International Surgery Journal
Aremu SK et al. Int Surg J. 2019 Oct;6(10):3884-3888
http://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

Review Article

DOI: http://dx.doi.org/10.18203/2349-2902.isj20194465

Immunotherapy for head and neck cancers

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Received: 09 July 2019
Accepted: 14 August 2019

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ABSTRACT

Head and neck squamous cell carcinoma (HNSCC) is a frequent tumour which arises from various anatomical areas in the head and neck region. HNSCC has multiple resistance mechanisms through which it evades the immune responses. It is particularly characterized by an immunosuppressive environment which includes the release of immunosuppressive factors, expansion, and expansion of immune cells which have inhibitory activity reduction of tumour immunogenicity. Human papillomavirus positive (HPV+) HNSCC tumours have one of the higher levels of T cells infiltration. Studies which explore this relationship to the prognosis of patients vary, with some showing benefit only with high CD8/Treg ratio as seen with HPV+ disease and others showing improved prognosis with a higher number of TIL Treg. High CD8+ TIL seen in HPV + disease has been shown in several studies to confer improved disease-free survival. The most successful vaccination strategy is preventive vaccination for HPV. Investigations using different approaches have been carried out on therapeutic vaccines for HPV-associated HNSCC. Despite immune responses being seen in a number of studies, these vaccines are still not effective for clinical use as of yet.

Keywords: Immunotherapy, Head and neck, Cancers, HPV, Infection

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is a frequent tumour which arises from various anatomical areas in the head and neck region. It accounts for more than 550,000 new cases and 380,000 deaths annually.[1,2] Radiotherapy or surgery is the general single modality early-stage treatment for the condition. For the tumours that have advanced, the treatment is multimodal. Palliative chemotherapy is the standard of care for metastatic HNSCC. There is limited prognosis and an urgent need for novel treatment approaches. HNSCC has multiple resistance mechanisms through which it evades the immune responses. It is particularly characterized by an immunosuppressive environment which includes the release of immunosuppressive factors, expansion, and expansion of immune cells which have inhibitory activity reduction of tumour immunogenicity. Proper clinical trials and rational design of immunotherapeutic approaches have resulted from an in-depth understanding of these mechanisms. Presently, only inhibitors of immune checkpoints have proven clinical efficacy in randomized phase III trials, PD-1 (programmed cell death 1) and PD-L1 (programmed cell death 1 ligand).[3,4] The only drug approved for platinum-refractory metastatic HNSCC is the PD-1 inhibitor nivolumab. Even so, a variety of other immunotherapeutic treatment options are being investigated. There are ongoing trails which investigate the immunotherapeutic approaches in the curative setting and therapy combination using a variety of immunotherapeutic approaches. This article provides a comprehensive overview of the development of immunotherapeutic approaches and the role of the immune system in the progression and development of HNSCC. It particularly focuses on the currently approved immunotherapy and the promising immunotherapeutic approaches under clinical investigation.

IMMUNOLOGY OF CANCER

The immune system ideally recognized tumor cells in a premalignant state and destroys these cells. However, tumor cells are able to develop mechanisms to thwart immune response and recognition – a process called immunoediting, which leads to immune escape.[5] IR (inhibitory checkpoint receptors) expressed on activated immune cells Monocyte-derived dendritic cells from 16 patients were loaded with two modified HLA-class I p53 peptides and were injected into inguinal lymph nodes. The frequencies of p53-specific T cells were increased in 11 of 16 patients (69%), with interferon-γ secretion detected in 4 of 16 patients. Moreover, the rate of Tregs was decreased after vaccination.[6] The expression of these inhibitory receptors often signifies an exhausted T cell, which has lost its normal function, which includes reduced cytolytic activity. This state of dysfunction can, however, be reversed by IR blockade. Resistance mechanisms to this T cell reinvigoration process may arise from expression of multiple IR or other acquired cellular changes.

IMMUNOLOGY OF HNSCC

The modifications in immune systems in HNSCC patients show that cancer is an overall immunosuppressive process. HNSCC patients, in the peripheral bloodstream, have a lower number of white blood cells, which is comprised of a greater proportion of suppressive regulatory T cells. Within the HNSCC tumours there are even more suppressive population of Treg cells than in the peripheral bloodstream of HNSCC patients.[7]

Human papillomavirus positive (HPV+) HNSCC tumours have one of the higher levels of T cells infiltration. Studies which explore this relationship to the prognosis of patients vary, with some showing benefit only with high CD8/Treg ratio as seen with HPV+ disease and others showing improved prognosis with a higher number of TIL Treg.[8,9] High CD8+ TIL seen in HPV + disease has been shown in several studies to confer improved disease-free survival.[9,10] These cell populations express IR that can be targeted by inhibitory checkpoint receptor blockade therapy (ICR).

VACCINES

Basically, the principles of therapeutic cancer vaccines can be summarized as follows.

- Peptide-based vaccines which are produced through the combination of one of more proteins or peptides which is commonly expressed in the specific tumour with an adjuvant. The immune system, in response to the adjuvant, will also respond to the tumour cells which express the respective antigens.
- DNA/RNA-based vaccines use nucleic acids which have been exogenously manipulated so that when injected, expresses a tumour specific antigen. The antigen-presenting cells process this antigen and induce a specific immune response toward tumour specific cells which express the same antigen.
- Viral vectors and attenuated bacteria can serve as vectors for delivering plasmids encoding genes or proteins of interest in vaccines.[11,12]
- For dendritic cell vaccines, an isolation of the dendritic cells from the blood of cancer cells is done through leucapheresis and stimulated with a tumour antigen. The cells are re-injected and serve to activate the T-cells, which are specific to the tumour.

Peptide/protein-based vaccines

The incidence of HPV-associated oropharyngeal carcinoma has increased rapidly during the last decades in developed countries worldwide, although the incidence of smoking- alcohol-induced HNSCC is declining steadily.[13] HPV16 caused approximately 90 percent of these cases, and the remainder is caused by other oncogenic HPV types.[13,14] By 2020, it is estimated that the annual number of cervical cancers diagnosed in the U.S. will be surpassed by the number of HPV-positive HNSCCs.[13] Randomized prophylactic HPV vaccine trials have shown effectiveness in preventing high-grade cervical lesions associated with HPV18 and HPV16.[15] Therefore the current recommendation for preventing genital warts, anal, vulva, vaginal and cervical precancerous lesions worldwide is prophylactic HPV vaccination with quadrivalent (HPV16/18/8/11) or bivalent (HPV16/18) vaccines, including Switzerland.[16]

Additional randomized trials have showed that the vaccines are associated with significantly reduced HPV-associated anogenital lesions in males.[17] As a result, the prophylactic vaccination has been approved for boys and young males. A recent cross-sectional study showed that HPV vaccination reduced the prevalence of oral HPV16/18/6/11 infections significantly.[18] While the effectiveness of prophylactic HPV vaccination is high, its administration and general adoption is poor.

HPV-associated cancers strongly and consistently overexpress the cyclin-dependent kinase inhibitor p16(INK4a). A study published recently investigated a p16(INK4a)-based peptide vaccine in patients who had advanced HPV-positive HNSCC.[19] The participants were 20 patients who received at least four injections, and their immune response was evaluate. In 14 of the 20, CD4+ T cells were detected, and in 5 patients CD5+ cells were detected, and antibodies in 14 of 20 patients. Vaccination was safe with low toxicity rates. Tumour response could be assessed in 14 patients. Of these, nine patients (64%) had a stable disease as their best overall response. In the VICORYX-2 trial, this vaccination is being investigated in combination with cisplatin-based chemotherapy in patients with advanced HPV-positive cervical, vulvar, vaginal, penile, anal or head and neck cancer (NCT02526316).[20]

Another study had utilized an immunomodulatory peptide vaccine for melanoma antigen, and HPV-positive A3-positive tumours elicited antibody responses and antigen-specific T cells to the respective vaccines but did not have clinical efficacy.[21] In a different phase, I/II study, the safety profile of Allovax is being investigated in patients with recurrent HNSCC.[22] AlloVax is a vaccine made up of patient-specific tumour antigen derived from chaperone-rich tumour cell lysate. Personalized neoantigen vaccines have recently been developed and investigated. The basis of this approach is parallel sequencing so that all coding mutations within tumours are detected, and machine learning approaches utilized to predict which of the mutated peptides have high affinity binding of autologous human leukocyte antigen (HLA) molecules.

DNA/RNA-based vaccines

There have been multiple attempts to use therapeutic HPV vaccines. A DNA-based cancer vaccine MEDI0457 (previously called INO-3112) has two main components: INO-9012 which is a DNA plasmid which contains immune activator interleukin-12 and VGX-3100 which is a DNA plasmid with modified sequences for E7 and E6. A phase I/II trial's preliminary results showed that this DNA based immunotherapy could generate HPV-specific CD8 T cell immunity safely in patients who have locally advanced HPV-related HNSSC.[23] All the patients who had been tested showed positive cellular immune responses in at least one assay. The ongoing phase I/II study of MEDI0457 is combining the anti-PD-L1 antibody durvalumb in patients with HPV-positive recurrent HNSCC.

A recent phase II trial which utilized a multipeptide vaccine for three cancer-testis-antigens (IMP3, LY6K, and CDCA1) showed a significant benefit of survival when compared to the untreated cohort in metastatic HNSCC.[24]

Attenuated bacterial and viral vectors

ADXS11-001 is a live attenuated *Listeria monocytogenes* (Lm)-listeriolysin O (LLO) immunotherapy which is biologically engineered to produce a secretion of an HPV-E7 tumour antigen as a truncated LLO-E7 fusion protein in cells which are capable of presenting antigen. A study which is still ongoing includes HPV-positive oropharyngeal prior to surgery. The ongoing phase I/II trial is investigating the combination of ADXS11-001 with durvalumab and the efficacy of durvalumab compared alone. DPX-E7 is an HPV16-E711-19 nanomer vaccine currently investigated in HPV-positive cancers.

Dendritic cell vaccines

There has also been the investigation of HPV-targeting dendritic cell vaccines against cervical cancer. While the measure of HPV-specific cytotoxic T lymphocytes was possible, there was no observable clinical response.[25] The activity of dendritic cell vaccines, in preclinical trials, have been improved through a recombinant adenovirus expressing codon-optimized HPV E6/E7 fusion proteins. A test was carried out of a dendritic cell-based vaccination against p53 in a phase I trial in patients with resected HNSCC.[26] Monocyte-derived dendritic cells from 16 patients were loaded with two modified HLA-class I p53 peptides and were injected into inguinal lymph nodes. The frequencies of p53-specific T cells were increased in 11 of 16 patients (69%), with interferon-γ secretion detected in 4 of 16 patients. Moreover, the rate of Tregs was decreased after vaccination.

THE FUTURE OF IMMUNO-ONCOLOGY

The future of immunotherapy holds an exciting promise. There are trials underway for evaluating immunotherapy combine with the existing cytotoxic agents at varying dose regiments. Currently, the goals of immunotherapy clinical trials include developing appropriate regimen with the least toxicity with durable responses. The best chance for curative therapy is targeting the redundant pathway mechanisms which lead to the progression of cancer. Significant barriers to progress are the patients with tumours that have poor lymphocyte infiltration.

COMBINING IMMUNOTHERAPY AGENTS

In spite of the enthusiasm towards ICR, most patients do not benefit from anti-PDI therapy. As such interest has turned to the combination of ICR agents with the hope to overcome multiple resistance layers to increase efficacy in a synergistic manner, at the same time maintaining an acceptable toxicity profile. It is unclear how the blockade of one immune checkpoint receptor affects other checkpoint receptors, and whether that blockade leads to cross talk with other pathways or downstream. There is a profound synergy shown by the use of combination immunotherapies and a likelihood of further advances in treatment compared to the current cytotoxic regimens or monotherapy.

There are emerging trials which are trying to evaluate the targeting of checkpoint receptors other than PDI. Preclinical studies have shown numerous promising potential therapeutic targets, and there is an ongoing test of these agents in combination with other anti-PDI therapy. PDI and CTLA4 are considered pathways that are non-redundant. The test on melanoma patients confirms the synergism of blockade of these two IRs.[27] Trials are underway evaluating this combination in other solid tumors. Other combinations are being tested in HNSCC.

IMMUNOTHERAPY AND RADIATION

Radiation therapy has historically been considered an immunosuppressive treatment modality with the

mechanism of cell death related to direct DNA damage.[28, 29] In vitro studies, RT triggers ICD (immunogenic cell death), a process which converts the tumour which has been irradiated into a situ vaccine.[30] There are proposed theories which show the potential advantage that can be achieved through radiation with immunotherapy, one of which pushes that ICD has the potential of enhancing systemic responses via an 'abscopal effect'. Here, local therapy induces a systemic response capable of lasting beyond the RT treatment completion.[31] Such changes have the ability of altering the TME to make it more responsive to PDI pathway blocking agents. Preclinical abscopal responses demonstrate the additive effects the RT has when combined with anti-PDI therapy.

CONCLUSION

As it stands presently, the most successful vaccination strategy is preventive vaccination for HPV. Investigations using different approaches have been carried out on therapeutic vaccines for HPV-associated HNSCC. Despite immune responses being seen in a number of studies, these vaccines are still not effective for clinical use as of yet. It is noteworthy however, that combined with other immunotherapeutic strategies, namely immune checkpoint inhibitors might be promising. The future of immunotherapy holds an exciting promise. There are trials underway for evaluating immunotherapy combine with the existing cytotoxic agents at varying dose regiments. Currently, the goals of immunotherapy clinical trials include developing appropriate regimen with the least toxicity with durable responses. The best chance for curative therapy is targeting the redundant pathway mechanisms which lead to the progression of cancer. Significant barriers to progress are the patients with tumours that have poor lymphocyte infiltration.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Aremu SK, Adewoye KR, IbrahimT. Immunotherapy for head and neck cancers. Int Surg J 2019;6:3884-8.