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Review

Immunotherapy in the management of squamous cell carcinoma of the head and neck

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Abstract

Despite many advances in surgery, radiotherapy, and systemic treatments, only modest improvements in survival, function, and quality of life have been achieved after treatment of squamous cell carcinoma (SCC) of the head and neck. With a better understanding of the biology and genetics of tumours, the emergence of a paradigm shift towards the further development of non-surgical treatments may result in less morbidity and better outcomes than are seen currently. SCC of the head and neck is known to be a complex disease that has a sophisticated interaction with the human immune system. At the forefront of emerging treatments is immunotherapy, which has already been established in many other areas of oncology. The rapidly evolving nature of immunotherapeutic agents and, sometimes, their complex mechanisms can make the understanding of these concepts challenging, and could discourage clinicians from engaging in clinical trials. The aim of this paper therefore was to review the current premise for immunotherapeutic approaches, and to provide a contemporary evidence-based rationale for their use.

Keywords: head and neck squamous cell carcinoma; oral squamous cell carcinoma; immunotherapy

Introduction

Despite advances in the management of squamous cell carcinoma (SCC) of the head and neck, multimodal therapy such as surgery, radiotherapy, and cytotoxic chemotherapy still often result in permanent toxicity, impaired function, and decreased quality of life. Whilst there have been improvements in survival, the morbidity of current treatments and the poor outcomes for advanced local, recurrent and metastatic disease[1,2] have prompted the search for less toxic and more effective methods.

As part of this search, immunotherapeutic agents have increasingly been investigated in recurrent and metastatic disease and, more recently, as "up-front" methods of treatment. The safety and efficacy of some agents – for example, nivolumab, have already been shown in the palliative treatment of SCC of the head and neck,[3] whilst other agents (somewhat unusually) have moved directly to early-phase trials in the radical setting.[4,5]

In some patients, immunotherapeutic agents induce improvements in tumour control and survival. SCC of the head and neck is an obvious area in which to investigate these immune-modulating agents in window of opportunity trials, as ease of access to tumour tissue (both through biopsy and at definitive resection) facilitates much-needed translational research, which will hopefully also identify the pathological or molecular biomarkers that are associated with the response. Ultimately, success with these new agents may reduce the morbidity associated with current treatments for

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locally-advanced disease and metastatic disease or, at the very least, improve its control.

Despite the potential of these agents to augment current practice, the perceived complexity of immune mechanisms, and the interventions themselves, can be challenging and can deter surgeons from engaging in trials. Given that the success of these "window of opportunity" studies depends on close collaboration between multidisciplinary teams, we consider that clarity and understanding of the area by all are prerequisites to allow this to take place.

The aim of this paper therefore was to introduce the process of tumour interaction with the immune system, and explain some of the key therapeutic strategies that have been targeted in contemporary immunotherapy practice. To do this, we searched both the United States National Institute of Health[6] and the Cancer Research UK[7] websites, and grouped together trials with similar immunological targets. In this paper we also discuss current trials of immunotherapeutic interventions, describe the agents currently being used in these studies, and consider the future for immunotherapy in head and neck oncology.

The role of the immune system

The immune system has two major functions: first, to recognise self from non-self and secondly, to mount a response to foreign pathogens and abnormal cells and eliminate them. Burnett and Thomas first suggested the role of the immune system in cancer over 50 years ago. They described it as a "sentinel", which detected and eliminated cancer cells, and coined the term "immunosurveillence".[8] Contemporary understanding of the human immune system, however, suggests that in the context of malignant disease, immunosurveillance is only a small component of the newer and overarching concept of "immunoediting".[8,9]

Immunoediting is a process in which cancer cells and the immune system interact to "naturally select" cancer cells that have evolved to avoid recognition and subsequent destruction by the immune system. It has three phases: elimination, equilibrium, and escape. Elimination, in which the innate and adaptive immune system detects and eliminates tumour cells, occurs as a response to the tumour antigens that are produced. Equilibrium is the next phase in which subtypes of cancer cells with low immunogenicity persist within the host. This can last for several years, during which further cell lines, which are less immunogenic and more likely to persist, are selected. The final phase is escape, in which these highly-selected cells escape the confinement of the immune system and progress to clinically apparent cancers.

Ferris alluded to four mechanisms by which the immune system mounts a response to the tumour.[10] These include TCR:HLA (MHCI and MHCII) interaction, costimulatory interaction, the secretion of cytokines that can lead to inflamed and non-inflamed tumours, and extrinsic chemokines that help to shape the tumour's microenvironment. In an attempt to simplify these concepts further, we divided the mechanisms in which tumour cells avoid the immune system into three major groups that incorporated Ferris' main concepts: tumours that alter their own immunogenicity, those that establish tumour microenvironments; and those that promote immunosuppressive cells (Table 1).

Table 1
Immunological changes that favour the development and progression of cancer.

Alteration of immunogenicity	Down regulation of antigen-presenting mechanisms Checkpoint inhibition
Establishment of a cancer-promoting tumour microenvironment (TME)	Inflamed subtype: immune/inflammatory response occurs, but the cells are ineffective Non-inflamed subtype: failure of an immune/inflammatory response to be mounted
Promotion of immunosuppressive cells	Cancer cells recruit various haemopoetic cells, which have immunosuppressive or cytotoxic actions, to the microenvironment, and so promote tumour growth and metastasis. These include myeloid-derived suppressor cells (MDSC), CD4 regulatory T cells (Tregs), and tumour-associated macrophages (TAM)

Alteration of immunogenicity

There are several processes by which tumour cells develop the ability to manipulate their own immunogenicity to avoid the immune response. These are summarised below.

Down regulation or mutation of human leukocyte antigen (HLA) class I and components of antigen-presenting cell machinery

Normally, HLA works with the antigen-presenting cell machinery to ensure an effective immune response. The cancer genome atlas has shown large-scale mutations in specific HLA alleles and antigen processing machinery,[9–11] which have resulted in a host being unable to rely on its usual mechanisms for immunosurveillance or elimination to detect and destroy cancer cells. Such defects have been shown in a substantial number of SCC of the head and neck, and correlate with a poor prognosis.[12,13]

The HLA gene is highly polymorphic and codes for various major histocompatibility complex (MHC) proteins. Two main proteins serve multiple purposes that are relevant in oncogenesis: MHC I, which presents antigens from inside the cell to the cellular membrane to be recognised by natural killer (NK) cells; and MHC 2, which presents antigens from inside the cell to outside the cell to be recognised by T-helper cells.

SCC of the head and neck avoids the recognition of T cells (and the subsequent immune response) by down

regulating HLA (and the subsequent expression of MHC) without completely eliminating it. This is because while normal expression of MHC will prompt an immune response, a complete absence will trigger a reaction from the NK cells against the cancer cell. Cancer cells therefore have evolved a sophisticated capacity to express just the right amount of MHC to escape detection from the T cells and avoid the NK response.[9,10]

Checkpoint inhibition

Checkpoints are mechanisms by which circulating T cells "check" the identity of other cells in the body to distinguish self from non-self. This is achieved through a receptor-ligand interaction.[10] Under normal circumstances, a receptor binds to a corresponding ligand on a host cell, allowing the T cell to recognise it as a host cell, and preventing the triggering of an immune response (an interaction that is particularly important in the prevention of autoimmunity). Unfortunately, cancer cells have developed the ability to express this ligand, which "deceives" the host T cell, and avoids an immune response.

Examples of the receptors involved in this receptor-ligand interaction include: cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), lymphocyte-activation gene 3 (LAG 3; CD223), T cell immunoglobulin and mucin protein-3 (TIM-3), and programmed death receptor 1 (PD-1). Some of these will be discussed later.

Establishment of a cancer-promoting tumour microenvironment (TME)

Analysis of the TME, which is a matrix that comprises cancer and immune cells in a milieu of immunomodulatory cytokines, has shown that there are two major subsets of solid tumours: inflamed, and non-inflamed.[9]

Inflamed tumours attract CD8+ cytotoxic T cells, macrophages, and B cells to the tumour through the secretion of various immune signals and cytokines. Interestingly, these immune cells lose their ability to mount an effective immune response only when they are within the TME, which suggests that the loss is a consequence of the immune suppressing signals that are found within it. Inflamed tumours typically also show an increased mutational load, and generate a dense inflammatory stroma that acts as a barrier to immune cells. This has been associated with poorer outcomes in certain cancers such as those of the breast and ovary.[14] Fortunately, these immune cells give immunotherapies, such as checkpoint inhibitors, a substrate in the form of existing immune cells that can be re-activated to mount an immune response.[14]

In the non-inflamed subtype, immune failure seems to be the main cause of progression, decreasing the attraction of T cells to the lesion. The failure of immune cells to migrate to the site, leads to an inadequate antitumour response by insufficient effector cells. Treatments therefore must first focus on the recruitment of immune cells to the TME before they can be re-activated (as is the case with inflamed subtypes).[14]

Table 2
Inflammatory cytokines and their function on immune cells.

Cytokine	Effect
TGF-β	Suppresses natural killer (NK) and T-cell activation Involved in differentiation of CD4 regulatory T cells (Tregs)[12]
IL-6	Signals by STAT3 inhibit maturation of dendritic cells Inhibits activation of NK cells, T cells, neutrophils, and macrophages[13]
VEGF	Promotes angiogenesis that is present in 90% of head and neck SCC, and increases the ratio of immature:mature dendritic cells in the tumour microenvironment, which leads to the dysfunction and inactivation of T cells[7,8]

Some of these important cytokines and their effects are listed in Table 2.

Promotion of immunosuppressive cells

Various tumour cells can also secrete cytokines that recruit various haemopoetic cells (cytotoxic and immunosuppressive) to the TME. Immunosuppressive cells include myeloid-derived suppressor cells (MDSC), T-cell regulators (Tregs; CD4 cells), and tumour-associated macrophages (TAM).

Myeloid-derived suppressor cells (MDSC)

These comprise a diverse cellular population of myeloid origin and they suppress the function of immune cells. They have a range of immune suppressing abilities that include the inhibition of activated T cells,[10,15] and the production of nitric oxide and reactive oxygen species, which inhibit the interaction and activation of the T-cell receptor HLA.[16] They also assist in the activation of CD4 regulatory T cells (Tregs).[15] Expanded MDSC in the TME, as well as in peripheral blood, have been found in metastatic and recurrent disease.[17,18] Basal levels increase with age and may partly account for the correlation of age with cancer.[10]

CD4 regulatory T cells (Tregs)

Tregs form a subset of T cells. They prevent autoimmunity, but can also promote the progression of cancer by causing anergy, apoptosis, and the cell-cycle arrest of activated T cells, which occurs through the production of IL-10, TGFβ, and direct cell-to-cell contact.[19] They also inhibit the function of dendritic cells and NK cells.[10,15] In patients with SCC of the head and neck, Tregs are present in the peripheral blood, but notably large numbers are also found within the tumour, as a likely consequence of the TME.[15] Tregs are also inversely proportional to the number of dendritic and CD8 + T cells in these patients.[10]

Tumour-associated macrophages (TAM)
These can be derived directly from the bone marrow or from the MDSC that differentiate into macrophages in the presence of cytokines within the TME.[15]

TAM can produce epidermal growth factors (EGF) IL-6, and IL-10, and have been associated with angiogenesis, local tumour progression, and metastasis.[20] They are initially recruited to the tumour and, once in the TME, are driven into an immunosuppressive role by the various cytokines that are present. High concentrations of these immunosuppressive TAM have been associated with metastasis and poor prognosis.[15]

Therapeutic strategies currently included in research studies

A summary of the agents and their indications for use is given in Table 3.

Monoclonal antibodies

An antibody is a protein (synthesised by the immune system) with a specific capacity to recognise a particular target protein or proteins. A monoclonal antibody is an identical clone of an antibody with the same function. Antibodies have several different roles in the regulation of immune function: they trigger the immune system, act as checkpoint inhibitors, and block mitotic signals. Many are currently under investigation, but we will discuss only a few key agents that have shown some promise in the treatment of SCC of the head and neck.

Anti OX-40
OX40 is a tumour necrosis factor (TNF) receptor that is located on the surface of T cells. When stimulated, it functions as a co-stimulator to improve the T-cell response in patients with metastatic disease.[21] The role of monoclonal antibodies in the form of anti-OX40 is now being investigated to ascertain their effects in stimulating such a response. The utility of this approach has been investigated both as monotherapy and in combination with other treatments, but as data have yet to be published, its use is currently restricted to trials.[21]

Checkpoint inhibitors
This group of antibodies is now the focus of a several clinical trials and research studies. Cancer cells can avoid attack from the immune system by the expression of surface ligands that bind to checkpoint receptors on T cells. This interaction inhibits the effect of the T cells, and prevents the triggering of an immune response. Checkpoint inhibitors are antibodies that bind to the checkpoint receptor on the T cell and prevent it from binding to the inhibitory ligand on the tumour cell. Without this inhibitory interaction, an immune response is triggered. Many important co-stimulatory and inhibitory interactions occur between antigen-presenting cells and T cells, but the discussion of many of them is beyond the scope of this paper.[22] Two of the more commonly researched targets are the PD ligand and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). The monoclonal antibodies that block these expressed ligands are discussed below.

Table 3
Therapeutic strategies.

Examples of agents	Mechanism of action	Current indications for use
Checkpoint inhibitors:		
Pembrolizumab, nivolumab, durvalumab, ipilimumab	Bind to the checkpoint receptor on T cells, allowing for activation of the immune response	Pembrolizumab – trial only Nivolumab – approved in UK for second-line palliative setting Durvalumab – trial only Ipilimumab – trial only
Anti-OX 40	Binds to TNF receptor on T cells to drive T-cell response in metastatic diseases	Trial only
Adoptive cell transfer	Most effective tumour-infiltrating lymphocytes are harvested and identified from a patient and reimplanted into a lymphodepleted patient	Trial only
Vaccination:		
Vaccination Therapeutic vaccination (given as treatment once tumour has already developed)	Introduction of a weakened or attenuated pathogen to precipitate an immune response to fight tumour cells	Trial only
Oncolytic virus treatments:		
Reolysin	Uses viruses to invade and destroy cancer cells	Trial only
Cytokines:		
IRX-2	Proteins that alter immune response and cellular function	Trial only

Ipilimumab. T-cell activation occurs after the interaction of the CD28 receptor with the CD80/CD86 receptors on antigen-presenting cells. In a cancer state the CD80/CD86 ligand binds to the CTLA-4 receptor on the T cell and results in T-cell inhibition. The function of ipilimumab is to block the CTLA-4 receptor, which prevents T-cell inhibition and enables an effective response against the tumour.[2]

In 2010, Hodi et al showed a modest increase in the survival of patients with metastatic melanoma (10 months in the ipilimumab group compared with 6.4 months in the control group).[23] These results at the time were a breakthrough for the role of immunotherapy, but further advances in check-

point inhibitors have seen ipilimumab lose relevance as a single-agent treatment.[24] There are, to our knowledge, no studies on SCC of the head and neck that show its efficacy as a single agent, and the focus now is on its use with other agents. Outcomes in patients treated with a combination of ipilimumab and nivolumab for malignant melanoma and non-small-cell lung carcinoma were better than when either agent was used alone, and the toxicity profile was acceptable.[24,25] Studies on this combination for the treatment of recurrent or metastatic SCC of the head and neck are ongoing.[26]

Pembrolizumab. In steady state, the PD-1 receptor on the surface of the T cell (usually activated CD4+ and CD8+) binds to the PD-1 or PD-2 ligands on other cells to inhibit activation of the T cell, which is essential for the regulation of autoimmunity. Tumour cells in SCC of the head and neck use this mechanism and express PD-1 ligands, which interact with T cells to suppress them.[27]

Pembrolizumab is a high-affinity, humanised IgG4-κmonoclonal PD-1 antibody[27] that binds to the PD-1 receptor on the T cell, and blocks the binding of the PD-1 ligand on the tumour cell. This prevents immune suppression of the PD-1 ligand.

Keynote-012 was a phase Ib, multicentre, non-randomised, open-label trial that showed the safety, tolerability, and activity of pembrolizumab in recurrent or metastatic SCC of the head and neck.[27,28]

Keynote-55 (single-arm, phase II study) examined its efficacy in SCC of the head and neck that was refractory to platinum and cetuximab.[29] Results were encouraging in this group with poor prognoses. The overall response rate was 16%, median survival was eight months, and the adverse events acceptable.[29]

Unfortunately, KEYNOTE-040,[30] a randomised phase 3 trial that compared pembrolizumab with standard of care (investigator's choice of methotrexate, docetaxel, or cetuximab), failed to reach its primary efficacy endpoint of improvement in median overall survival (8.4 compared with 7.1 months). It should be noted, however, that the group again consisted of patients with poor prognoses (progression after a platinum-containing regimen for palliative treatment, or within three to six months of chemoradiotherapy with platinum). Responses were more frequent and durable in the pembrolizumab arm (objective response rate (ORR) 14.6% compared with 10.1%, median duration of response 18.4 compared with 5.0 months). The incidence of adverse events of any grade was lower with pembrolizumab than it was with standard of care (63.0% compared with 83.8%), particularly events that were grades 3–5 (13.4% in the pembrolizumab arm compared with 36.3% in the standard of care arm). After the study, crossover in the standard of care arm (12.5 % of the patients went on to be given an immune checkpoint inhibitor) may have confounded the analysis of overall survival.

Based on tumour response and durability of response, pembrolizumab was approved by the US Food and Drug Administration (FDA) for patients with progressive recurrent or metastatic SCC of the head and neck on or after treatment with platinum-containing chemotherapy. It is also noteworthy that it was the first drug to be approved by the FDA for the treatment of solid tumours on the basis of the presence of a cancer biomarker (microsatellite, instability-high (MSI-H), or mismatch repair deficiency), rather than on the tumour's site of origin. It has not been approved for use the UK, but studies are continuing.

A phase 3 trial of pembrolizumab as a first-line treatment for recurrent or metastatic SCC of the head and neck, is comparing pembrolizumab monotherapy, pembrolizumab plus platinum/5-fluorouracil, and the EXTREME regimen (NCT 02358031).[31] KEYNOTE-412 is examining the use of pembrolizumab in the radical setting, adding it or placebo to chemoradiation for locally-advanced SCC of the head and neck (NCT 03040999).[32]

Nivolumab. Nivolumab, another checkpoint inhibitor with a similar mechanism of action to that of pembrolizumab, blocks interaction of the PD-1 receptor ligand with the tumour and T cells to prevent suppression of the immune response.

To date, the most important trial to explore its efficacy is the CheckMate 141 trial.[33] This was a randomised, open-label, phase 3 trial in which patients were assigned in a ratio of 2:1 nivolumab: investigator's choice (methotrexate, docetaxel, or cetuximab) for the treatment of recurrent, platinum-refractory SCC of the head and neck. Overall survival was significantly longer with nivolumab than with standard of care (7.5 compared with 5.1 months).

Response rates were 13.3% in the nivolumab arm and 5.8% in the standard of care arm. One-year survival of 36.0% in the nivolumab arm compared with 16.6% in the other is probably the most significant aspect of this trial, together with the longer time before patients reported a deterioration in quality of life, and fewer drug-related side effects.[10,33] As a result of this study, nivolumab was approved by the FDA in the US and the National Institute of Health and Care Excellence (NICE) and Scottish Medicines Consortium (SMC) in the UK for the treatment of progressive recurrent or metastatic SCC of the head and neck, or after platinum-based therapy.

Durvalumab. Like nivolumab and pembrolizumab, durvalumab works through the PD-1 receptor/ligand pathway. It is a human monoclonal antibody that inhibits the binding of PD-L1. The phase 2 CONDOR trial looked at the safety and efficacy of durvalumab alone, durvalumab in combination with tremelimumab (anti CTLA-4), and tremelimumab alone, in previously treated patients with recurrent or metastatic SCC of the head and neck and low expression of PD-L1.[34] When compared with other PD-/PDL1 inhibitors, the efficacy of durvalumab was similar (overall response rate of 9.2% with durvalumab alone compared with 7.8% in combination with tremelimumab, and 1.6% with tremelimumab alone). Median survival was highest in the combination group (7.6 months); for durvalumab alone it was 6 months and for tremelimumab alone 5.5 months.[35]

The HAWK study examined the use of durvalumab in the second-line palliative setting for patients with SCC of the head and neck and high expression of PD-L1. Twelve-month survival was 33.6% with an increased response in patients with human papillomavirus (HPV)-positive disease. The safety profile was acceptable, with an 8% incidence of adverse events of grade 3 or above.[36] Phase III studies of durvalumab with or without tremelimumab (anti-CTLA-4) in recurrent or metastatic SCC of the head and neck are currently being conducted (EAGLE trial).[37]

Adoptive cell transfer

Adoptive cell transfer involves the harvesting of autogenous tumour-infiltrating lymphocytes from a tumour. These are then grown in vitro and tested against the tumour to establish their tumour-killing properties. When the most effective anti-tumour populations have been selected, T cells are expanded and implanted back into the patient, who has had non-ablative lymphodepletion, with the aim that they will mount an immune response against residual tumour cells.[38,39]

This technique has been effective against a variety of malignancies including metastatic melanoma, cervical cancer, lymphoma, leukemia, cholangiocarcinoma, and neuroblastoma.[38] To our knowledge only a few case series have looked into the use of adoptive cell transfer in cancer of the head and neck, and while they suggest some potential benefit, the numbers are too small to draw any meaningful conclusions.[40] There is also interest in the investigation of adoptive cell transfer in combination with other immunotherapies such as PD-1 checkpoint inhibitors (NCT 02858310),[41] and the results of these trials are eagerly awaited.

Vaccination

Vaccinations work by exposing the immune system to a weakened or attenuated form of a virus, which allows for the production of antibodies without exposure to the dangers of the actual pathogen. These antibodies are then able to mount a response from memory B cells in the presence of a future infection.

Once the link was established between HPV and cervical cancer, the search for a possible vaccine began. HPV 16 and 18 were targeted specifically, as they are the two most oncogenic strains, and HPV 16 is present in 95% of HPV-positive tumours of the oral cavity and oropharynx. HPV causes malignant transformation by the secretion of E6 and E7 proteins, which affect the function of p53, pRb, and telomerase, driving tumour progression.

The Future II study showed a significant reduction in high-grade cervical intraepithelial neoplasia in patients who had had HPV vaccinations compared with those who had been given placebo.[42]

Whilst this work has obvious potential, our understanding of the value of such vaccines in SCC of the head and neck is largely speculative, and is based on our knowledge of the pathogenesis of HPV-positive disease and the inferences we draw from our understanding of its use in other anatomical sites.[43] Because of the inherent difficulty of large population studies over long periods of time, and the relatively low incidence of HPV-positive oropharyngeal cancer in the general population, it is unlikely that we will be able to run large randomised controlled trials on the benefit of vaccination in this group of patients. Instead, we will need to rely on HPV infection within the population and the incidence of HPV-positive oropharyngeal SCC as a surrogate with which to establish benefit.

Therapeutic vaccines are used to treat cancers that have already developed. They are intended to delay or stop the growth of cancer cells, cause the tumour to shrink, prevent the cancer from coming back, or eliminate any cancer cells that have not been killed by other forms of treatment. They work by activating cytotoxic T cells and directing them to recognise and act against specific types of disease, or by inducing the production of antibodies that bind to molecules on the surface of cancer cells.

Work done in cases of HPV-related vulvar intraepithelial neoplasia showed that 9 of 19 patients had responded completely to the therapeutic vaccination at one year.[44] The use of therapeutic vaccinations with checkpoint inhibitors are now being studied on animals to find out if combining different types of immunotherapy will improve their effectiveness. It is hoped that these initially positive findings will translate to improved outcomes for patients with HPV-positive cancer of the head and neck. The HARE-40 study is currently recruiting such patients (either those who have been treated successfully or those with advanced disease). It is a phase I/II vaccine dose escalation study that aims to establish a safe, tolerable, and recommended dose of HPV vaccine.[45]

Further population studies on preventative vaccinations, or clinical trials on therapeutic vaccinations, will be required before we can verify the actual utility of such interventions. Finally, it must be considered that poor uptake of a preventative vaccination in certain populations could be a potential barrier to the complete eradication of the disease.

Oncolytic virus therapies

Oncolytic viruses use their capacity to infect and replicate to invade and destroy cancer cells selectively.[46] This is typically done by genetically engineering a virus that can replicate, and invade and destroy cancer cells without harming normal tissues. Methods used to produce these viruses include the selection of a virus that is non-virulent to human cells, or the genetic engineering of one with the required characteristics.[46]

Reolysin® (Oncolytics Biotech Inc) a variant of the reovirus, is a non-pathogenic, double-stranded RNA virus that is located in the gastrointestinal or respiratory tract of humans.[47,48] It exhibits oncolytic activity to cells with activated Ras signalling (as in malignancy), and research is currently being done in metastatic cancer of the head and neck. The results of the NCT 01166542 trial, which

investigated its efficacy in combination with paclitaxel and carboplatin in platinum-refractory head and neck cancers,[49] are not yet published.

Further work with oncolytic viruses includes research into their combined use with other immunotherapy agents such as checkpoint inhibitors.[46]

Cytokines

Cytokines are small proteins released by cells that have an impact on cellular interaction and function. Some, as described above, help to potentiate immune suppression, whilst others have an anticancer effect by the activation of an immune response. The chemical manipulation of an immune response was initially promising in phase 1 trials, but phase 2 trials so far have failed to show any improvement in survival.[50,51] One explanation for this is the fact that a particular cytokine will have various effects on other cells, and some of them may not be intended and occasionally unfavourable.

The INSPIRE trial,[5] a phase 2 trial of a neoadjuvant chemokine agent used in SCC of the head and neck before resection, has completed recruitment and results are pending.

There is also interest in the role of cytokines in the context of their use as an adjunct to other forms of immunotherapy. For example, the use of IL-2 and IL-15 to stimulate T cells to work in synergy with other forms of immunotherapy, and as biomarkers for response rather than treatment.[52] High-dose IL-2 therapy, which is known to be associated with significant toxicity (capillary leak syndrome), is delivered only in specialist centres that have experience of its use and direct access to critical care.

Immunotherapy with radiotherapy

As well as direct and indirect effects on target-volume cellular DNA, radiotherapy has both local and systemic effects. Locally, non-irradiated tissues adjacent to the tumour trigger the release of immune and inflammatory factors to precipitate an immune response known as the "bystander" effect.[9] The resultant inflammatory process subsequently mediates a response, which often has an immunologically-derived antitumour effect.

Radiotherapy can initiate a systemic immune response through the abscopal effect. This refers to the ability of radiation delivered to a local site to minimise or eradicate metastases at distant sites. The immune system is crucial to this, as it is the immune-mediated response secondary to tissue damage that allows for the production of inflammatory mediators. The immune response that is triggered includes the recruitment and activation of T cells, secretion of cytokines, improvements in tumour recognition, and an increase in antigen presentation.[9]

There has been renewed interest in the exploitation and maximisation of the abscopal effect of radiation in combination with immunotherapy, and success in doing so has been shown in prostate cancer and melanoma.[53]

When combined, checkpoint inhibitors and ionising radiation have a synergistic relation. Anti PD-1 and anti CTLA-4 allow for the activation of T cells, but an effective antigen-presenting cell function is still required to trigger the response. As mentioned above, radiotherapy can improve the effect of antigen-presenting cells, and therefore the ability of T cells to recognise and trigger an immune response against cancer cells.

Trials using a combination of radiotherapy and immunotherapy are underway in locally-advanced head and neck cancer, and may lead to a new combined approach – for example, with nivolumab and pembrolizumb.[54,55]

Immunotherapy with chemotherapy

Chemotherapy was previously thought to have predominantly immunosuppressive effects, but new research has shown that systemic antitumour immunity can result from the triggering of antigen presentation and the arming of T cells.[9] Clinical trials are currently underway to investigate the efficacy and subsequent safety of such combinations to support the early promising results that were seen in animal models.

Disccusion

The role of biomarkers

To maximise success with immunotherapy we need to select the patients who are most likely to respond to a particular treatment by identifying predictive biomarkers. Tumour biomarkers include those associated with the tumour cell, and they include expression of PD1/PD-L1 receptors, cellular mutations, mismatch repair deficiency, indoleamine 2-3-dioxygenase inflammatory genes or mediators, and tumour neoantigens.[56,57] Biomarkers of the immune response include tumour infiltrating immune cells, microbiota, single neucleotide polymorphisms, absolute neutrophil/lymphocyte count, peripheral blood markers, and tumour-specific antibodies or T cells.[57] Most of the work on the correlation of biomarkers and drug response has been done in cancers not of the head and neck, and results so far have failed to show a predictable correlation between the biomarkers expressed and response to treatment. This is because of the complete and dynamic interaction between the immune system and tumour cell, which varies according to the particular immune or inflammatory response that is mounted, the temporal sequence of events, and the mutational landscape of the cell. As such a simple correlation cannot be derived in a predictable fashion, reported findings have varied.[3,57]

With specific reference to SCC of the head and neck, Ferris showed in Checkmate 141, that there was a increased response to nivolumab in patients with a PD-1 expression of more than 1% when compared with those in whom expression was lower than 1%, but there was still a response

Table 4
Adverse effects from immunotherapy.

System	Adverse effect
Central nervous system	Neuropathy, encephalopathy, myasthenia gravis, Guillain Barré syndrome, depression, behavioural changes
Ocular	Uveitis, episcleritis
Skin	Rash, puritis, Stevens-Johnson syndrome
Endocrine	Thyroid dysfunction (hypo/hyper), hypopituitarism, hypophysitis, adrenal insufficiency
Pulmonary	Pneumonitis, pulmonary oedema
Renal	Nephritis, renal failure
Gastrointestinal	Nausea and vomiting, colitis, diarrhoea, derangement of pancreatic enzymes
Hepatic	Raised liver enzymes
General	Fevers, chills, lethargy

in PD-L1-negative tumours compared with conventional chemotherapy.[3,58] In the UK therefore, expression of PD-1 is not a mandatory requirement for the use of checkpoint inhibitors.[3,58] In the US, PD-1 is used by the FDA as a criterion for their use, but this area of research is still experimental, and ongoing translational investigations (particularly in "window of opportunity" studies in SCC of the head and neck) will contribute to this knowledge.

The emergence of neoadjuvant immunotherapy

The initial promise of immunotherapy has naturally led to the consideration of its use in the neoadjuvant setting. Some of the reasons for this include the possibility of reducing the size of the tumour, which may in turn lessen the functional and aesthetic impact of ablation (a factor that is particularly critical in the head and neck). Others include improving marginal clearance; reducing the risk of metastatic disease by providing early systemic treatment, and potentially allowing for earlier treatment, as complex resection and reconstruction can take weeks to coordinate. Several trials are underway in head and neck cancer to evaluate the role of immunotherapy, and specifically of checkpoint inhibitors as neoadjuvant treatment in SCC. Most of them are active and still recruiting.[59]

Adverse effects of immunotherapy

Various adverse effects of the drugs associated with immunotherapy affect major systems in the body, It is beyond the scope of this publication to go into detail, however a brief smmary of effects are presented below. These include, but are not limited to, the systems listed in Table 4.[60–62]

Conclusions

Recent developments in immunotherapy across oncology have resulted in important gains in tumour control and survival for a subset of patients with diseases that have responded to these new agents. The ability to select the patients who are most likely to respond is key, but the correlation of outcomes with clinical features or molecular biomarkers is as yet unclear. Studies must continue to address this challenge, and to incorporate translational as well as clinical endpoints.

Research workers studying cancer of the head and neck are well placed to conduct these trials and are now at the forefront of immuno-oncological research with new agents being tested before, or together with, definitive treatment in the radical setting. The ability to access tumour tissue in a relatively safe and straightforward manner lends itself to excellent opportunities for the translational research that is associated with these new drugs. Clinical success with immune modulating agents in the radical setting may ultimately allow us to use less morbid treatments than those that are presently required to treat locally advanced disease or to improve disease control. Success of these novel approaches, however, depends on close collaboration between the clinicians who treat patients with these diseases. The involvement of multidisciplinary teams is crucial, as no single specialty can conduct these studies in isolation. The investigation of immunotherapeutic agents in the neoadjuvant setting in particular is an exciting opportunity for the surgical community to engage with, and contribute to, a new treatment paradigm.

Ethics statement/confirmation of patients' permission

Not applicable, as this is a review article. Patients' permission was also not necessary.

Conflict of interest

We have no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.bjoms.2019.08.002.

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