. However, due to the advent of radiotherapy and limited success rates, the idea was abandoned. It wasn’t until the 1980s that the role of T cells in cancer prevention was recognized, leading to the development of modern immunotherapy drugs.

Class of Immunotherapy

Immunotherapy has several classes of agents that can be given, which in the immunotherapeutic approach are divided based on their mechanism of action, including checkpoint inhibitors, cytokines, monoclonal antibodies, vaccines, and adoptive cell transfer.

Checkpoint Inhibitors

Within the HNSCC tissue, there is a notable decrease in the population of lymphocytes, which are a critical component of the immune system responsible for recognizing and eliminating abnormal cells. This diminished presence of lymphocytes can impair the body’s immune response against the cancer cells, limiting the ability to mount an effective antitumor immune defense. This tissue is called a cold tumor. Its caused by the presence of immune checkpoints, namely molecules whose job is to maintain T cell tolerance to host cells and protect surrounding cells by suppressing the immune response. Drugs such as ipilimumab have become standard therapy for melanoma with metastases.

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 produce IFN-γ. Research conducted in 2006 reported a good response in patients with melanoma who were injected with interferon alfa-2b. This drug, PegIntron, was approved by the FDA as a treatment for melanoma with metastases in 2011.

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 aberrant EGFR signaling and impede tumor growth, a monoclonal antibody called cetuximab has been developed. Cetuximab is designed to bind to EGFR with high specificity, effectively inhibiting its activity and downstream signaling cascades. By binding to EGFR, cetuximab blocks the 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 exerts its anticancer effects is through the inhibition of EGFR-mediated cell proliferation. By blocking EGFR signaling, cetuximab interferes with the intracellular pathways that drive cell division and replication. This impediment to cell growth can lead to the suppression of tumor growth and potentially induce cancer cell death.

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 laherparepvec (Imlygic) as an intralesional injection for melanoma. Ongoing research focuses on brain tumor patients.

Adoptive cell therapy

During the early 2000s, research focused on T cells for cancer treatment, including adoptive T cell therapy and chimeric antigen receptor (CAR) T cells. Interleukin-2 (IL-2) was explored to enhance cell transfer. Genetically engineered T cells showed promising responses in lymphoma and leukemia patients, suggesting their potential for cancer treatment. This research laid the foundation for further studies on adoptive T cell therapy and genetically modified T cells in cancer treatment.

Immunotherapy in Head and Neck Cancer

Immune Response to Head and Neck Cancer Cells

Within the context of head and neck cancer, genetic mutations affecting the human leukocyte antigen (HLA) and antigen processing machinery (APM) genes can significantly impede the ability of cytotoxic T cells (CTL) to identify and eliminate cancer cells. These mutations have a negative impact on the prognosis of patients. Identifying these mutations is crucial for developing effective treatment strategies. Restoring the function of HLA and APM genes may enhance CTL-mediated immune responses and improve patient outcomes. CTL activation and regulation are influenced by signals mediated by T cell receptor (TCR), B7 molecules, CD28, and immune checkpoint re
ceptor CTLA-4. CTLA-4 can suppress T cell function and cause immune suppression. Understanding these mechanisms can help develop targeted therapies for head and neck cancer.\textsuperscript{2,13,14}

In head and neck cancer, increased PD-L1 expression contributes to immunosuppression and poor prognosis. TIM-3 expression is associated with metastasis and recurrence. 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 decreased CD8+ function. Tumors induce immune suppression through regulatory T cells and cytokine production, both locally and systemically. Understanding and addressing these mechanisms can help develop effective treatments for head and neck cancer.\textsuperscript{13,14,15}

Tumor cells employ various mechanisms to evade the immune system, including loss of antigen expression, secretion of immunosuppressive cytokines, recruitment of immunosuppressive cells, and exploiting immune checkpoint pathways like PD-1. The interplay between immunostimulatory and immunosuppressive events within the tumor environment is crucial to consider, especially in the context of immunotherapy. Pro-inflammatory cytokines and cytotoxic T cells play significant roles in combating tumor cells.\textsuperscript{13,14}

Use of Immunotherapy in Head and Neck Cancer

Immunotherapy aims to inhibit the evasion of cancer cells from the immune system. It can be achieved through various techniques such as targeting EBV, kinase inhibitors, PD-1 inhibitors, dendritic cell therapy, CAR-T therapy, and cancer vaccines to generate anti-cancer immune responses.\textsuperscript{7,14,15}

Immunotherapy Targeted with Epstein-Barr Virus

In EBV-targeted immunotherapy, the goal is to manipulate cytotoxic T lymphocytes to attack the infected cancer cells by targeting specific epitopes.\textsuperscript{7,8}

Kinase Inhibitor Therapy

Kinase inhibitor therapy, exemplified by drugs such as erlotinib, can bolster the antitumor immune response through two mechanisms: immunogenic modulation and heightened susceptibility of tumor cells to immune-mediated destruction. Erlotinib, specifically a tyrosine kinase inhibitor, impedes the proliferative impact of EGFR by inhibiting its phosphorylation and disrupting intracellular signaling. As a result, erlotinib induces apoptosis and impedes the growth of tumor cells.\textsuperscript{7}

Therapy Programmed Death (PD-1) Inhibitors

PD-1 inhibitors are important immunotherapy techniques used to prevent immune suppression by tumor cells. Drugs like nivolumab and pembrolizumab target PD-1 and have shown promising results in clinical trials for various cancers, including head and neck cancer.\textsuperscript{12}

Nivolumab and pembrolizumab are PD-1 immune checkpoint inhibitors that have shown effectiveness in treating head and neck cancer.\textsuperscript{14,15}

Dendritic Cell Therapy

Dendritic cells, derived from CD34+ stem cells, are antigen-presenting cells that can be activated to enhance the immune response against tumors. Immunotherapy utilizing dendritic cells involves delivering antigens directly to specific dendritic cells or using dendritic cell agonists to stimulate immune responses. Further research is needed to optimize dendritic cell-based immunotherapy for clinical use.\textsuperscript{7}

Therapy Chimeric Antigen Receptors (CAR-T)

CAR-T, a synthetic receptor, boosts T cell function against cancer cells, with the third generation exhibiting superior efficacy compared to earlier versions. This method holds promise for enhancing patient outcomes and minimizing side effects linked to conventional cancer therapies.\textsuperscript{7,9}

Cancer Vaccine

Cancer vaccines stimulate strong immune responses against specific antigens and cells to overcome cancer cell immunity. One type of vaccine involves the use of p53 peptide mutations, which form neo-antigens on tumor cells and increase immune cell responses. Another study focuses on the overexpressed FJX1 antigen in nasopharyngeal carcinoma, showing immunogenicity and potential as a vaccine-based therapy. These vaccines have the potential to be effective treatments for cancer patients.\textsuperscript{13,15}

Toxicity

Adoptive cell transfer therapy is a personalized treatment method utilizing modified T cells to precisely target tumor-associated antigens. This therapy shows pro
mise in effectively eliminating cancer cells while minimizing side effects. However, toxicity related to anti-CTLA-4 therapy can occur, with symptoms including enterocolitis, autoimmune hepatitis, dermatitis, and other less common disorders. Patients experiencing these symptoms should seek medical attention promptly.

References
