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REVIEW

New developments in the management of head and neck cancer – impact of pembrolizumab

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Abstract: Head and neck squamous cell carcinoma (HNSCC), a heterogeneous group of upper aerodigestive tract malignancies, is the seventh most common cancer worldwide. Tobacco use and alcohol consumption were the most identified risk factors of HNSCC. However, human papilloma virus, a sexually transmitted infection, has been determined as another primary cause of HNSCC. Early-stage disease is treated with surgery or radiotherapy. Recurrent or metastatic HNSCC is associated with poor prognosis with a median overall survival of 10 months. The EXTREME protocol is commonly used in first-line setting. Recently, pembrolizumab, an anti-programmed death-1 agent, has been approved by the US Food and Drug Administration for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy. It demonstrated a durable objective response rate with a good safety profile and quality of life. Many ongoing trials are evaluating the use of pembrolizumab for the treatment of HNSCC in various indications such as adjuvant and neoadjuvant setting, maintenance and recurrent disease, alone or in combination with chemotherapy, radiation and targeted therapy. Finding those biomarkers predictive of response to immune checkpoints inhibitors has been a major concern. However, markers have been identified, such as PD-L1 expression, human papilloma virus infection, interferon-γ signature score, microsatellite instability and neoantigen production.

Keywords: epidemiology, HPV, pharmacokinetics, PD-1/PD-L1 inhibitors, immunotherapy, biomarkers

Introduction

Head and neck squamous cell carcinoma (HNSCC), a heterogeneous group of upper aerodigestive tract malignancies, is the seventh most common cancer worldwide.[1] Major risk factors for HNSCC include tobacco smoking and alcohol consumption.[2] Human papillomavirus (HPV) infection is another important risk factor and is being increasingly recognized.[3] Early stage disease (stages I and II) is treated with single-modality surgery or radiotherapy contributing to high cure rates. However, locally advanced HNSCC requires aggressive multimodality treatment combining locoregional intervention and systemic treatment using chemotherapy and targeted therapy.[4] Ten to twenty percent of patients with early stage show recurrent disease during follow-up, whereas the recurrence rate is ~50% in patients with locally advanced disease, predominantly in locoregional pattern.[5] Recurrent/metastatic HNSCC is associated with poor prognosis, and the median overall survival (OS) is <1 year. The EXTREME regimen which combines 5-fluorouracil to cisplatin/carboplatin and cetuximab followed by maintenance cetuximab is commonly used in first-line treatment and shows the best median OS (10 months) in patients with recurrent/metastatic disease in this setting.[6] Beyond first line, few drugs can be used, such as taxanes and methotrexate,

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and the median OS drops to 6 months indicating the necessity of novel therapeutics in order to improve the prognosis of HNSCC.[7] This poor outcome evokes the need for novel treatment options in the management of locally advanced or recurrent/resistant disease. Multiple emerging data have shown that immune checkpoint inhibitors are efficacious in HNSCC. Pembrolizumab (Merck & Co., Inc., Whitehouse Station, NJ, USA) and nivolumab (Bristol-Myers Squibb, New York, NY, USA), which are monoclonal programmed death-1 (PD-1) antibodies, were approved by the US Food and Drug Administration in 2016 for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after a platinum-based therapy.[8,9] We review in this paper the epidemiology, etiology and risk factors of HNSCC, pharmacology, mechanism of action and pharmacokinetics of pembrolizumab, its efficacy and tolerability, and quality of life of patients treated with pembrolizumab.

Epidemiology and risk factors of HNSCC

The incidence of HNSCC greatly varies depending upon the anatomic region and geographic origin.[10] Approximately 61,760 new cases and 13,170 deaths of HNSCC were estimated in 2016 in the USA.[11] Oral cavity and laryngeal squamous cell carcinomas are the most frequent subtypes of head and neck cancers (HNCs) worldwide.[12] Historically, the majority of HNCs was mainly caused by tobacco and alcohol consumption, but HPV, a sexually transmitted infection, has been determined as another primary cause of HNSCCs. HNSCCs are more frequent in men than in women with a sex ratio of 3:1, and the incidence increases with age.[13]

Smoking

Tobacco smoking is a well-established independent risk factor for HNC.[2] A history of tobacco use is found in ~90% of patients. Smoking is associated with 4- to 5-fold increased risk of oral cavity, hypopharynx and oropharynx cancers and 10-fold increase in risk of developing laryngeal cancer. Furthermore, tobacco-related carcinogenesis is dose dependent. The risk of HNC increases synergistically with alcohol consumption.[14,15] Marron et al reported that cessation of tobacco smoking contributes to HNC risk reduction of ~30% compared to current smoking and decreases the risk of laryngeal cancer by 60% after 10–15 years.[16] It has been shown that smoking induces tumor hypoxia associated with resistance to radiotherapy, and that resistance to apoptosis is attributed to the mutation of p53 gene.[17] More recently, the Cancer Genome Atlas demonstrated that smoking-related HNSCCs show universal loss-of-function TP53 mutations, CDKN2A loss of function and chromosome 3q amplification.[18]

Alcohol consumption

Alcohol consumption is another major independent risk factor for HNCs with a 2-fold increased risk in non-smoking patients, particularly hypopharyngeal cancers.[14,19] However, the most carcinogenic effect of alcohol is observed with concomitant consumption of tobacco. Blot et al reported a 35-fold increased risk of HNCs among humans who consume two or more packets of cigarettes and more than four alcoholic drinks per day.[20] The benefit of alcohol use cessation on the risk of developing HNCs is not seen earlier than 20 years after cessation.[16]

Premalignant lesions and conditions

Erythroplakia and leukoplakia are common premalignant lesions. Multiple significant clinical predictors of malignant transformation have been determined, such as subsite (high risk in lateral tongue and low risk in floor of mouth), non-smoking status, size >200 mm, higher histologic grade and non-homogenous appearance. Malignant transformation occurred after mean 4.3 years following biopsy in 12.1% of oral dysplasia cases.[21] The premalignant role of oral lichen planus is controversial.[22] Several premalignant inherited conditions are associated with increased risk of HNSCC. These conditions include Fanconi anemia, ataxia telangiectasia, Li–Fraumeni syndrome and Bloom's syndrome. Patients with Fanconi anemia are at high risk of developing HNSCC, especially after hematopoietic stem cell transplantation.[22]

Human papilloma virus

HPV, a sexually transmitted infection, has been recognized to cause HPV-positive HNC, a subset of HNCs arising from the lymphoid tissue of the oropharynx including the base of tongue, tonsils and other parts of the pharynx.[23] HPV-positive HNCs are caused by oral HPV infection. HPV16 accounts for the vast majority of HPV-positive cases (90% of patients).[24] Kreimer et al reported that HPV DNA of HPV16 was detected in 34.8% of patients with oropharyngeal cancers.[25] The natural history and the time of progression from first oral HPV infection to HPV-positive HNCs remain unclear. The time is estimated to be >10 years.[25] Recently, the Cancer Genome Atlas reported that HPV-positive HNCs are dominated by helicase domain mutations of the oncogene PIK3CA, novel alterations involving loss of TRAF3 and amplification of the cell cycle gene.[18]

HPV-positive HNC patients are younger than patients with HPV-negative HNC (median age lower by 3–5 years at diagnosis). There is a strong association with sexual behaviors (consistent with acquisition of oral HPV infection) and

weak association with tobacco and alcohol consumption. In contrast, HPV-negative HNC patients present a strong association with tobacco and alcohol consumption and moderate association with poor oral hygiene.[23] HPV-positive HNC patients are predominantly male, white, have higher socioeconomic status and are married, compared with patients with HPV-negative HNCs. Furthermore, these patients have better prognosis than HPV-negative HNC patients. The incidence of HNC changes over time and its trend depends strongly on tobacco use. Tobacco consumption typically increases in men, followed by a rise in smoking in women. After years of rising number of HNCs, the impact of tobacco smoking cessation (which began in 1965) was observed with the first decline in the incidence of HNC since 1990.[13] However, the incidence of HPV-positive HNSCC has risen dramatically since 1970 in the USA, especially in middle-aged white men and predominantly in the oropharynx. It increased from 0.8 per 100,000 in 1988 to 2.6 per 100,000 in 2003, with a total increase of 225%.[26] Mehanna et al reported an overall HPV prevalence in oropharyngeal cancer of 47.7%. It increased significantly over time: from 40.5% (95% CI: 35.1–46.1) before 2000 to 64.3% (95% CI: 56.7–71.3) between 2000 and 2004, and to 72.2% (95% CI: 52.9–85.7) between 2005 and 2009 ($p<0.001$).[27] In contrast, the incidence of HPV-negative HNC decreased by 50% during the same time period.[26] This trend is equally observed in several developed countries such as Australia, Canada and Sweden.[28] However, developing countries experience increasing or stable incidence of tobacco use and HPV-negative HNC without an increase in HPV-positive cancers.[13]

Rationale of immunotherapy in HNSCC

It has been demonstrated that HNSCC is an immunosuppressive disease associated with low absolute lymphocyte count,[29] altered natural killer cell function[30] and impairment of tumor-infiltrating T lymphocytes with an important impact on clinical outcome.[31] It has also been reported that suppressive regulatory T-cells secrete cytokines such as transforming growth factor-beta and interleukin-10 and express cytotoxic T-lymphocyte associated protein 4 linked to tumor progression.[32] Several mechanisms of immune escape have been described in HNSCC, such as development of T-cell tolerance to persistent HPV infection or overexpressed/mutated antigens, downregulation of interferon regulatory factors and activated signal transducer and activator of transcription 1 and downregulation or mutation of human leukocyte antigen class 1.[33] Immune checkpoint pathway plays a major role in the tumor microenvironment and constitutes an important mechanism of tumor immune escape.[34] This pathway is generally regulated by interactions between ligands and receptors such as PD-1 and its ligands PD-L1 and PD-L2. PD-1 is a receptor expressed on the surface of activated T-cells, B-cells and myeloid cells.[35] The ligands PD-L1 and PD-L2 are expressed on both normal and cancerous cells. Tumor infiltration by PD-1-positive T lymphocytes or high tumor expression of PD-L1 can contribute to immune escape by conducting inhibitory signals that downregulate T-cell activation.[36] Recent data suggest that PD-L1 is present in 50%–60% of HNSCC.[37] Furthermore, Lyford-Pike et al reported a localized expression of PD-L1 within deep tonsillar crypts in non-cancerous adult tonsil tissues which are the sites of origin of HPV-positive HNCs. There is no PD-L1 expression on the surface of epithelium, which means that deep crypts represent an immune-privileged site that facilitates immune evasion at initial infection with HPV. They also found that PD-1 expression is statistically higher in $CD8^+$ tumor-infiltrating lymphocytes compared with $CD8^+$ T-cells in benign chronically inflamed tonsils (75.5% vs 35.5%, $p<0.0001$). In addition, 70% of HPV-positive HNC tumors were PD-L1 positive and significant levels of mRNA of interferon-γ (IFN-γ) were found in HPV-positive, PD-L1-positive HNCs. The authors concluded that PD-1/PD-L1 interaction is implicated in initial viral infection and adaptive immune escape, which can be a rationale for therapeutic blockade with PD-1/PD-L1 inhibitors in HPV-positive HNCs.[38]

Pharmacology, mechanism of action and pharmacokinetics of pembrolizumab

Pembrolizumab is a highly selective humanized monoclonal antibody that binds to PD-1 receptor and inhibits the interaction between PD-1 and its ligands PD-L1 and PD-L2. It is an IgG4 kappa immunoglobulin with a molecular weight of 140 kDa. Pembrolizumab is administered intravenously with immediate and full bioavailability.[8]

The clearance of pembrolizumab is low (~0.22 L/day) and similar to other monoclonal antibodies. Its volume of distribution is 6 L, indicating limited distribution beyond extracellular space reflecting adequate availability of the drug to bind its target on circulating T-cells. Pembrolizumab has an elimination half-life of 27.3 days, showing that the concentration remains clinically significant as long as 3 weeks post-dose.[39] These findings are similar to the pharmacokinetic characteristics of other monoclonal antibodies.[40] The time to reach steady-state concentration by pembrolizumab is 129 days with a repeated dose every 3 weeks and with a

modest systemic accumulation of 2.2-fold.[8] In a model-based analysis of KEYNOTE-001, Elassaiss-schaap et al reported a linear clearance of pembrolizumab with doses between 1 and 10 mg/kg every 3 weeks. Simulations in ex vivo models showed that saturation of target engagement began at a dose of 1 mg/kg every 3 weeks and suggested that a steady-state dose of 2 mg/kg every 3 weeks is needed to obtain 95% of target engagement.[41] The activity of 2 mg/kg every 3 weeks has been confirmed in randomized comparative pembrolizumab dose levels.[42,43] Since the elimination of monoclonal antibodies such as pembrolizumab is mediated by protein catabolism in different tissues, its clearance does not depend on a specific organ.[40] Furthermore, a model-based analysis of pooled data from KEYNOTE-001, -002 and -006 trials demonstrated that intrinsic variants such as age, gender, renal impairment and mild hepatic impairment have no clinically relevant effect. Although the Eastern Cooperative Oncology Group performance status, cancer type, initial tumor burden and previous ipilimumab treatment statistically influenced pembrolizumab clearance, none of these factors were associated with clinical effect. Interestingly, the prolonged use of glucocorticoids does not affect pembrolizumab exposure.[39]

Drug outcomes

The main studies of efficacy of immune checkpoint inhibitors are reviewed in Table 1. The first evidence of pembrolizumab efficacy in HNSCC was shown in the Phase Ib trial KEYNOTE-012. This trial includes patients with positive PD-L1 status (>1% of tumor cells by immunohistochemistry). In this initial study, 60 patients were included, of whom 23 (38%) were HPV positive and 37 (62%) were HPV negative. The overall response rate (ORR) was 18% as evaluated by Response Evaluation Criteria in Solid Tumors. Impressively, it was 25% in patients with HPV-positive tumors and 14% in HPV-negative HNSCC. The median duration of response was 53 weeks, and the OS in the responder group was not reached.[44] In the expansion cohort of KEYNOTE-012 of 132 patients irrespective of PD-L1 and HPV status, the ORR was unchanged (18%). The ORR was 32% (9/28 patients) and 14% (15/104 patients) among patients with HPV-positive and HPV-negative disease, respectively. When PD-L1 status was evaluated in tumor cells, only the probability of response was not statistically different between PD-L1 positive (>1%) and negative (<1%) tumors (p=0.21). However, when PD-L1 expression analysis was done in tumor and immune cells, the ORR was significantly higher in PD-L1-positive patients. Interestingly, some responses were durable and the median duration of response was not reached. In addition, four patients (3%) achieved a complete response.[45]

Pembrolizumab demonstrated a durable overall response rate in a subgroup of patients in an international, multicenter, single-arm, non-randomized trial of 171 patients with recurrent or metastatic HNSCC who had disease progression on or after platinum-containing chemotherapy (KEYNOTE-055). The ORR was 16% and the median response duration was 8 months. Response rates were similar in all HPV and PD-L1 subgroups.[46] Recently, the results of KEYNOTE-040, which an open-label, Phase III trial comparing pembrolizumab with standard of care in patients with recurrent or metastatic HNSCC after a platinum-based chemotherapy, were presented at European Society for Medical Oncology 2017 Congress in Madrid. The median OS was only marginally higher in

Table 1 Main studies of immune checkpoint inhibitors in HNSCC

References	Phase/n	Treatment	Indication	Outcome
Seiwert et al[44]	Ib/n=60	Pembrolizumab 10 mg/kg every 2 weeks	Recurrent or metastatic PD-L1-positive HNSCC	RR =18%
Bauml et al[46]	II/n=174	Pembrolizumab 200 mg every 2 weeks	Platinum and cetuximab pretreated patients	RR =16% mDR: 8 months mOS: 8 months mPFS: 2 months
Chow et al[45]	Ib/n=131	Pembrolizumab 200 mg every 2 weeks	Recurrent or metastatic HNSCC, irrespective of PD-L1 status	RR =18% mDR: not reached 6-month OS: 59% 6-month PFS: 23%
Segal et al[49]	I/II/n=62	Durvalumab 10 mg/kg every 2 weeks	Recurrent and metastatic HNSCC	RR =11% 1-year OS: 62%
Ferris et al[48]	III/n=361	Nivolumab 3 mg/kg every 2 weeks	HNSCC progressing within 6 months after platinum-based chemotherapy	RR =13% mPFS: 2 months mOS: 7.5 months

Abbreviations: HNSCC, head and neck squamous cell carcinoma; mDR, median duration response; mOS, median overall survival; mPFS, median progression-free survival; PD-L1, programmed death-1 ligand; RR, response rate.

the pembrolizumab arm compared with the chemotherapy arm (8.4 vs 7.1 months, hazard ratio [HR] 0.81, 95% CI: 0.66–0.99; p=0.0204). However, among patients with PD-L1 expression in >50% of tumor cells, median OS was 11.6 vs 7.9 months, respectively (HR 0.54; 95% CI: 0.35–0.82; p=0.0017). This trial did not reach its primary endpoint of OS. Subsequent immunotherapy in the standard-of-care arm may have confounded OS analysis.[47]

Nivolumab, another anti-PD1 checkpoint inhibitor, showed positive results in a Phase III randomized trial of 361 patients comparing nivolumab with investigator's choice of chemotherapy (either cetuximab, methotrexate, or docetaxel) in patients with recurrent or metastatic HNSCC with disease progression on or within 6 months of receiving platinum-based chemotherapy. A statistically significant and clinically meaningful improvement in OS was reported in the nivolumab arm vs the chemotherapy arm (7.5 vs 5.1 months, respectively).[48] Durvalumab (Astrazeneca, Gaithersburg, MD, USA), an anti-PD-L1 agent, was evaluated in Phase I/II, multicenter, open-label study in recurrent or metastatic HNSCC heavily pretreated. Seven patients of 62 responded; the duration of response of 6 of them exceeded 12 months.[49]

Safety of pembrolizumab in HNSCC

Pembrolizumab was well tolerated with a good toxicity profile. In the KEYNOTE-012 trial, treatment-related adverse events (AEs) of any grade occurred in 63% of patients. The most common side effects were fatigue, pruritus, nausea, decreased appetite and rash. Ten of 60 patients (17%) presented grade 3–4 drug-related toxicity, which included increased alanine and aspartate aminotransferase, hyponatremia, fatigue, rash, atrial fibrillation and congestive heart failure. No drug-related death was reported.[44] Similarly, 62% of patients had drug-related AEs of any grade, which included fatigue, hypothyroidism and decreased appetite in the expansion cohort. Grade 3 or 4 treatment-related AEs occurred in 9% of patients and were most frequently decreased appetite, facial swelling and pneumonitis. No treatment-related death was reported.[45] The same proportion of patients experienced treatment-related toxicity of any grade in the KEYNOTE-055 trial (64% of patients). The most common side effects were fatigue, hypothyroidism, nausea, aspartate transaminase increase and diarrhea. Grade 3 or higher AEs were reported in 15% of patients. One patient died of drug-related pneumonitis.[46]

Quality of life

To date, no clinical studies have evaluated the quality of life and patient satisfaction in patients with HNSCC treated with pembrolizumab. However, few recent data reported that pembrolizumab was associated with better quality of life compared to chemotherapy in metastatic melanoma, advanced non-small cell lung cancer and urothelial carcinoma. In the KEYNOTE-002 trial which compared pembrolizumab with chemotherapy in patients with metastatic melanoma after progression on ipilimumab, the authors concluded that global health status/health-related quality of life scores were maintained to a higher degree in pembrolizumab arms in comparison with chemotherapy arm (p=0.01).[50] In addition, Brahmer et al reported that the proportion of improved global health status/quality of life score at week 15 was 40% in pembrolizumab arm compared with 26.5% in chemotherapy arm and time to deterioration of Quality of Life Questionnaire Lung Cancer 13 was prolonged in pembrolizumab arm compared with the chemotherapy arm (p=0.029).[51] Treatment with pembrolizumab was also associated with a better health-related quality of life in previously treated advanced urothelial cancer patients in comparison to investigator-choice chemotherapy.[52]

Ongoing trials

Many ongoing trials are evaluating the use of pembrolizumab for the treatment of HNSCC in various indications such as adjuvant and neoadjuvant setting, maintenance and recurrent disease, alone or in combination with chemotherapy, radiation and targeted therapy. Rechallenging with pembrolizumab is also under investigation. All current clinical trials with pembrolizumab in HNSCC are listed in Table 2.

Biomarkers of response to pembrolizumab in HNSCC

Finding biomarkers of response to immune checkpoint inhibitors has been a major concern since only a subset of patients responds to this therapy. In HNC, the Phase Ib KEYNOTE-012 study showed that a PD-L1 of >1% on tumor and immune cells was associated with a better response to pembrolizumab. This finding was not confirmed in the Phase II study KEYNOTE-055, where the response rates to pembrolizumab were similar in all PD-L1 expression subgroups.[44] Emerging data showed that clinical response to pembrolizumab in patients with HNSCC may be partly related to inhibition of PD-1/PD-L2 interactions. Yearley et al reported that response to pembrolizumab was higher in patients who were positive for both PD-L1 and PD-L2 than those who were only positive for PD-L1 (27.5% vs 11.4%), and that PD-L2 was a significant predictor of progression-free survival with pembrolizumab independent of PD-L1.[53]

Table 2 Ongoing trials of pembrolizumab

	References	Phase/patients	Patients population	Agent	Endpoint
Adjuvant setting, surgically resectable HNSCC	NCT02641093	II/80	Resected HNSCC	Pembrolizumab + cisplatin and radiation	Toxicity and DFS
	NCT02296684	II/46	Surgically resectable, locally advanced HNSCC	Neoadjuvant pembrolizumab + surgery + adjuvant therapy (radiation therapy + cisplatin ± pembrolizumab)	Locoregional recurrences rates, distant failure rate
	NCT03057613	II/37	Resected, high-risk cutaneous HNSCC	Pembrolizumab + postoperative radiotherapy	Number of subjects with DLTs, PFS
	NCT02769520	II/45	Relapsed, locally recurrent HNSCC after salvage surgery	Pembrolizumab vs placebo	DFS
First-line locally advanced or metastatic setting	NCT02759575	I–II/47	Previously untreated, locally advanced laryngeal SCC	Pembrolizumab + cisplatin + radiation	Toxicity and laryngectomy-free survival in locally advanced laryngeal SCC
	NCT03114280	II/55	Untreated, unresectable, locally advanced HNSCC, stage III or IV without metastases	Induction therapy (docetaxel + cisplatin + 5-fluorouracil + pembrolizumab) followed by radiotherapy combined with carboplatin	PFS
	NCT02777385	II/44	Intermediate or high-risk, previously untreated, locally advanced HNSCC	Pembrolizumab started 3 weeks after completion of cisplatin + radiation vs pembrolizumab given 1 week prior to the start of cisplatin + radiation and given every 3 weeks	1-year PFS, 1-year failure rate, acute toxicity rate
	NCT02586207	I/39	Stage III–IVB HNSCC	Pembrolizumab + standard cisplatin-based definitive chemoradiotherapy	Monitor and grade AE
Cisplatin-ineligible patients	NCT03193931	II/100	Elderly, frail or cisplatin-ineligible patients with HNSCC	Pembrolizumab vs methotrexate	OS rate
	NCT02609503	II/29	Locally advanced HNSCC not eligible for cisplatin	Pembrolizumab + radiation	PFS
	NCT02707588	II/114	Locally advanced HNSCC not suitable for cisplatin-based chemotherapy	Pembrolizumab + radiotherapy vs cetuximab + radiotherapy	Locoregional control
Recurrent disease: pembrolizumab alone	NCT02252042	III/495	Recurrent HNSCC considered incurable by local or systemic disease and metastatic HNSCC considered incurable by local therapies	Pembrolizumab vs standard treatment (methotrexate, docetaxel or cetuximab)	OS for all participants
Recurrent disease: pembrolizumab combined to other therapies	NCT03082534	II/83	Recurrent/metastatic HNSCC	Pembrolizumab + cetuximab	ORR
	NCT02718820	I–II/22	Recurrent or metastatic HNSCC, progressing following receipt of cisplatin and/or carboplatin-based regimen independent of whether patient progressed during or after platinum-based therapy	Pembrolizumab + docetaxel	ORR
	NCT02358031	III/825	Recurrent or metastatic HNSCC considered incurable by local therapies	Pembrolizumab alone vs pembrolizumab + a platinum-based drug (cisplatin or carboplatin) + 5-fluorouracil vs cetuximab + a platinum-based drug (cisplatin or carboplatin) + 5-fluorouracil	PFS in PD-L1-positive expression, OS in PD-L1-positive expression, PFS in all participants, OS in all participants
	NCT02538510	I–II/50	Recurrent unresectable and/or metastatic HNSCC	Pembrolizumab + vorinostat	Incidence of toxicity
	NCT02289209	II/48	Locoregional inoperable recurrence or second primary HNSCC, in patients who have received only prior radiation treatment course with a curative intent	Re-irradiation + pembrolizumab	PFS
	NCT02626000	I/40	Recurrent or metastatic HNSCC >18 years, Eastern Cooperative Oncology Group Performance Status 0.1	Talimogene laherparepvec + pembrolizumab	Incidence of DLTs

Recurrent disease: pembrolizumab combined to other therapies after a treatment with checkpoint inhibitors	NCT03238638	II/30	HNSCC, with either prior response to anti-PD-1/PD-L1 and subsequent (acquired) resistance, or suboptimal benefit from prior PD-1/PD-L1 therapy	Pembrolizumab + epacadostat	RR
	NCT02454179	II/74	Advanced (recurrent, metastatic or unresectable) HNSCC that has either progressed during or after platinum-based chemotherapy administered for metastatic disease or has recurred during or within 6 months after the completion of platinum-based neoadjuvant or adjuvant therapy	Acalabrutinib + pembrolizumab vs pembrolizumab	ORR in each arm
	NCT03085719	II/26	Metastatic HNSCC considered incurable by local therapies, with progression or stabilization on prior PD-1 therapy	Pembrolizumab + high-dose radiation vs pembrolizumab + high-dose + low-dose radiation	ORR
Maintenance treatment	NCT02892201	II/24	HNSCC patients who have residual disease following definitive therapy with radiation (with or without systemic therapy)	Pembrolizumab	ORR
	NCT02841748	II/100	Stages IVA, IVB and select cases of stage III HNSCC at high risk of recurrence after completion of curative intent therapy	Pembrolizumab vs placebo	2-year PFS
	NCT03040999	III/780	Locally advanced HNSCC	Pembrolizumab + chemoradiation as maintenance therapy vs chemoradiation alone	EFS

Abbreviations: AE, adverse event; DLT, dose-limiting toxicity; EFS, event-free survival; HNSCC, head and neck squamous cell carcinoma; ORR, overall response rate; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; RR, response rate; SCC, squamous cell carcinoma; DFS, disease free survival.

HPV viral gene products could serve as tumor antigens increasing T-cell specificity. In addition, the presence of HPV-16 and HPV-18 E6 and E7 is essential for tumorigenesis and is, in theory, expressed in every tumor cell.[54] For these reasons, HPV+ HNSCC represents a potential target for immune checkpoint inhibitors. In fact, patients with HPV-positive tumors had higher response rate in the Phase I study of pembrolizumab in metastatic/recurrent HNC, with an ORR of 32% compared to 14% in patients with HPV-negative tumors.[44] However, Bauml et al reported the same ORR in HPV+ and HPV– tumors in a Phase II study.[46] More studies are needed to depict the role of PD-L1 and HPV expression as biomarkers of efficacy of pembrolizumab in HNC.

Tumors with mismatch repair deficiency responded profoundly to immune checkpoint inhibitors with an ORR of 42.9% for microsatellite instability-high non-colorectal cancers and 40% for microsatellite instability-high colorectal cancer, compared with mismatch repair proficient tumors where the ORR observed was 0%.[55,56] This led to accelerated approval of pembrolizumab in the treatment of solid tumors with mismatch repair deficiency which progressed after prior treatment with no satisfactory alternative treatment options. Field et al reported that the carcinogenesis of HNSCC was associated with microsatellite instability which could respond to PD-1 inhibitors.[57]

The six-gene IFN-γ signature (IDO1, CXCL10, CXCL9, HLA-DRA, STAT1, IFNG) as a potential immune correlative biomarker was investigated by the authors of KEYNOTE-012. The IFN-γ signature score was significantly associated with ORR, progression-free survival and OS (all $p<0.001$).[58]

Somatic mutational load is associated with more frequent neoantigen production and formation of neoepitopes which lead to response to immune checkpoint inhibitors.[59] In HNSCC, mutational load and gene expression profile are independent predictive factors of response to pembrolizumab in patients with HPV- and Epstein-Barr Virus-tumors. However, gene expression profile was predictive of response independently of viral status.[60]

Conclusion

PD-1 inhibitors became a cornerstone in the treatment of metastatic or recurrent HNSCC which is associated with dismal prognosis. Pembrolizumab and nivolumab are the two immune checkpoint inhibitors approved by the US Food and Drug Administration in this situation. Immunotherapy is associated with a good response beyond first-line setting with an ORR between 13% and 18%. It has a good toxicity profile and very well tolerated. Many clinical trials are evaluating PD-1 inhibitors for the treatment of HNSCC in various indications.

Disclosure

Nadine Khalife-Saleh and Khalil Saleh are hematologist-oncologists at Saint-Joseph University. The authors report no other conflicts of interest in this work.

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