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Review Article

Immunotherapy for head and neck cancer – The current scenario

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ABSTRACT

Anticancer immunity modulation is the current standpoint of research and has revolutionized the standard of care of platinum refractory recurrent/metastatic head and neck carcinoma of squamous cell origin (R/M HNSCC). Checkpoint inhibitors are targeted at PD-1/ PD-L1 axis, which is involved in the genesis, maintenance and progression of HNSCC. Head and neck cancer has an immunosuppressive character and a high inflammatory response component in the tumor microenvironment. The clinical settings in which these agents are highly useful are in study all around the globe. We discuss the current up to date clinical trial results and the future prospective of cancer immunotherapy in the field of HNSCC.

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1. Introduction

The current practice of oncology has drastically transformed with the advent of immunotherapy and targeted therapy. Immunotherapy treatment of cancer relies on the principle that cancer cells can be recognized as foreign by host immune cells and can be effectively targeted by an activated immune system. About less than a million cases develop head and neck cancer every year worldwide and approximately half of them die due to disease.¹ Treatment of head and neck cancer generally requires aggressive multimodality treatment strategies, still the overall 5 year survival of these patients is only 40-50%.² The ground breaking entry in targeted therapy for HNSCC came from EXTREME trial, which uses a triplet cis- or carboplatin, 5-fluorouracil (5-FU) and cetuximab with nominal increase of median survival to 10.1 months. The problem was high toxicity with a 82% rate of grade 3 and 4 adverse events

which is unacceptable.² So there is a great need to improve survival without extreme toxicity.

Immunotherapy is based on the principle that adaptations in immune surveillance and the tumor microenvironment allow immune escape. The biological rationale for antitumor immunotherapy specifically in HNSCC is built upon several observations. First, HNSCC has a relatively high tumor mutation burden (TMB).³ TMB in turn translates production of altered proteins which are antigenic from these mutated DNA. Immune Checkpoint Inhibitors (ICIs) can be targeted against these tumoral immune targets.

2. Immune system role in pathogenesis of HNSCC

Immune evasion is an important step in HNSCC development. It has been observed in patients with HIV/AIDS to have a 2 to 6 fold higher risk of developing HNSCC.^{4,5} Transplant recipients on iatrogenic immune suppression also has an increased incidence of HNSCC.⁶ The immunosuppressive state is believed to be induced by

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the tumor itself. Like other tumors, HNSCC can undergo immune system escape, thus resulting in new sub-clones that either are poorly immunogenic or can locally turn off immune responses. The process of antigen presenting and T cell activation is accurately regulated by co-stimulatory and inhibitory signals, named “immune checkpoints,” which prevent the occurrence of exaggerated immune reactions that could damage the individual. Tumors over activate these inhibitory pathways and eventually evade immune response. At present inhibition of PD-1/PD-L1 axis and CTLA-4 represents the approach with the most promising clinical results in the treatment of cancers including HNSCC. The CTLA-4 receptor is an inhibitory modulator of T cell activation found on the surface of cytotoxic T lymphocytes (CTL), which bind B7 ligands on antigen presenting cells (APC) - specifically CD80 and CD86. Its stimulatory counterpart is the CD28 receptor, which is responsible for the activation and proliferation of T cells. Both CTLA-4 and CD28 compete for binding B7 ligands. Additionally, it is known that CTLA-4 is also expressed on CD4+ regulatory T cells which, in turn of its activation, cause immunosuppression through the production of TGF β .^{7,8} PD-1 is a transmembrane type-I receptor that belongs to the CD28 receptor family and is expressed on the surface of activated T cells, B cells, NK cells, and monocytes. PD-L1 and PD-L2 are the main ligands of PD-1 receptor, and their interaction causes the release of cytokines that inhibit proliferation and activity of effector T cells. Treg-mediated inhibition of immune response against HNSCC was also discovered to be enhanced by the use of cetuximab.⁹ VEGF is overexpressed in 90% of HNSCC and it is associated with angiogenesis and T cell dysfunction and inactivation.¹⁰

3. Immune checkpoint inhibitors

Ipilimumab (anti-CTLA-4) was approved for the treatment of metastatic melanoma in 2011 based on a randomized phase III study demonstrating superior efficacy when compared with gp100 vaccine alone.¹¹ The efficacy and safety of anti-CTLA-4 in head and neck cancer is currently under investigation in a phase Ib trial (NCT01935921) in combination with cetuximab and intensity-modulated radiation therapy (IMRT) for patients with previously untreated stage III-IVB head and neck cancer.

The recent results of 2 trials of PD-1 checkpoint inhibition for patients with HNSCC have paved the way to a new standard of care. Checkmate 141, compared the anti-PD-1 antibody Nivolumab versus standard of care for metastatic HNSCC and was halted early when survival endpoints were met. Interim results have demonstrated improved survival in patients with HNSCC who progressed within 6 months of platinum first line treatment for R/M disease. Nivolumab reduced the risk of death by 30% compared with investigator’s choice of standard chemotherapy and doubled the 1-year OS from 16.6% in the

control arm to 36% in the Nivolumab arm. Median survival was 7.5 months for nivolumab and 5.1 months for patients assigned to investigator’s choice of chemotherapy.¹²

Pembrolizumab was tested in PD-L1 positive R/M HNSCC patients - defined as expressing PD-L1 on immunohistochemistry in >1% of tumor cells and tumor stroma. Seiwert and colleagues investigated another anti-PD-1 antibody i.e, Pembrolizumab in the phase I trial KEYNOTE-012 for patients with recurrent metastatic HNSCC. The overall response rate was 18% (25% in HPV-positive patients and 14% in HPV-negative patients).¹³ In 2016 US FDA has approved Pembrolizumab and Nivolumab in second line treatment of metastatic HNSCC.¹⁴ Phase III trial of pembrolizumab versus standard chemotherapy with methotrexate, docetaxel or cetuximab, and pembrolizumab did not meet the primary endpoint of OS. Patients receiving pembrolizumab had an overall 19% improvement in OS that did not meet the pre-specified difference for statistical significance. Nonetheless, pembrolizumab was less toxic compared with the investigator’s choice of chemotherapy, an important consideration in treatment of patients with a poor prognosis for recurrent metastatic platinum refractory HNSCC. Nevertheless, a significant improvement in OS was observed in the subgroups of patients with a PD-L1 expression $\geq 1\%$ and $\geq 50\%$. PD-L1 expression seems to retain a fundamental role in the selection of patients for the treatment with Pembrolizumab.¹⁵ Assessing response to therapy and treatment duration of these agents is a vast area, which would be not dealt in the constraints of this article. Randomized three-arm phase III KEYNOTE-048 trial in first-line R/M HNSCC examined 882 patients who received either a) pembrolizumab monotherapy or b) a novel combination of pembrolizumab, 5-FU and cisplatin or carboplatin or c) the EXTREME regimen of cisplatin, 5-FU and cetuximab as a control arm. This trial is the first trial in HNSCC to prospectively use a biomarker of PD-L1 expression level in the primary endpoint analysis. In this trial, combined proportion score (CPS) was used as a biomarker. CPS is defined as the sum of PD-L1 stained tumor cell and surrounding lymphocytes and macrophages divided by the total number of viable tumor cells multiplied by 100. The primary outcomes were OS and progression-free survival (PFS) tested sequentially for CPS ≥ 20 , CPS ≥ 1 , and total population. The second interim analysis and final analysis have been publically presented. Final analysis of this study identified that pembrolizumab plus chemotherapy significantly improved OS for the CPS ≥ 20 (14.7 vs. 11.0 months, HR 0.60, CI 0.45–0.82, $p=0.0004$), CPS ≥ 1 (13.6 vs. 10.4 months, HR 0.65, CI 0.53–0.80, $p < 0.0001$) and overall populations (13.0 vs. 10.7 months, HR 0.72, CI 0.60–0.87). Pembrolizumab monotherapy also significantly improved OS for the CPS ≥ 20 (14.8 vs. 10.7 months) and CPS ≥ 1 (12.3 vs. 10.3 months, HR 0.74) populations, and was noninferior to EXTREME in the

Table 1: Ongoing Phase III trials

Setting	Study	Population	Treatment arms
Neoadjuvant	KEYNOTE-689 (NCT03765918)	Stage III-IVA oral cavity/larynx/ hypopharynx and HPV – OPSCC or Stage III (AJCC 8th ed) HPV+ OPSCC	Neoadjuvant pembrolizumab and adjuvant pembrolizumab added to surgery and standard risk-based adjuvant therapy vs. surgery and standard risk-based adjuvant therapy
	JAVELIN (NCT02952586)	Stage III-IVB HPV – HNSCC or T4 or N2c/N3 (AJCC 7th ed) HPV+ OPSCC	Avelumab plus cisplatin/RT vs. cisplatin/RT
Definitive	GORTEC 2017-01 (REACH) (NCT02999087)	Stage III-IVB HNSCC	Cisplatin eligible patients: Avelumab plus cetuximab/RT vs. Cisplatin/RT Cisplatin ineligible patients: Avelumab plus cetuximab/RT vs. cetuximab/RT
	NRG HN-004 (NCT03258554)	Phase II/III, Cisplatin ineligible, Stage III-IVB oral cavity/larynx/ hypopharynx or HPV – OPSCC, Stage I-II HPV+ OPSCC with >10 pack years or Stage III OPSCC	Durvalumab/RT vs. cetuximab/RT
	NRG HN-005 (NCT03952585)	Phase II/III, HPV+ non-smoking associated OPSCC	Nivolumab/reduced dose RT (60 Gy) vs. Cisplatin/reduced dose RT (60 Gy) vs. cisplatin/standard dose RT (70 Gy)
	KEYNOTE-412 (NCT03040999) (NCT03349710)	Unresectable LA HNSCC oral cavity Unresectable LA HNSCC oral cavity	Pembrolizumab plus cisplatin/RT vs. cisplatin/RT Cisplatin eligible patients: Nivolumab plus cisplatin/RT vs. cisplatin/RT Cisplatin ineligible patients: Nivolumab/RT vs. cetuximab/RT
Adjuvant immunotherapy after definitive CRT	WO420242 (NCT03452137)	HNSCC requiring multimodality therapy	Adjuvant atezolizumab vs. placebo after definitive local therapy (surgery or RT)
	ECOG ACRIN EA3161 (NCT03811015)	Phase II/III trial, intermediate-risk HPV+ OPSCC (≥ 10 pack-year smoking and stage I AJCC 8th ed or <10 pack-year smoking and stage II-III AJCC 8th ed)	Nivolumab plus cisplatin/RT vs. cisplatin/RT

overall population (11.5 vs. 10.7 months, HR 0.83, CI 0.70–0.99, $P=0.0199$). Despite the inferior ORR, the OS benefit was driven by longer duration of response (DOR) in the pembrolizumab cohort (20.9 months vs. 4.5 months). Furthermore, the OS curve for the pembrolizumab cohort continues to run considerably above the PFS curve at 3 years suggesting that some patients who do not meet objective PFS criteria experience OS benefit from pembrolizumab.¹⁶ Addition of chemotherapy is justified by the fact that Chemotherapy disrupts the architecture in the tumor microenvironment, which may help to overcome immune exclusion and produce antigen shedding Chemotherapy also produces rapid responses, and may do so in patients who

would be unresponsive or progressive on ICI. Given the observation that pembrolizumab monotherapy response is lower in bulky tumors, chemotherapy-induced reduction in tumor volume might improve sensitivity simply on this basis.^{17,18}

Addition of anti-PD-1 to adjuvant therapy for patients with loco regionally advanced disease is currently under investigation, two phase I trials to investigate nivolumab (NCT02488759) and pembrolizumab (NCT02296684) before surgery are opened for accrual. Society for the Immunotherapy of Cancer Head and Neck Guidelines Subcommittee consensus guidelines provide some guidance for treatment decision-making.¹⁹

The combination of different immune checkpoint inhibitors is also possible and is being studied in HNSCC. The rationale behind the combination of two immune checkpoint inhibitors is based on the fact that each of these drugs targets a specific receptor in different steps in induction or maturation of T cells and that single agent activity seems to provide a limited benefit.²⁰

4. Conclusion

Therapeutic landscape in HNSCC treatment is changing rapidly due to new research in the field of immunotherapy. Hunt for improved survival and reduced treatment toxicity have now pushed immune checkpoint inhibitors from second to first line of treatment in R/M setting of HNSCC. Other scenarios are also being investigated currently. Results from ongoing phase III trials will shed a light on the future of immune checkpoint inhibitors and the direction looks promising. Possibility of de-escalation in HPV associated cancer is also in investigation. The major challenges would be selection of patients, cost of treatment, bio markers for assessment of treatment response, optimization of combination regimens of immunotherapeutics, sequence and timing of these drugs, combination approaches etc. When compared to other tumors, the use of immunotherapy in HNSCC is in its infancy. Learning how to optimally combine the different types of immunotherapy and with other established form of treatments, including surgery, radiotherapy and chemotherapy, will hopefully lead to improved clinical results. A new era of immunotherapy awaits with high optimism for improving outcomes in patients with HNSCC.

5. Conflicts of Interest

All contributing authors declare no conflicts of interest.

6. Source of Funding

None.

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