Tumor Immunology and Immunotherapy for Head and Neck Squamous Cell Carcinoma

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J.M. Moskovitz¹ and R.L. Ferris²

Abstract

The immune system plays an important role in the evolution of malignancy and has become an important target for novel antineoplastic agents. This review article focuses on key features of tumor immunology, including the role of immunotherapy in general and as it pertains to head and neck squamous cell carcinoma. Side effects, resistance mechanisms, and therapeutic monitoring strategies pertaining to immunotherapy are discussed.

Keywords: cancer biology, clinical trials, checkpoint receptors, immune resistance, T lymphocyte, neoadjuvant immunotherapy

Introduction

Background of Head and Neck Squamous Cell Carcinoma and Immunotherapy

The field of immuno-oncology has developed rapidly since the advent of immunotherapy (IT) and continues to evolve alongside the increased understanding of the role of the immune system in tumor elimination. Tumors acquire immune resistance through several mechanisms. The goal of IT is to offset these resistance mechanisms, allowing for tumor rejection by the endogenous immune system. Several factors have allowed for the realization of IT: 1) the identification of molecularly defined tumor antigen has provided well-defined moieties to be used as immunogens and as markers to monitor the immune response; 2) the characterization of the molecular steps leading to an immune response has facilitated the development of effective immunization strategies and strategies to overcome immune cell exhaustion; and 3) the availability of cytokines has provided reagents to modulate the immune response (Davis et al. 2003; Brinkman et al. 2004).

Head and neck squamous cell carcinoma (HNSCC) is an immunosuppressive disease characterized by a lower absolute lymphocyte count and poor antigen-presenting function as compared with healthy subjects (Kuss et al. 2004; López-Albaiteiro et al. 2006). The varied etiology of HNSCC (environmental and viral) may contribute to a diverse repertoire of tumor antigen that could make this disease process an ideal target for IT. Prior to the advent of IT, prognosis for patients with HNSCC with recurrent/metastatic (R/M) disease remained dismal, and the lack of novel therapies introduced for this disease left few options for curative treatment (Szturcz and Vermorken 2017). The recent success of immune-modulating agents in patients with refractory solid tumors demonstrates

proof of concept that immune system activation is efficacious as a therapeutic modality.

Tumor Immunology and Inhibitory Checkpoint Receptors

Activation of naïve T cells requires a complex signaling interplay through the immune synapse with engagement of T-cell antigen receptor and major histocompatibility complex in the presence of engaged costimulatory molecules CD28 (cluster of differentiation 28) and B7. After activation from an antigen stimulus, memory cells develop as the antigen is cleared. In chronic antigen stimulation, such as that seen in chronic viral infections and cancer, T cells transition to memory cells and anergic or tolerant T cells (Wherry and Ahmed 2004; Wherry et al. 2007; Blackburn et al. 2009). These dysfunctional anergic T cells allow for tumors to escape immune system surveillance and undergo a process known as *immunoediting*. Cancer immunoediting involves 3 phases: elimination, equilibrium, and escape phases (Dunn et al. 2002). The immune escape phase results from chronic antigen stimulation leading to an exhausted T-cell phenotype. Inhibitory receptors (IRs), or immune checkpoints, are expressed upon T-cell activation, leading to signaling that dampens the cellular immune response as antigen is cleared. Sustained expression of multiple IRs signify an

¹Department of Otolaryngology, University of Pittsburgh, Pittsburgh, PA, USA

²UPMC Hillman Cancer Center, Pittsburgh, PA, USA

Corresponding Author:

J.M. Moskovitz, Department of Otolaryngology, University of Pittsburgh, 200 Lothrop Street, Suite 300, Pittsburgh, PA 15213, USA.
Email: moskovitzjm@upmc.edu

exhausted T-cell state characterized by a decrease in effector function of that T-cell subset (Blackburn et al. 2009; Wherry and Kurachi 2015).

Several IRs have been characterized for use as therapeutic targets in an attempt to reverse this dysfunctional exhausted state, including program death 1 (PD1), cytotoxic T lymphocyte antigen 4 (CTLA4), lymphocyte activation gene 3 (LAG3), and T-cell immunoreceptor with Ig and ITIM domains (TIGIT; Wherry and Kurachi 2015).

Cytotoxic T-lymphocyte Antigen 4. CTLA4, a competitive antagonist of the CD28-B7 interaction, is a crucial regulator of T-cell activation. In addition to its role in harnessing immune system activation, CTLA4 is constitutively expressed on regulatory T cells (Tregs), a subset of cells that maintain self-tolerance in healthy patients yet hamper antitumor immunity (Pedros et al. 2017). Preclinical studies with CTLA4 knockout mice demonstrated profound autoimmunity resulting in death; however, CTLA4 blockade demonstrated a surprising effect: tumor regression without overt immune toxicities (Peggs et al. 2009; Simpson et al. 2013; Sandin et al. 2014; Pedros et al. 2017).

Program Death 1. PD1 surface expression on T cells functions in dampening tissue inflammatory responses (Pardoll 2012). Binding of PD1 to its ligands program death ligand 1 (PDL1) and PDL2 results in a signaling cascade that downregulates T-cell activation. PD1 is expressed not only on T cells but also on NK and B cells (Terme et al. 2011). PDL1 overexpression has been noted on multiple solid tumor types, with about 60% of human papillomavirus (HPV)-positive HNSCC tumors expressing this ligand (Concha-Benavente et al. 2016).

Lymphocyte Activation Gene 3. Exhausted T cells coexpress multiple IRs, with LAG3 frequently being coexpressed with PD1 (Grosso et al. 2009; Okazaki et al. 2011). The higher number of IRs expressed on a T cell typically reflects a higher level of exhaustion of that cell. However, IR expression on T cells may lead to enhancement or diminishment of that cell's effector function. For example, LAG3 surface expression on Tregs enhances suppressive function, while CD8 LAG3 surface expression decreases its cytolytic capacity (Workman and Vignali 2005).

T-cell Immunoreceptor with Ig and ITIM Domains. TIGIT engagement with its ligand inhibits T-cell proliferation and cytokine production (Levin et al. 2011; Joller and Kuchroo 2017). TIGIT is highly expressed on Tregs, contributing to the suppressive function of these cells (Joller et al. 2014).

Immuno-oncology of HNSCC

Two anti-PD1 agents, nivolumab and pembrolizumab, were recently approved for use as monotherapy in the second-line setting for patients with platinum-refractory R/M HNSCC.

Pembrolizumab

Food and Drug Administration approval of pembrolizumab was based on 2 early-phase trials, KEYNOTE-012 and KEYNOTE-055, conducted among patients with platinum-refractory disease. KEYNOTE-012 included 174 patients treated biweekly with 10 mg/kg of pembrolizumab, with an expansion cohort receiving a fixed dose of 200 mg every 3 wk (Seiwert et al. 2016). KEYNOTE-055 enrolled 171 patients treated at the fixed-dose regimen. The objective response rate in both trials was 16%, with similar responses between patients with and without HPV (Chow et al. 2016; Seiwert et al. 2016; Bauml et al. 2017). In a follow-up phase III trial conducted among 495 patients, the increase in objective response rate as compared with investigator's choice did not reach statistical significance (14.6% vs. 10%; Cohen et al. 2017).

Nivolumab

Food and Drug Administration approval of nivolumab for platinum-refractory R/M HNSCC resulted from the Checkmate 141 trial. This phase 3 trial assessed 361 patients randomized to receive nivolumab (3 mg/kg, biweekly) or standard single-agent systemic therapy (docetaxel, cetuximab, or methotrexate). Randomization was based on prior cetuximab therapy, and patients were enrolled regardless of tumor PDL1 or HPV status. Baseline characteristics were generally balanced among the groups: 90% had stage IV disease; 66% had ≥ 2 lesions; 45%, 34%, and 20% received 1, 2, or ≥ 3 prior lines of systemic therapy, respectively; and 25% were HPV positive (Ferris et al. 2016).

Objective response rate, as measured with RECIST 1.1 criteria (Response Evaluation Criteria in Solid Tumors), confirmed an objective response for 13.3% of patients (32 of 240). In addition, 2.5% of patients (6 of 240) demonstrated complete response, and 22.9% had stable disease (55 of 240). The median time to response was 2.1 mo (1.8 to 7.4 mo), with a median duration of 9.7 mo (2.8 to >20.3). With a minimum follow-up of 11.4 mo, the overall survival was 7.5 mo (5.5 to 9.1) in the nivolumab group (Ferris et al. 2016), as compared with 5.1 mo (95% confidence interval, 4.0 to 6.0) for the standard therapy group.

Patient Monitoring and Response Evaluation with IT. Patients responding to IT have a durable and long-lived response; however, unlike cytotoxic therapy, response to IT may not be appreciated soon after treatment initiation. Initial tumor progression prior to response, called *pseudo-progression*, is thought to result from increased tumor immune cell infiltrate. Because of this phenomenon, investigators have begun to evaluate clinical response to IT with alternative clinical endpoints and radiologic criteria, such as immune response criteria (Hodi et al. 2008). Pseudo-progression has been observed in about 10% of melanoma patients soon after IT initiation, although this is rare in HNSCC (Szturcz and Vermorken 2017); therefore, increased tumor size should not prompt immediate change in therapeutic management. Unlike the traditional radiologic

modality, RECIST criteria, immune response criteria require repeat measurement in 4 wk and do not account for the appearance of new lesions (Wolchok et al. 2009; Hodi et al. 2016).

IT Side Effects and Adverse Events. Most patients report a better quality of life on IT agents as compared with cytotoxic chemotherapy (Ferris et al. 2016; Malkhasyan et al. 2017). The side effect profile for IT agents, though different from traditional cytotoxic therapies, should not be minimized. IT agents can lead to autoimmune reactions in any organ system. Some agents are more commonly associated with specific autoimmune reactions. For example, ipilimumab is often associated with colitis (Champiat et al. 2016). Most side effects resolve with steroid therapy and withholding of the IT agent, but clinicians should be aware that the length of time to resolution may vary (Larkin et al. 2015). Of note, some patients do not respond to corticosteroid therapy and may require anti-tumor necrosis factor agents (Kyi et al. 2014).

For patients with HNSCC who were treated in the Checkmate 141 trial, nivolumab was discontinued in 14% and delayed in 24% due to an adverse event (AE). The most common AEs, occurring in $\geq 10\%$ of patients treated with nivolumab and at a higher incidence than investigator's choice, were cough and dyspnea. Serious AEs occurred in 49% of patients treated with nivolumab—the most frequent of which, in at least 2% of patients, were pneumonia, respiratory tract infection, dyspnea, respiratory failure, and sepsis (Ferris et al. 2016). The most common laboratory abnormalities, occurring in $\geq 10\%$ of patients treated with nivolumab and at a higher incidence than investigator's choice, were hypercalcemia, hyperkalemia, and elevations in alkaline phosphatase, thyroid-stimulating hormone, and amylase (Ferris et al. 2016). AEs and laboratory abnormalities with nivolumab treatment were similar among patients with HNSCC who were treated in Checkmate 141 as compared with other trials of patients with melanoma and non-small cell lung carcinoma (Ferris et al. 2016).

Future of IT

Prognostic Biomarkers of Response

Although no biomarkers of response have been prospectively validated, 5 groups of correlative biomarkers for cancer IT have been proposed: tumor-related, peripheral blood mononuclear cell-related (circulating Tregs), serum-related (cytokines and antibodies), imaging-related (positron emission tomography/computed tomography), and microbiome-related (stool and saliva; Bauman et al. 2017). Tumor-related biomarkers include PD1/PDL1 and CTLA4 expression, as well as an interferon gamma (IFN γ) gene signature. The 6 genes evaluated in this signature—IFN γ , human leukocyte antigen-DR, chemokine C-X-C motif ligand 9 (CXCL9), CXCL10, indolamine 2,3-dioxygenase 1, and signal transducer and activator of transcription—together serve as a predictor of patient response to anti-PD1 therapy (Rieke et al. 2016). Unlike colorectal carcinoma—where PDL1 is almost exclusively expressed on tumor-infiltrating immune cells—certain cancers, including

HNSCC, express PDL1 on tumor cells and tumor-infiltrating immune cells (Taube et al. 2014). PDL1 has also been noted to vary over time and in different anatomic sites from the same patient. PDL1 expression may be useful for patients with multiple treatment options as a means to prioritize treatment sequencing; however, the relationship between PDL1 expression and long-term outcomes from anti-PD1 therapy is not yet firmly established (Topalian et al. 2016). Future trials will incorporate these proposed correlative biomarkers to elucidate which are clinically relevant. Furthermore, standardization of PDL1 detection methods will likely resolve conflicting data of expression and relation to prognosis in solid tumor treated with anti-PD1 therapy (Topalian et al. 2016). Additional biomarkers in conjunction with or substituting for PDL1 will provide improved capability for predicting patient response.

Overcoming Innate and Acquired Tumor Resistance

Despite the exciting results from IT, the majority of patients are nonresponders (Hodi et al. 2008; Topalian et al. 2012; Pitt et al. 2016; O'Donnell et al. 2017) and thus may have tumors with an innate mechanism of resistance to IT (primary resistance). Among patients who initially respond to IT, the response is often prolonged (Ferris et al. 2016; Pitt et al. 2016; O'Donnell et al. 2017; Szturz and Vermorken 2017). However, some develop recurrent disease despite initial response to IT through acquired resistance. Understanding the mechanisms underlying primary and acquired resistance has provided insight for intelligent clinical trial design. One such explanation for primary resistance is exemplified by poorly immunogenic tumors, referred to as *cold tumors*, which are limited by a lack of immune cells within the tumor microenvironment (TME) that IT agents could target (O'Donnell et al. 2016, 2017).

Methods to increase tumor immune cell infiltrate and, thus, response to IT are under investigation. More traditional therapies, such as radiation and cytotoxic chemotherapy at altered dosing regimens, released tumor antigens resulting in immune system stimulation and recruitment of antigen-specific immune cells into the TME (Multhoff and Radons 2012; de Biasi et al. 2014).

For patients with immune cell-rich tumors, the PD1/PDL1 has garnered attention in explaining these mechanisms. One such resistance mechanism results from tumor antigen-stimulated T-cell production of IFN γ that leads to upregulation of PD-L1 on the tumor cell surface. PDL1 then binds PD1 on other TME immune cells, rendering them less active (Pardoll 2012; Taube et al. 2012; O'Donnell et al. 2017).

Trials combining IT with radiation and/or chemotherapy in the neoadjuvant and adjuvant settings developed from the understanding of how immune cells are recruited into the TME. One trial treats patients with locally advanced (LA) HNSCC by adding nivolumab to 2-dose regimens of cisplatin prior to definitive chemotherapy and radiation. The results of this trial and other similarly designed trials will not only inform if and at what dose cytotoxic therapy increases immune cell infiltrate in the TME but also determine if the addition of IT to

Table. Selected Immunotherapy Trials in HNSCC.

Agent	Trial Number / Acronym	Phase	Status	Eligible Patients	Trial Details
Anti-PDL1: avelumab	NCT02952586 / JAVELIN HEAD AND NECK 100	3	Monotherapy trials Recruiting	LA HNSCC	Compared with SOC CRT
Anti-PD1 Pembrolizumab	NCT03040999 / KEYNOTE 412	3	Recruiting	LA HNSCC	IT + CRT vs. IT + placebo
Nivolumab	NCT02764593	1	Recruiting	LA HNSCC	IT + CRT (cetuximab or cisplatin or high-dose cisplatin)
	NCT03247712	2 ^a	Not yet recruiting	LA HNSCC	Neoadjuvant with radiation prior to definitive surgery
Anti-CTLA4: ipilimumab	NCT02812524	1	Recruiting	LA HNSCC	Intratumoral injection prior to definitive surgery
			Combination trials		
Anti-PD1 + anti-LAG3	NCT01968109	1 / 2	Recruiting	Multiple solid tumor types	PD1 nonresponders
Anti-PD1 + anti-CTLA4	NCT02823574 / Checkmate 741	2	Recruiting	R/M HNSCC	Compares combination with placebo
	NCT02919683	2	Recruiting	LA HNSCC	Neoadjuvant (prior to surgery)
	NCT02741570 / Checkmate 651	3	Recruiting	R/M HNSCC	Compared with EXTREME regimen as first-line treatment
Anti-PDL1 + anti-CTLA4	NCT02319044	2	Active, not recruiting	R/M HNSCC	PDL1-negative patients

CRT, chemotherapy and radiation therapy; CTLA4, cytotoxic T-lymphocyte antigen 4; HNSCC, head and neck squamous cell carcinoma; IT, immunotherapy; LA, locally advanced; LAG3, lymphocyte activation gene 3; PD1, program death 1; PDL1, program death ligand 1; R/M, recurrent/metastatic; SOC, standard of care.

^aPhase I safety lead-in.

standard of care (SOC) therapy is superior to SOC alone (Table).

Combinatorial IT in R/M HNSCC and First-line IT for LA HNSCC

The results from trials with IT among patients having failed multiple prior therapeutic modalities generated interest in the use of these agents in treatment-naïve patients as a means to improve SOC. Safety information from trials with IT in the perioperative setting for treatment-naïve patients with surgically resectable LA HNSCC will determine if patients have increased surgical risk or delay to definitive treatment with IT in the neoadjuvant setting (Table).

Combinatorial IT trials will assess synergistic mechanisms of IRs to overcome innate and acquired immune resistance. The addition of anti-LAG3 to anti-PD1 to overcome PD1 resistance among nonresponders is being assessed in multiple solid tumor types, including HNSCC, melanoma, and non-small cell lung carcinoma. Completed trials that combined anti-PD1 with anti-CTLA4 agents in patients with advanced melanoma demonstrated that this combination was superior to either monotherapy alone (Wolchok et al. 2017). Trials evaluating agents targeting the PD1 pathway with anti-CTLA4 in R/M HNSCC are now underway. The safety and efficacy of this IT combination are also being assessed in the first-line setting for patients with surgically resectable oral cavity squamous cell carcinoma (Table).

Conclusion

The development of IT agents has led to a rapidly changing field in oncology. These agents have led to optimism about the ability to provide patients with an additional option for therapy after treatment with multiple other modalities has been exhausted. The future of IT will rest on intelligent combinatorial trials as well as evaluation of these agents in the first-line setting and in early-stage disease.

Author Contributions

J.M. Moskovitz, contributed to conception and design, drafted the manuscript; R.L. Ferris, contributed to conception, design, and data interpretation, critically revised the manuscript. Both authors gave final approval and agree to be accountable for all aspects of the work.

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