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Immunotherapy for Head and Neck Squamous Cell Carcinoma

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Abstract

Head and neck squamous cell carcinoma has been found to be an immunosuppressive malignancy, with many defects in the host immune system contributing to the progression of disease. A greater understanding of these defects has led to the identification and investigation of new therapeutic strategies, targeting immune system dysfunction in an effort to improve the outcomes of this disease. This article provides a brief review of the knowledge regarding the immune defects present in head and neck cancer, as well as a review of the current therapeutic strategies being investigated for use.

Keywords

immunology; squamous cell carcinoma; head and neck cancer

Introduction

As our understanding of squamous cell carcinoma of the head and neck (HNSCC) has grown over the last several decades, it has become clear that HNSCC is an immunosuppressive malignancy, associated with a variety of both quantitative and functional immunologic defects. In particular, patients with HNSCC have been found to have lower absolute numbers of T lymphocytes¹ and increased apoptosis of existing T lymphocytes², higher levels of immunosuppressive cytokines³ and higher numbers of immunosuppressive regulatory T cells (Tregs).⁴⁻⁶ Functionally, it has been shown that patients with HNSCC have defects in antigen presenting machinery⁷, impaired function of the remaining T lymphocytes⁸ and NK cells⁹, and impaired maturation of dendritic cells¹⁰. In addition, many of these abnormalities feedback upon each other, which further strengthens the immune tolerance produced by the tumor environment⁴. For example, up-regulation of the immunosuppressive cytokines in the tumor environment is associated with the formation of immunosuppressive cells including myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and Tregs⁴. These immunosuppressive cells have been shown to further suppress T cell and NK cells activation, as well as inhibit T cell proliferation¹¹.

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Compliance with Ethics Guidelines

Conflict of Interest

Rebecca C. Hoesli and Jeffrey S. Moyer declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

A greater understanding of the role of the immune system in cancer surveillance and of the various immune defects present in HNSCC has lead to directed research in immune targets for therapeutic strategies. Research is on going and has shown great promise in developing additional therapeutic strategies to treat HNSCC. Although there are a wide variety of new therapies currently under development, they can generally be divided into one of several different therapeutic strategies: 1) Monoclonal antibody therapies; 2) Adoptive T-cell transfer; 3) Cancer Vaccines; and 4) Cytokine therapy. Each of these therapies will be discussed in more detail below.

Monoclonal antibody therapies

In the human immune system, antibodies promote targeted destruction of foreign invaders by various pathways. They mediate target cell lysis by binding to the target and signaling a process known as antibody-dependent cellular cytotoxicity (ADCC), and they also promote target destruction by activating the complement cascade and membrane attack complex in a process known as complement-dependent cytotoxicity (CDC)¹². It is primarily the former process that has been investigated for its anti-tumor properties¹², and several therapies based on this concept have been developed and are currently being used. In fact, usage of antibodies as a therapeutic strategy against cancer, termed monoclonal antibody therapy, is currently the most widely used immunotherapy in cancer patients, and is the standard of care in many human malignancies such as breast cancer and hematopoietic cancers¹². There are a variety of different targets for monoclonal antibodies, including direct tumor antigens, checkpoint inhibitors, and cytokine targeted monoclonal antibodies. Each of these categories will be discussed briefly below.

Tumor antigen targeted monoclonal antibodies

In HNSCC, the most widely studied target for monoclonal antibodies is epidermal growth factor receptor (EGFR), which transmits signals along the RAS/MAPK and PI3K/Akt pathways¹³. EGFR was found to be over-expressed in 80-90% of HNSCC patients¹⁴ and was correlated with a poor prognosis due to its association with cell proliferation and invasion, angiogenesis, and tumor survival^{15,16}. There are a variety of monoclonal antibodies therapies targeting EGFR that are currently being investigated including Cetuximab, Nimotuzumab, Cixutumumab, and Panitumumab (Table 1). Cetuximab is the most studied, and is a FDA approved monoclonal antibody for treatment for HNSCC. It is a chimeric IgG1 isotype containing a human constant region and a mouse variable region, and is thought to mediate antigen-specific anti-tumor activity by direct tumor cell killing via ADCC by NK cells and monocytes^{17,18}, and by opsonization of the tumor^{4,19}. Cetuximab's reliance upon immune mechanisms for its function is suggested by studies that have shown that inhibiting the EGFR pathway directly does not produce a significant clinical response^{20,21}. Additionally, Penitumumab, a fully humanized IgG2 antibody with the same antigen target as Cetuximab, does not improve survival in recurrent HNSCC unlike Cetuximab²². Studies have shown that Penitumumab and Cetuximab vary in their affinity for the receptors on NK cells, and Penitumumab does not successfully trigger the adaptive immune response, suggesting that the immune response plays a significant role in Cetuximab's efficacy¹⁹. Usage of Cetuximab has been associated with an increase in overall

survival²³, but further investigation is still required, as response rate to Cetuximab is still low in recurrent tumors²⁴ and overexpression of EGFR does not predict benefit from Cetuximab^{25,26}.

Nimotuzumab, like Cetuximab, is chimeric monoclonal antibody targeting EGFR. It has been studied in two Phase II trials, and in both trials, was shown to increase overall survival^{27,28}. Additionally, in the study by Basavaraj, EGFR overexpression correlated with overall survival²⁷.

Checkpoint Targeted Monoclonal Antibodies

Proper function of the immune system requires a careful balance between activation and suppression of the immune system, as over-activation of the immune system causes autoimmune diseases and over-suppression can lead to opportunistic infections and life-threatening illness. This balance is maintained by feedback and checkpoint systems, which as discussed above are exploited by HNSCC to create an immunosuppressive environment, permitting tumor growth and immune escape. Several immunosuppressive targets have been identified which are inhibited in the tumor environment, and a few different monoclonal antibodies have been evaluated for use in reactivating these inhibited targets.

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) is a co-inhibitory receptor that suppresses activation of T-cells after MHC presentation of antigen. It competitively binds to the B7 ligand found on antigen presenting cells, preventing binding to CD28 on the T-cell, which would cause T-cell proliferation²⁹. Ipilimumab is an IgG1 monoclonal antibody that targets the CTLA4 receptor, allowing for binding of APCs with the stimulatory CD28 receptor, causing T-cell proliferation. Usage of Ipilimumab has shown increased survival in melanoma patients, both alone and in combination with other therapies^{30,31}. Although no studies published to date have tested use of Ipilimumab in HNSCC particularly, CTLA4+ cells have been found to be elevated after treatment with Cetuximab and were correlated with poor prognosis³². As such, investigations into the usage of Ipilimumab and other CTLA4 inhibitors in combination with other therapies such as Cetuximab may be promising.

Programmed death-1 (PD-1) is another immune escape mechanism that normally functions to prevent against self-reactive T-cells. PD-1 is normally expressed on activated T cells, NK cells, B lymphocytes, monocytes and DCs, and functions to decrease T cell activity during an inflammatory immune response in order to prevent autoimmunity³³. However, when this pathway is co-opted by cancer cells, it serves to promote immune escape and immune tolerance of cancer cells. The ligand for PD-1, PD-L1, is found on the surface of many malignancies including HNSCC^{34,35}, and studies have found that PD-L1 was present on 66-87% of HNSCC^{35,36}. This receptor ligand combination thus makes an attractive target for anti-cancer therapies for HNSCC. Nivolumab and Pembrolizumab are both monoclonal antibodies developed against PD-1. Nivolumab has been studied in other solid tumor cancers including melanoma, colorectal cancer, prostate cancer, renal cell carcinoma, and non-small cell lung cancer. In a phase I study was found to have both partial and complete responses with a duration of greater than one year³⁷. In an on-going trial, Pembrolizumab has preliminarily shown minimal adverse effects when administered in head and neck cancer patients³⁸, and further updates on this trial showed that Pembrolizumab was twice as

effective as cetuximab in HNSCC, with disease control of 50% and tumor shrinkage in 57% of patients³⁹. An on-going trial showed that interferon-gamma predicted benefit from Pembrolizumab usage⁴⁰, which could be used to tailor treatment in the future to Pembrolizumab responders. Another trial currently on-going evaluating the use of an anti-PD-L1 antibody (MEDI4736) has shown tumor response preliminarily in patients with multiple tumor types, including HNSCC⁴¹. There are currently several trials involving the use of anti-PD-1 and anti-PD-L1 that are on-going²⁹ and preliminary data is pending.

Cytokine Targeted Monoclonal Antibodies

As discussed above, there are several cytokines that are upregulated in HNSCC. Among them is vascularized endothelial growth factor (VEGF), which is an angiogenic factor that stimulates angiogenesis by increasing vascular permeability and by serving as a mitogen for endothelial cells⁴². Although angiogenesis is necessary for physiologic processes, it is also necessary for tumor growth and progression⁴³, and VEGF has been found as one of the most potent angiogenic factors⁴⁴. Additionally, VEGF has also been found to increase the ratio of immature to mature dendritic cells⁴⁵, which is thought to contribute to T-cell dysfunction and inactivation⁴⁶. As such, VEGF is a promising target for monoclonal therapy, and has been well-studied, as elevated pretreatment levels are associated with poorer overall survival and more aggressive disease in HNSCC^{44,47}. Bevacizumab is a recombinant monoclonal antibody against VEGF, and was the first FDA approved agent against VEGF. In HNSCC, it has been evaluated for use in a variety of studies in combination with other therapeutic strategies including radiation, various chemotherapeutic medications, and other immunotherapeutics including cetuximab⁴⁸⁻⁵³. Most recently, a phase II study of the addition of Bevacizumab to Cisplatin plus intensity modulated radiation therapy (IMRT) did not show any significant increase in toxicity, with a 2 year PFS rate of 76% and overall survival rate of 88%⁵⁴. With the addition of Cetuximab to the above regimen, the same authors showed an improved progression free survival to 89% and overall survival to 93%⁵⁵. Cetuximab and bevacizumab have also been evaluated together in recurrent or metastatic HNSCC and showed tumor growth inhibition both *in vitro* and *in vivo*, and in the clinical trial showed a disease control rate of 73% and OS of 7.5 months⁵⁶. Interestingly, a preclinical trial evaluating pretreatment with Bevacuzimab prior to Cetuximab administration as compared with simultaneous administration showed that there was an increase in tumor specific uptake of Cetuximab when the murine model was pretreated with Bevacuzimab. This shows promise to improve immunotherapy results with Cetuximab⁵⁷, and will need further study. Bevacizumab has also been combined with docetaxel and radiation with an overall survival of 68% and 3 year recurrence free survival of 80.5%⁵⁸.

Axitinib is a multi-receptor small molecule tyrosine kinase inhibitor that inhibits several VEGF receptors and c-kit. A recently completed phase II trial with Axitinib showed good tolerance of axitinib, disease control rate of 77%, and increased overall survival, although the trial was stopped due to an interim analysis which only showed a 6 month PFS of 27%⁵⁹.

Adoptive T-cell Transfer

Adoptive T cell therapy (ACT) is another therapeutic strategy that reactivates the patient's existing immune cells to recognize and eliminate tumor cells, with the ultimate goal of creating memory cells which will in theory create long-term anti-tumor immune responses¹². In this therapy, T cells which have been externally manipulated to specifically target tumor antigens are administered to a patient. These T cells can be derived from the patient's tumor infiltrating lymphocytes (TIL) or peripheral bone marrow cells (PBMCs), which are then expanded *ex vivo* and then administered to the patient⁶⁰. However, this requires a well-equipped laboratory facility and is quite labor intensive, and so other approaches have been investigated¹². These include use of genetically modified T cells that express tumor-specific antigen receptors, as well as the use of chimeric antigen receptors (CARs), which combine an extracellular antibody with a T cell receptor. The CARs ensure antigen specific activation via the high affinity extracellular antibody, and combine this with the effects of a cytotoxic T cell¹². In HNSCC specifically, the use of adoptive T cell transfer was evaluated in 43 HNSCC patients in combination with radical resection and chemotherapy. In the patients receiving adoptive T cell therapy, more lymphocytes infiltrated into the tumor site, and overall survival and regression was improved in comparison to the patients treated with chemotherapy alone. This therapy was well tolerated, with the adverse events consistent with the previously described side effects of the chemotherapeutic agents⁶¹.

Cancer Vaccines

Cancer vaccines involve the presentation of tumor-specific antigens (TSA) or tumor-associated antigens (TAA) in combination with a peptide-major histocompatibility complex (MHC) in order to activate the adaptive immune system⁶⁰. Various vaccine strategies have been proposed, including the presentation of peptides or proteins in combination with immunogenic recombinant bacteria or viruses, usage of DNA-based vaccines encoding TAAs, delivery of whole killed tumor cells, or delivery of protein or peptide activated dendritic cells^{60, 62, 63}. The usage of DNA based vaccines involves the delivery of encoded TAAs constructs which are then taken up and expressed by APCs⁶⁴ to activate the adaptive immune system. However, in this method, only a limited number of TAAs are able to be delivered for targeting, and thus tumors without the targeted antigens could escape detection by this method. The delivery of whole inactivated tumor cells resolves this issue by presenting all TAAs as possible immunogens; however, this can diminish the expression of a particular target and thus diminish its processing and presentation by APCs⁶⁵. Finally, the delivery of protein or peptide activated dendritic cells involves collecting circulating monocytes expanding them *ex vivo*. These cells are then pulsed with the peptide or proteins of interest and administered to the patient⁶². In HNSCC, p53 targeted dendritic cell vaccination was tested as an adjuvant treatment in a phase I trial⁶⁶. Two year disease free survival was promising at 88%, and no significant toxicities were noted. Interestingly, the absolute number of Tregs was also decreased after vaccination⁶⁶. Additionally, a recent study in a murine model looking at a cancer stem cell (CSC) targeted dendritic cell vaccination showed significantly reduced growth of subcutaneous tumors, increased survival, and decreased pulmonary metastasis⁶⁷.

Cytokine therapies

As discussed above, HNSCC has been found to have an increased level of immunosuppressive cytokines, including TGF-beta1, IL-6, IL-10, and VEGF⁶⁸. This results in dysfunction of NK cells, DC maturation, and CTL activation^{69,70}. Strategies to improve the immunosuppressive state of HNSCC include both targeting cytokines with monoclonal antibodies as discussed above with monoclonal antibodies against VEGF, as well as administering immunostimulatory cytokines to counteract the immunosuppressive tumoral environment, which will be primarily discussed here. The best-studied cytokine for use in HNSCC is interleukin-2 (IL-2), which functions to increase antigen-specific expansion of T cells, as well as to increase the activity of NK cells⁶⁰. High dose intravenous interleukin-2 (IL-2) was initially approved in 1992¹², and its usage has since been evaluated in HNSCC by various studies, with varying success. Systemic therapy with IL-2 was ineffective in nasopharyngeal carcinoma, with 50% of patients with stable disease, and 50% with progression of disease⁷¹. However, intranodal injection of IL-2 was shown to increase overall survival at five years and disease free survival rates in another study in HNSCC⁷². In a separate study, peritumoral and intranodal injections of IL-2 were shown to increase the number of T-cells and NK cells in the tumoral stroma, as well as increased cytolytic activity of tumor infiltrating lymphocytes. Interestingly, peritumoral and intranodal injections of IL-2 also increased *systemic* NK and lymphokine-activated killer cell activity⁷³.

With the limited success of IL-2 but theoretical potential of using cytokines as a therapeutic strategy, other investigators have evaluated the combined use of multiple interleukins. One of these combinations, IRX-2, is a combination of IL-1, IL-2, IL-6, IL-8, tumor necrosis factor-alpha, interferon-gamma, and GM-CSF. It was initially studied for safety in 2011, and toxicity was found to be minimal. Additionally, overall survival at two years was 73%⁷⁴. In a phase II study, lymphocyte infiltration was increased and was associated with reduction in tumor size. Improved survival was also noted with increased lymphocyte infiltration⁷⁵. Another study evaluating the effect of IRX-2 on NK cells shows improved NK cell cytotoxicity, restoration of activating NK-cell receptors, and protection of NK cells from suppression by TGF-beta⁷⁶. An additional study by the same author looking at dendritic cells matured with IRX-2 showed that these dendritic cells carried a higher density of tumor antigen, and cytotoxic T cells primed by these dendritic cells had higher levels of cytotoxicity⁷⁷.

Other cytokines have been evaluated for use alone and in combination with other cytokines, but studies have been limited in HNSCC. Both interferon-gamma and interferon-alpha have been studied in smaller studies either alone or with other therapies, with mixed results⁷⁸⁻⁸⁰.

Chemotherapy and Radiation Therapy

A comment should be made upon the usage of chemotherapy and radiation therapy in head and neck squamous cell carcinoma, as both are currently widely used in the treatment of HNSCC. While both chemotherapy and radiation were initially thought to primarily cause their effects by a direct cytotoxic effect on tumor, there is also increasing preclinical and clinical evidence suggesting that immune system activation by these therapies plays a role in

tumor death. The role of the immune system in tumor elimination was initially suggested by the abscopal bystander effect (i.e. the noted regression of tumor outside of the radiation treatment field)⁸¹. Regression in two patients with melanoma was associated with an increased presence of elevated tumor-specific antibodies and T-cell activation, which suggested that tumor eradication may be related to immune function^{82,83}. A larger study on the abscopal effect in melanoma showed promising responses of nodal disease to radiotherapy⁸⁴ and continue to support the hypothesis that radiation has an immunomodulatory effect, but further studies are warranted.

High dose chemotherapy is well known to suppress the function of the immune system, but there is also accumulating evidence that low dose chemotherapy may in fact be immunostimulatory⁸⁵. Conventional chemotherapy is administered at close to the maximal tolerated dose every several weeks. However, the period between treatments was noted to allow tumor growth and vascularization, with robust mobilization of the circulating endothelial progenitor (CEPs) inducing the vasculogenesis necessary for tumor growth and rapid drug resistance⁸⁶. As a result, clinicians evaluated the use of low-dose more frequent chemotherapy, termed metronomic chemotherapy. In studies, this showed a decrease in the CEP numbers and more durable inhibition of tumor growth⁸⁶. Metronomic chemotherapy was initially thought to exert its effects by anti-angiogenic mechanisms, but additional evidence shows that an anti-tumor immune response plays a role in tumor eradication⁸⁷. It is believed that metronomic chemotherapy exerts its effects by direct tumor eradication by the immune system⁸⁸, improved maturation of dendritic cells⁸⁹, improved induction of CTLs by dendritic cells and increased cytotoxicity of these CTLs⁹⁰, and decreased Tregs^{91,92}.

As a result of the immunomodulatory and immunotherapeutic effects of both chemotherapy and radiation therapy, their combination with other immunotherapeutics is promising. As stated above, many of the immunotherapy medications or therapeutic strategies currently under investigation are combined with radiation, chemotherapy, or both. Other combinations offer promise for future therapeutic strategies.

Conclusions

Immunotherapy is a rapidly advancing field with many promising new therapies and opportunities for investigation. As more is understood about the role of the immune system in HNSCC and the activation of immune surveillance, more targeted therapies will likely lead to greater success in the treatment of HNSCC. Although considerable progress has been made in the usage of immunotherapies in the treatment of HNSCC, further investigation will need to be performed on the combined usage of many of these therapies, as the multi-faceted immunosuppression induced in HNSCC will likely need to be counteracted with immunotherapeutic regimens that target multiple pathways.

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Table 1

Therapeutic Monoclonal antibody inhibitors against EGFR being investigated in HNSCC

Drug Name	Brand Names	Most common uses
Cetuximab	Erbix (Bristol-Myers Squibb)	FDA approved for non-small cell lung cancer, HNSCC, and colon cancer. Under investigation for use in breast cancer ¹
Nimotuzumab	-	Under investigation for HNSCC and non-small cell lung cancer
Cixutumumab	-	Under investigation for HNSCC, neuroendocrine tumor, sarcoma, and other solid tumors
Panitumumab	Vectibix (Amgen)	FDA approved for colon cancer. Under investigation for use in HNSCC breast cancer ⁵