Novel Treatment Options in Head and Neck Cancer

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Introduction

In head and neck squamous cell carcinoma (HNSCC) tumor escape mechanisms can be observed even in early tumor stages [1]. These protective mechanisms are manifold and include i) expression of immunosuppressive factors in the tumor micromilieu, ii) activation and expansion of suppressive immune cell populations, iii) downregulation of tumor associated surface antigens, and iv) suppression of an adequate co-stimulation.

On the other hand, HNSCC cells present many somatic mutations and genetic clusters, which could be targeted by specific immunotherapy [2–5]. Currently, immunotherapeutic approaches in routine clinical use are limited to antibodies applied in a palliative setting and sporadic combinations with radiation in curative efforts [6]. The expansion of therapeutic indications, e.g. adjuvant or neoadjuvant, would be desirable to improve survival rates for HNSCC patients.

Immunotherapeutic interventions are divided into 4 subgroups based on their approach: active vs. passive, and specific vs. nonspecific (fig. 1). Active immunotherapy induces an immune response in the host with a long-lasting potential. Passive immunization is based on the transfer of immune cells or antibodies with an antiproliferative effect on tumor cells. Both approaches can target specific tumor-associated antigens (TAA). Nonspecific immune approaches induce a general activation of the immune system, which is suppressed by a variety of tumor escape mechanisms. A selection of novel immune approaches is listed and discussed below.

Cytokines

In the past, a variety of cytokines, e.g. interferon(IFN)-α, IFN-γ, interleukin(IL)-2 and IL-12, have been tested for the treatment of HNSCC with limited success [1]. However, a new approach is based on a mix of cytokines that is harvested from in vitro-stimulated allogenic lymphocytes. The product is defined by its concentration of IL-2 and injected peritumorally in a neoadjuvant setting to increase the recruitment of beneficial immune cells into the tumor environment [7, 8].

Currently, phase III studies are ongoing for 2 similar products (IRX-2®, Multikine®) with a large number of participants (NCT01265849, NCT02609386). The influence of subcutaneous injection of recombinant IL-15 is being tested in 2 parallel phase I

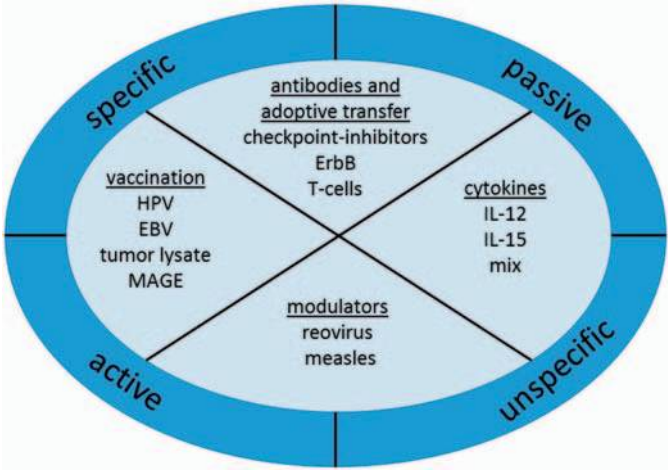

Fig. 1. The immune modulatory approaches can be subdivided into active and passive, as well as specific and nonspecific for tumor-associated antigens.

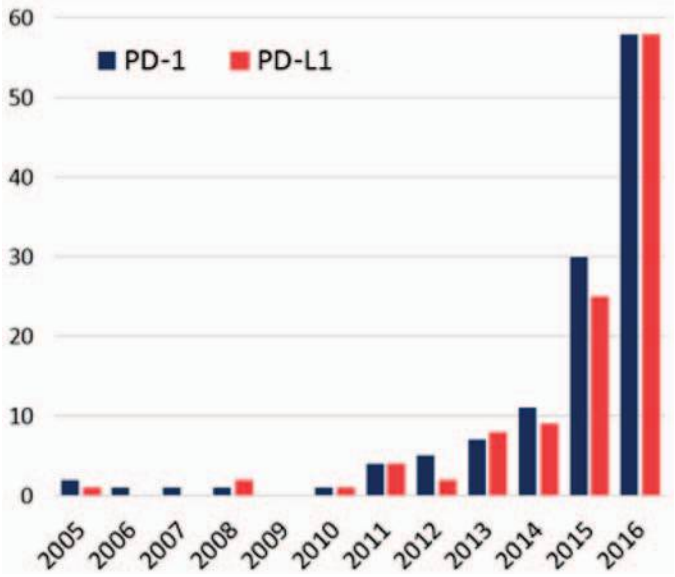

Fig. 2. The clinical success of immune checkpoint inhibitors is mirrored by the exponential increase of publications in this field. Numbers on the y-axis represent the results when searching for 'head and neck cancer' AND 'PD-1' or 'PD-L1' in the openly available PubMed database.

studies (NCT01727076, NCT02452268). IL-15 has been shown to be a homeostatic factor for natural killer (NK) cells and killer T (T_K) cells. Interim results of the first study support these findings in a cohort of 18 cancer patients [9].

Antibody-Based Therapy

The number of clinical studies with specific antibodies has risen exponentially in the past few years. This development is due to the improvement in industrial manufacturing methods and the associated reduction in antibody production costs as well as repeated reports of clinical improvement under antibody therapy. The potential effects of antibodies against cell surface markers include i) activation of complement; ii) NK-mediated cytotoxicity; iii) activation of apoptotic signals; iv) inactivation of proliferation signals; and v) checkpoint modulation [1]. In particular, the fast-growing group of checkpoint inhibitors has entered the field of clinical studies over the last 2 years.

Epidermal Growth Factor Receptor Antibodies

The epidermal growth factor receptor (EGFR) is a suitable target for antitumor therapy as it is regularly overexpressed in HNSCC. Its activation induces cell proliferation, invasion, and angiogenesis in the tumor. The last 10 years of experience have shown that for the EGFR inhibitor cetuximab the response rate is 15–20% for palliative patients. Therefore, cetuximab is often applied in combination with other experimental regimens [10]. In most cases, clinical response is clearly correlated with an acneiform skin rash, which is a sign of the immunological reaction via EGFRs in the skin [11]. A representative clinical study compared cetuximab with mitomycin/fluorouracil (5-FU) in a phase IV setting (NCT02015650). The group of Boockvar employed an innovational approach in which cetuximab is injected intra-arterially to increase the antibody concentration in the tumor tissue (NCT02438995) [12].

The surface molecule c-Met (synonymous with hepatocyte growth factor receptor, HGFR) is normally expressed on stem cells and progenitor cells and has an effect on tumor growth similar to EGFR; various clinical trials have already been reviewed [13]. Antibodies against c-Met are currently evaluated in combination with cetuximab in phase I and II studies for HNSCC (NCT01696955, NCT01332266). The only known ligand for c-Met is HGF. Therefore, the HGF-c-Met axis can also be inhibited by the HGF inhibitor ficlatuzumab, which is currently being tested in a phase I study (NCT02277197).

Therapeutic antibodies against the toll-like receptors (TLRs) are immunomodulatory oligonucleotides with an agonistic effect. In the past, the TLR-9 agonist EMD1201081 showed a good tolerance in a phase II study but no therapeutic improvement over cetuximab [14]. However, another study with the same TLR-9 agonist in combination with cisplatin was terminated ahead of schedule due to safety concerns (NCT01360827). Recently, the preliminary results of a phase I/II study with 13 HNSCC patients receiving the TLR-8 agonist motolimod were published. A disease control rate was achieved in 54% of patients when motolimod was combined with cetuximab [10].

Immune Checkpoint Modulation

Immune checkpoint inhibitors show great therapeutic potential for HNSCC. 4 years ago, no studies for immune checkpoints were registered for HNSCC [1]. Today, the majority of studies are based on this group of antibodies with encouraging results in the clinical setting. This is mirrored by the exponential increase of publications on this topic (fig. 2). Activation of specific T cells is induced either by antigen-presenting cells (APCs) via MHC-II or by tumor cells via MHC-I. A co-stimulatory signal, e.g. CD28, and an activating cytokine milieu are also requisite. T-cell activation can be

regulated by a variety of checkpoint molecules, e.g. CTLA-4, PD-1, OX-40 and CD27 (fig. 3). The functional mechanism of immune checkpoint inhibitors is described in detail elsewhere [15]. Inhibition of the programmed death receptor (PD-1) and its ligand (PD-L1) has shown relatively good success rates in melanoma patients. In particular, the repeated reports on long-term responders were unexpected and enabled clinical trials even for other tumor entities, e.g. HNSCC [16]. Despite the success rate in melanoma patients, checkpoint inhibition seems to have no effect in patients with mucosal melanoma; the exact reasons for this remain unclear [17].

Currently, 2 PD-1 antibodies, pembrolizumab and nivolumab, are under evaluation for HNSCC therapy. The approval study for pembrolizumab included 132 patients with recurrent or metastasized HNSCC, all of whom had received at least 1 palliative regimen in the past. The overall response rate (complete or partial response) was 25%, and clinical responses were independent of the patient's human papillomavirus (HPV) status (keynote-012) [18]. The response rate is not exceptional when compared to 15–44% for other palliative first-line regimens [19]. However, even in HNSCC, a high percentage of responders were identified with long-term disease control. 2 HNSCC-specific randomized phase III trials have recently completed patient accrual. In the first study, pembrolizumab is compared to standard therapy in a palliative setting, e.g. methotrexate, docetaxel, or cetuximab (n = 600, keynote-040, NCT02252042). The second study evaluates pembrolizumab as a first-line palliative regimen in combination with cisplatin and 5-FU (n = 780, keynote-048, NCT02358031). The potential application of pembrolizumab in a neoadjuvant or adjuvant setting is being tested in 2 long-term phase II studies before or after surgical therapy of advanced HNSCC (NCT02296684, NCT02641093). The adjuvant capacity of pembrolizumab in combination with primary radiochemotherapy will be evaluated in a large cohort of HNSCC patients (NCT03040999). Another single-arm phase II study combines pembrolizumab with re-radiation in recurrent HNSCC (NCT02289209). Due to the unexpected success of the PD-1 inhibitors, several trials are now investigating their combination with other immunotherapeutic inhibitors, e.g. against the Bruton's kinase (BTK, NCT02454179) or the macrophage colony-stimulating factor receptor (M-CSFR, NCT02452424). BTK is essential for B-cell development, and M-CSFR is involved in the development of breast cancer and acute myeloid leukemia (AML).

The second PD-1 inhibitor nivolumab has also been tested successfully in HNSCC (n = 360, checkmate-141) [20]. The median survival time was 7.5 months for nivolumab as compared to 5.1 months for standard therapy, namely methotrexate, docetaxel, or cetuximab. The response rate in the nivolumab arm was 13.3%. 2 open phase II/III studies evaluate the combination of nivolumab and the CTLA-4 inhibitor ipilimumab in the palliative setting (NCT02823574, NCT02741570) or neoadjuvant setting (NCT03003637). However, a high rate of adverse events is expected in this approach [21]. Other experimental combinations with nivolumab in clinical trials include inhibitors of SYK (NCT02834247) and the checkpoint CD27 (NCT02335918), or agonists for TLR-8 (NCT02124850) and others.

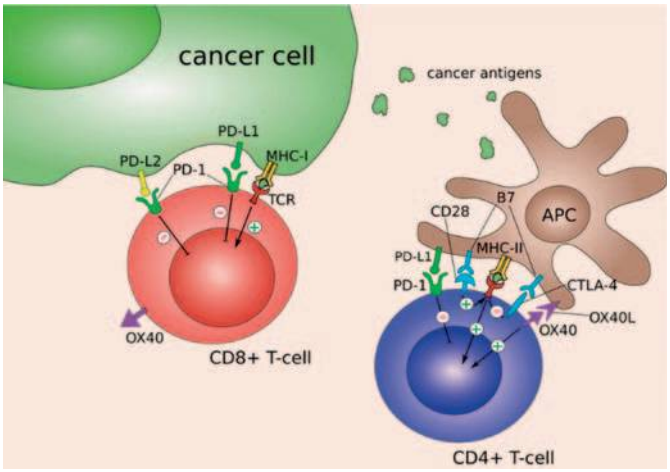

Fig. 3. Activation of specific T cells is induced either by antigen-presenting cells via MHC-II or by tumor cells via MHC-I. A co-stimulatory signal, e.g. CD28, and an activating cytokine milieu are also requisite. T-cell activation can be regulated by a variety of checkpoint molecules, e.g. CTLA-4, PD-1, OX-40 and CD27. Figure modified from [19].

Inhibition of the checkpoint PD-1 can also be achieved by antibodies against its ligand PD-L1. Most studies in HNSCC patients have been performed with the PD-L1 inhibitor durvalumab. It is currently being tested in 2 non-randomized phase II studies either for cisplatin-refractory palliative patients (NCT02207530) or for palliative solid tumors (NCT01693562). Durvalumab is also being tested in combination with the CTLA-4 inhibitor tremelimumab in a randomized phase II study in palliative HNSCC patients (NCT02319044). Again, the increased percentage of adverse events, which has led to the premature closure of a similar study in lung cancer patients [22], should be considered. Lastly, in a phase II study of HNSCC patients (NCT02499328), durvalumab is combined with an inhibitor of the STAT3 pathway by the antisense molecule AZD9150. In cancer cells, activation of STAT3 induces proliferation and inhibits apoptosis [23]. In a phase I study on solid tumors, a second inhibitor of PD-L1, atezolizumab, is combined with an inhibitor of indoleamine 2,3-dioxygenase (IDO), which leads to immune suppression in the tumor microenvironment by reduction of tryptophan (NCT02471846) [24]. The third PD-L1 inhibitor, BMS-936559, is not currently being evaluated in HNSCC patients.

TNF Receptor Superfamily

In contrast to the antagonistic function of the above-described checkpoint inhibitors, activation of the TNF receptor superfamily induces an immune-stimulatory pathway in T cells [25]. The most prominent members of this group with therapeutic potential are (1) OX40/OX40 ligand, (2) CD137/4-1BB ligand, and (3) CD27/CD70. The co-stimulatory factor OX40 is expressed on activated but not on resting T cells. Stimulation of OX40 by agonistic antibodies prevents cell apoptosis and induces the production of immune stimulatory cytokines. The only HNSCC-specific study evaluates the OX40 agonist MEDI6469 in a non-randomized, neoadjuvant trial before surgery in advanced tumor stages (NCT02274155).

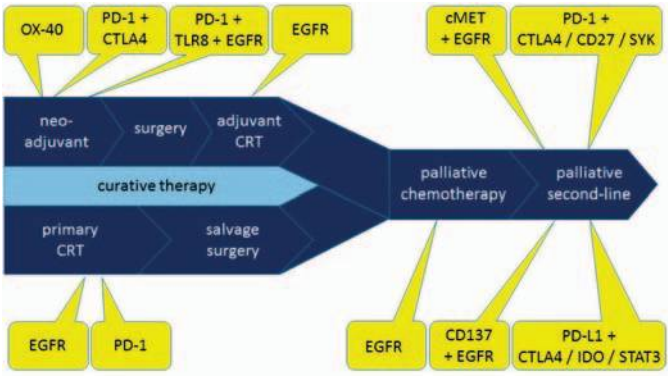

Fig. 4. In head and neck cancer, therapeutic antibodies can be applied at different disease stages in a curative or palliative setting.

Two other agonistic OX40 antibodies, MEDI0562 and PF-04518600, are currently being tested in phase I studies for solid tumors (NCT02318394, NCT02315066). The antibody urelumab activates the receptor CD137, which is expressed on the surface of various immune cells. T_K cells, which have a direct anti-neoplastic activity, are highly sensitive to this approach. A one-armed phase I study includes patients with HNSCC or colon carcinoma and combines urelumab with cetuximab (NCT02110082). In solid tumors, the CD27-agonist varlilumab is tested in combination with the PD-1 inhibitor nivolumab as described above (NCT02335918). Activation of CD27 induces production of the antibody in plasma cells and may support the anti-neoplastic immune stimulation.

The therapeutic options for patients with head and neck cancer have been clearly expanded by immune modulatory approaches that have proven their effectiveness in a long list of clinical trials (fig. 4).

Tumor Vaccination

Antigen-specific tumor vaccination is regarded as an approach with great potential as it can induce a long-lasting immune response against tumor cells. In HNSCC, several clinical vaccination trials have been performed in the past without achieving a noteworthy survival benefit [1]. Targeted structures included, among others, p53 [26], tumor lysate [27], MAGE, and HPV [28]. Recently, a phase II study was published vaccinating HNSCC patients against 3 cancer testis antigens. In comparison to the untreated patient group, median survival was prolonged by 1.4 months for vaccinated patients [29].

Two current, HNSCC-specific, non-randomized phase II studies focus on therapeutic vaccination against the HPV. In the first study, HPV^+ patients receive the plasmids for HPV-16 (E6/7), HPV-18 (E6/7), and IL-12 by intramuscular electropermeabilization (NCT02163057). The plasmids are administered either before and after tumor surgery (arm 1) or after chemotherapy (arm 2).

The second study is also performed in a neoadjuvant setting. Before tumor surgery, patients receive living listeria bacteria that are bioengineered to continuously produce the HPV-specific oncogene E7 (NCT02002182). The vaccination study with synthetic long peptides of HPV-16 E6 and E7 (ISA-101) in combination with the PD-1 antibody nivolumab in HPV^+ solid tumors is not yet open for patient accrual (NCT02426892).

The idea to induce antigen presentation by lethally radiated fibroblasts is being developed for an HNSCC-specific phase I study. The allogenic fibroblasts are transfected with autologous tumor DNA before intradermal injection (NCT02211027). A specific immune response against the Epstein Barr virus (EBV) is induced by vaccination against the EBV proteins EBNA1 and LMP2 in EBV^+ carcinomas of the nasopharynx [30]. The follow-up phase II study in a larger patient cohort has been closed and the results are being evaluated (NCT01800071). Vaccination of HNSCC patients against MAGE-3 by intramuscular peptide injection in an adjuvant setting has been tested successfully in the past [28]. The following multicenter phase II study is nearing patient recruitment (NCT02873819).

Immune Transfer

In cancer patients, APCs are often impeded in their function by tumor-induced immune suppression [31, 32]. This problem may be solved by the adoptive transfer approach in which autologous or allogenic immune cells are stimulated in vitro and reinfused into the patient. Early trials with immune transfer in HNSCC patients have already been reviewed [6]. The transfer of EBV-specific T cells has doubled the survival time in a phase I study in 24 patients with nasopharynx carcinoma (NPC) when compared with a historic patient group [33]. Based on these positive results, similar phase I/II studies were initiated in NPC patients, which currently hold recruitment or evaluation status. These studies either used autologous (NCT00834093, NCT00953420) or allogenic (NCT01447056) EBV-specific T cells.

Encouraging results were also published on the immune transfer of autologous tumor-infiltrating lymphocytes (TIL). In a phase II study, TIL were harvested and stimulated in vitro before reinjection together with IL-2 and the chemotherapeutic agents aldesleukin and cyclophosphamide. After a single injection, 3 of 9 HNSCC patients showed a clinical response [34]. Another phase II study for patients with NPC or HNSCC is based on NK cells, which are expanded in vitro. NK cells are reinfused together with the EGFR antibody cetuximab, utilized as a target marker for NK cells in $EGFR^+$ tumors (NCT02507154).

The in vitro transduction of a second, chimeric antigen receptor on the surface of autologous helper T cells is a technical challenge. This approach is being evaluated in several phase I studies with ErbB-specific receptors in HNSCC patients (NCT01818323) or with NY-ESO-1- and MAGE-A4-specific receptors in solid tumors (NCT02366546, NCT02096614). It is believed that this additional receptor for tumor-specific antigens can help improve the recognition of tumor cells and the tumor-specific immune response [35]. In case of intracellular antigens, e.g. NY-ESO-1 or MAGE-A4, an additional cytotoxic therapy is compulsory to release these antigens.

Conclusions

The therapeutic options for patients with head and neck cancer have been clearly expanded by immune modulatory approaches that have been proven effective in a long list of clinical trials. Based on these observations, the landscape of clinical studies has changed considerably from antibody-based growth factor inhibition towards immune checkpoint modulation. Since the approval of checkpoint inhibitors for palliative treatment, new indications in the adjuvant and neoadjuvant setting are being tested in large patient cohorts. Even the combination of 2 or more immune modulatory approaches and the correct synchronization with standard cancer therapy is promising and warrants suitable clinical trials.

Disclosure Statement

T.K.H.: Advisory Board for Merck KGaA and MSD Sharp & Dome GmbH; P.J.S.: Advisory Board for Bristol-Myers Squibb GmbH & Co. KGaA; S.L.: Advisory Board for AstraZeneca; L.B.: Advisory Board for Bristol-Myers Squibb GmbH & Co. KGaA and consultant for Merck Serono GmbH. The authors declared no potential conflicts of interest with respect to their research, authorship, or publication of this article.

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