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Immunotherapy for head and neck squamous cell carcinoma

Qiao Li, Mark E.P. Prince, Jeffrey S. Moyer *

University of Michigan Comprehensive Cancer Center, 1500 E Medical Center Dr., Ann Arbor, MI 48109, United States

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SUMMARY

Objectives: To review the current state of immunotherapy of head and neck squamous cell carcinoma.
Materials and Methods: Review of the literature with emphasis on clinical trial data.
Results: Patients with head and neck squamous cell carcinoma (HNSCC) have long been known to be immunosuppressed. This impairment of the immune system is believed, at least in part, to underlie the poor outcomes in this patient population. Modulating the immune system to improve cancer outcomes is an attractive concept in this difficult to treat population.
Conclusion: New studies have started to unravel the mechanisms of immunosuppression and new therapies are being developed to exploit this new information.

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Immune defects in HNSCC and immunotherapy

Many human malignancies, including head and neck squamous cell carcinoma (HNSCC) are associated with quantitative and qualitative deficiencies in the immune system. Patients with HNSCC have lower absolute lymphocyte counts [1], higher immunosuppressive regulatory T (Treg) cells [2,3], and higher tumor-associated macrophages [4] when compared to healthy controls. These immune defects also include down-regulation of tumor leukocyte antigen expression [5] and spontaneous apoptosis of cytotoxic T-lymphocytes (CTLs) [6] along with the direct inhibition of immune defenses by the tumor secretion of vascular endothelial growth factor (VEGF) [7], prostaglandin E_2 [8,9], transforming growth factor(TGF)-ß [10], and interleukin (IL)-10 [10]. Qualitative abnormalities also include impaired natural killer (NK) activity [11,12], impaired maturation of plasmacytoid dendritic cells (DCs) [13], and poor antigen-presenting function [14–17].

With an enhanced awareness of the immune defects present in HNSCC as well as much greater understanding of the basic mechanisms of the immune system in carcinogenesis, rationale therapeutic strategies are being developed to take advantage of this new knowledge. Five broad approaches are gaining popularity in the immunotherapy of HNSCC: (1) monoclonal antibody therapy; (2) cytokine therapy; (3) cancer vaccines; (4) T cell-based therapy, and (5) immunological targeting of HNSCC cancer stem cells.

Conventional chemotherapy and radiation-conferred antitumor immune effects

There is a greater appreciation for the role of the immune system in the mechanisms of tumor eradication with conventional treatment modalities. Conventional thinking is that cytotoxic chemotherapy and/or therapeutic external beam radiation act directly on the tumor. While certainly true in many instances, a growing body of preclinical and clinical data would suggest that the immune system plays a significant and meaningful role in tumor elimination with these standard treatment approaches.

Initially introduced in 1953, the abscopal bystander effect is the regression of tumor outside of the radiation field [18]. Typically seen in melanoma, lymphoma, and renal-cell carcinoma, this effect is believed to be dependent on an intact immune system [19]. Several reports in humans have demonstrated distant tumor responses outside the radiation fields that were correlated with elevated tumor-specific antibodies and T-cell activation [20,21]. Taken together, these observations lend indirect support to the concept that the immune system is involved in chemoradiation.

More direct support for the immune system's involvement in chemoradiation comes from the danger signals released by dying cells. Apetoh et al. [22] describe a pathway in both mice and humans where dying tumor cells release a protein [high mobility-group box 1 (HMGB10)] that can activate the innate and adaptive immune system through Toll-like receptor 4 (TLR4) expressed on dendritic cells (DCs). In this study [22], patients with breast cancer who possess a TLR4 loss-of-function allele recur more quickly after chemoradiotherapy than those carrying the wild-type TLR4 allele.

* Corresponding author at: University of Michigan Medical Center, 1500 E Medical Center Drive, TC 1904, Ann Arbor, MI 48109, United States.
E-mail address: jmoyer@umich.edu (J.S. Moyer).

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High dose, or maximally tolerated doses (MTD), chemotherapy is well known to be immunosuppressive through direct effects on the immune system. However, low dose or metronomic chemotherapy may be more immunostimulating than immunosuppressive [23]. The immunostimulatory effects of metronomic chemotherapy include immunogenic cell death by increased antigen presentation [24–26], depletion of immunosuppressive Treg [27–30] and myeloid-derived suppressor cells (MDSC) [31], and enhancement of cytotoxic effector cells [32,33].

The effects of cytotoxic chemotherapy and radiation alone on the immune system make this an attractive approach to use in conjunction with immunotherapeutic strategies. Modulating the tumor microenvironment or the host immune system to be more receptive to systemic immunotherapy has strong support in preclinical models [34–37]. The use of chemotherapy and/or radiation along with immunotherapy in humans will be discussed below.

Monoclonal antibody therapies

Monoclonal antibody therapy is currently the most widely used form of immunotherapy in cancer patients [38]. Monoclonal antibodies directed against CD20 and HER-2 are standard of care in hematopoietic malignancies and breast cancer, respectively [38].

Epidermal growth factor receptor

Monocloncal antibodies targeting the epidermal growth factor receptor (EGFR) are the most common immunotherapy in HNSCC [39]. EGFR leads to proliferation, survival, and metastasis in HNSCC and is mediated by oncogenic signaling along the RAS/MAPK and PI3K/Akt pathways [40]. While 90% of HNSCCs overexpress EGFR [41], high levels of EGFR do not predict response to cetuximab [42,43] and EGFR pathway inhibitors (intracellular tyrosine kinase) are not associated with meaningful clinical responses [44,45]. These observations argue for additional mechanisms of antitumor activity rather than just the inhibition of the signaling cascade with EGFR activation. Innate and adaptive immunity including antibody-dependent cellular cytotoxicity (ADCC) appear to have a significant role in the mechanism of action of cextuximab [46].

Cetuximab is the first and best studied monoclonal antibody against EGFR and is a chimeric IgG1 isotype containing a human constant region and a mouse variable region. Bonner et al. [47] studied 424 patients with HNSCC that were randomized to either radiation alone or radiation and cextuximab and found a significant increase in overall survival from 29 months to 49 months with the addition of cextuximab. Much of this survival advantage was seen in oropharyngeal patients where HPV status may have played a role in treatment efficacy. Nimotuzumab is also a human/mouse chimeric monoclonal antibody targeting EGFR and has been studied in several Phase II clinical trials of patients receiving definitive chemoradiation [48,49]. In both studies of advanced-stage HNSCC, the addition of nimotuzumab conferred a significant survival advantage.

Panitumumab, a fully humanized monoclonal antibody specific to EGFR, has also been studied in HNSCC with less demonstrated efficacy. The SPECTRUM trial was a Phase 3 trial in 657 patients with recurrent or metastatic HNSCC comparing cisplatin and fluorouracil with and without panitumumab. The trial did not show improved overall survival but did demonstrate improved progression-free survival [50]. These finding are in contrast to the EXTREME study where overall survival was improved in patients who received cetuximab in addition to cisplatin or carboplatin and fluorouracil [51]. While one explanation for the difference between the studies may be study methodology, the fact that panitumumab is a fully humanized IgG2 isotype may be relevant. Unlike cetuximab, panitumumab does not induce NK-DC cross priming [52]. It is unclear whether the different isotype of panitumumab, the lack of murine variable region, or other factors are responsible for the effect difference between panitumumab and cetuximab despite both binding to EGFR. However, one likely explanation is the difference in the immunogenicity (mouse versus human variable regions) between these different monoclonal antibodies.

Vascularized endothelial growth factor

Elevated pretreatment serum vascularized endothelial growth factor (VEGF) levels tend to indicate a more aggressive disease state and a poorer overall survival in advanced laryngeal carcinoma [53]. In a meta-analysis of 12 studies that examined VEGF levels in over 1000 HNSCC patients, tumors that overexpressed VEGF measured by immunohistochemistry were associated with 1.88× greater risk of death at 2 years [54].

Several studies have examined the use of bevacizumab in HNSCC. Bevacizumab is a recombinant humanized IgG1 monoclonal antibody that binds VEGF-A and was the first agent against this protein approved by the Food and Drug Administration. Fury et al. [55] undertook a phase 2 trial of bevacizumab with cisplatin and intensity-modulated radiation in advanced HNSCC that demonstrated a 2-year overall survival (OS) rate of 88% and progression-free survival (PFS) rate of 76%. Bevacizumab was also studied with standard radiation therapy and docetaxol with encouraging results. In 30 patients with over 3 years median follow-up, OS and PFS were 62% and 68%, respectively [56]. The combination of cetuximab and bevacizumab has also been investigated in recurrent or metastatic HNSCC. Forty-six patients were enrolled in this Phase 2 study that demonstrated a median PFS interval of 2.8 months and OS of 7.5 months in a patient population that was highly resistant to standard therapy (73% of patients recurred within 6 months of prior curative therapy) [57].

Despite the decrease in VEGF levels in patients treated with bevacizumab, the actual VEGF levels post-treatment have not been shown to be consistently associated with efficacy. Similar to cetuximab, bevacizumab has been shown, however, to have significant impacts on immunological parameters that are distinct from the VEGF pathways. In metastatic melanoma and ovarian cancer, treatment with bevacizumab is associated with significant increases in CD8+ effector cells [58,59] and a reduction in circulating T reg cells [58]. It would be reasonable to conclude that similar mechanisms may be present in HNSCC.

Immune checkpoint blockade

The immune response is a carefully orchestrated balance between potentiation and inhibition. While the lack of potentiation may be responsible for anergy and tumor progression, the lack of immune inhibition can result in autoimmunity and an unchecked immune response. In cancer immunotherapy, however, where immune suppressive mechanisms are elevated, pathways that limit the breaks on the immune system can be exploited. One pathway where this interaction is important in tumor formation is the stimulatory B7/CD28 pathway of antigen presenting cells and T cells and the inhibitory effects of CTLA4 and PD-1 on activated T cells that act as a break on this response. Monoclonal antibodies that block CTLA4 and PD-1 and release the breaks on the immune response have been used with success in several clinical trials.

In 2010, ipilimumab became the first FDA-approved monoclonal antibody that blocks the inhibitory CTLA4 pathway. This approval was based on a randomized trial where ipilimumab alone was found to offer a survival benefit for patients with metastatic melanoma [60]. Long-term survival beyond 2 years was seen in

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