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Role of Immunotherapy in Head and Neck Cancer

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Immune system dysfunction plays a role in both the development and progression of head and neck squamous cell carcinoma (HNSCC), highlighting the potential role for immunotherapy to improve outcomes in this disease. The application of anti-PD-1 therapies for recurrent or metastatic HNSCC has found promising results. This has led to interest in combining immunotherapy with radiation therapy (RT) for the primary treatment of locally advanced HNSCC. RT with concurrent cetuximab is an option for patients who are medically unfit to receive cisplatin, and ongoing trials seek to determine to role of cetuximab-RT in treatment de-intensification for HPV+ oropharyngeal HNSCC. Other ongoing trials are evaluating the use of anti-PD-1 and anti-PD-L1 therapies in the upfront setting for newly diagnosed high-risk, locally advanced HNSCC, in an effort to improve disease control. Finally, early phase I studies are now investigating the use of anti-PD-1 therapy in conjunction with RT for refractory recurrent or metastatic HNSCC.

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Background

Immune system dysfunction appears to play a role in both the development and progression of head and neck cancer. Immunosurveillance is mediated largely by cytotoxic T-lymphocytes, and the presence of tumor cell antigens triggers a natural T-cell response, which could potentially target and kill tumor cells. Disruption of this T-cell response, whether by immunosuppression or various tumor immune evasion mechanisms, may play an integral role in the progression of head and neck squamous cell carcinoma (HNSCC).

Many human tumor cells express high levels of growth factor receptors, which can be targeted with tumor antigen-specific monoclonal antibodies. Epidermal growth factor receptor (EGFR) overexpression can be identified in 80%-90% of HNSCC and is associated with tumor cell proliferation and worse survival outcomes.[1] Cetuximab, a mouse-human chimeric IgG1 monoclonal antibody targeted against EGFR, has been increasingly utilized for neck squamous cell carcinoma in recent years.[2] Antitumor antigen monoclonal antibodies such as cetuximab stimulate an antigen-specific immune response via 2 main mechanisms. First, tumor lysis can be directly induced via antibody-dependent cellular cytotoxicity, mediated by NK cells and likely monocytes and neutrophils as well.[3] Secondly, tumor antigen-specific monoclonal antibodies interact with FcγRs on antigen-presenting cells to promote the opsonization of tumor for phagocytosis and antigen processing. This, in turn, elicits a tumor antigen-specific cytotoxic CD8+ T-cell response.[4]

Blockade of immune checkpoints, which regulate the duration and extent of immune responses, is another approach by which antitumor T-cell immunity may be activated. Immune checkpoints serve to modulate physiologic immune responses in order to prevent excessive inflammatory responses or the development of autoimmunity. For instance, interaction between programmed death receptor-1 (PD-1) and its ligands PD-L1 and PD-L2 has been shown to downregulate T-cell activation in both mouse models and human systems, and has been implicated in tumor immune evasion in HNSCC.[5] PD-1 is a member of the CD28 family of T-cell costimulatory receptors that is expressed on activated T-cells, B-cells, and myeloid cells.

Overexpression of PD-L1 by tumor cells, or immune infiltration by PD-1+ T-lymphocytes, can result in immune

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evasion. PD-L1 is overexpressed in >50%-60% of HNSCC.[6] It has been reported that among head and neck cancer patients, there is higher expression of immune checkpoint inhibitors such as CTLA-4 and PD-1 in intratumoral regulatory T-cells compared to peripheral blood samples.[7] Others have reported that tumor infiltration by PD-1+ CD8+/CD4+ lymphocytes is paradoxically more common in human papilloma virus (HPV)-positive than HPV-negative tumors, and is a favorable prognostic biomarker in HPV-positive disease.[8] This finding may reflect a previous immune response against tumor that might be reactivated by PD-1/PD-L1 blockade. Together, these findings point to the PDL-1 pathway as promising potential target in the treatment of HNSCC.

Clinical Application of Immunotherapy for Recurrent or Metastatic HNSCC

Patients with recurrent or metastatic HNSCC who fail platinum-based chemotherapy have a dismal survival of <6 months,[9] and historically, no therapy has been able to prolong survival in this subset of patients. Recently, the application of immunotherapy for this population has found promising results. In a single-arm phase II trial of cetuximab monotherapy in 103 patients with recurrent or metastatic HNSCC after failure of platinum-based chemotherapy, the objective response rate was 12.6% with a median survival of 5.9 months.[10] There was no relationship between the level of baseline EGFR expression and response to cetuximab. The EXTREME randomized trial found that the addition of cetuximab to platinum-fluorouracil chemotherapy significantly prolonged median overall survival from 7.4 months to 10.1 months, when given as first-line therapy for recurrent or metastatic HNSCC.[11] This trial established a new standard of care, although survival remains poor.

The anti-PD-1 monoclonal antibodies nivolumab and pembrolizumab have been shown to improve progression-free survival and overall survival in advanced melanoma, nonsmall cell lung cancer, and urothelial cancer, compared to standard systemic therapy.[12-17] Utilization of these agents has also been investigated in HNSCC. The recently published KEYNOTE-012 trial was the first to demonstrate the efficacy of immune checkpoint inhibition in HNSCC. This was a phase 1b trial aimed at evaluating the clinical efficacy and safety of pembrolizumab for advanced solid tumors, including recurrent or metastatic HNSCC. In the initial cohort of 60 HNSCC patients, all of whom had at least 1% PD-L1 expression in tumor and stromal cells, patients received pembrolizumab at 10 mg/kg IV once every 2 weeks. The objective response rate was 21% by clinician review, the median duration progression-free survival was 2 months, and overall survival was 13 months.[18] Grade 3 drug-related adverse events occurred in 17% of patients.

In a subsequent expansion cohort, 132 additional patients with HNSCC were enrolled regardless of PD-L1 expression status, and a less frequent dosing schedule of 200 mg IV once every 3 weeks was used.[19] The overall response rate was 18% by central imaging review, at the cost of grade 3 drug-related adverse events in 9% of patients. The 6-month progression-free survival was 23%. The degree of PD-L1 expression was found to be strongly predictive of best overall response, progression-free survival, and overall survival. The overall response rate was 22% for patients who were PD-L1 positive (≥1%), compared to 4% for patients who were PD-L1 negative (<1%) ($p = 0.021$). In addition, patients with HPV-associated disease had a higher overall response rate of 32%, compared to 14% for those with HPV-negative disease. Median overall survival was 8 months, which approaches the 10-month overall survival achieved with first-line cisplatin, 5-FU, and cetuximab for recurrent or metastatic HNSCC,[11] despite the fact that the majority of patients in this trial had already received 2 or more lines of prior therapy.

Although cross-trial comparisons should be interpreted with caution, these promising survival data suggest that future studies investigating pembrolizumab as a first-line therapy are indicated. Based on the early results of KEYNOTE-012, the FDA granted accelerated approval of pembrolizumab for recurrent and metastatic HNSCC in August 2016. The utility of pembrolizumab for recurrent or metastatic HNSCC is to be confirmed in a randomized phase III study, KEYNOTE-040, which assigns patients to pembrolizumab or standard single-agent methotrexate, docetaxel, or cetuximab. This study is ongoing, but closed to recruitment,[20] with results eagerly awaited.

The recently published Checkmate-141 randomized phase III trial assigned 361 patients with recurrent HNSCC who had progressed within 6 months after platinum-based chemotherapy to nivolumab at 3 mg/kg once every 2 weeks, or standard second-line single-agent systemic therapy consisting of either docetaxel, methotrexate, or cetuximab, as per investigator choice.[21] This study demonstrated that compared to standard therapy, nivolumab significantly improved overall survival from a median of 5.1 to 7.5 months (HR = 0.70, CI: 0.51–0.96), with the 1-year overall survival rate nearly doubled for those treated with nivolumab (16.6% vs 36.0%). The response rate was 13.3% for nivolumab, compared to 5.8% for standard therapy. Exploratory biomarker analysis showed that the overall survival benefit remained, regardless of PD-L1 expression or p16 status, although those with PD-L1 positive or HPV-associated disease benefited the most. Among patients receiving nivolumab, overall response rates were 17% vs 12.3% if PD-L1 positive (≥1%) vs PD-L1 negative (<1%), and 15.9% vs 8.0% if p16 positive vs p16 negative.

With the exception of Grades 1-2 rash, all treatment-related toxicities were less frequent in the nivolumab arm. Grades 3-4 toxicities occurred in 13.1% of nivolumab-treated patients, compared to 35.1% of those receiving standard therapy, with the most common nivolumab-related adverse events consisting of fatigue, nausea, rash, decreased appetite, and pruritus. This trial also included a patient-reported quality-of-life analysis, wherein patients receiving standard therapy reported worsening quality-of-life in multiple domains, while these measures were stable or slightly improved in those receiving nivolumab. This is a significant finding considering the