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Review

Rationale for neoadjuvant immunotherapy in head and neck squamous cell carcinoma

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ABSTRACT

The clinical benefit of immunotherapy in recurrent, metastatic head and neck squamous cell carcinoma has fueled interest in revisiting neoadjuvant approaches to complement definitive treatment. Neoadjuvant strategies incorporating immune checkpoint inhibitors and other novel immune-based therapies in head and neck cancer are reviewed here, with particular attention paid to the rationale for these approaches from both a clinical and biologic discovery standpoint. The potential benefits of neoadjuvant immunotherapy include reduction of extent of surgery and the intensity of adjuvant therapy by tumor downstaging, reduction of the risk of distant metastatic spread by early introduction of systemic therapy, conversion of unresectable to resectable disease, and early evaluation of biomarkers of tumor response. We await early trial results utilizing these approaches to confirm both safety and initial efficacy in head and neck cancer.

Introduction

In patients with locoregionally advanced squamous cell carcinoma of the head and neck (SCCHN), current treatment guidelines recommend surgery with post-operative adjuvant therapy or definitive chemoradiotherapy (CRT) as standard of care. Despite these intensive multimodality treatments, recurrence of disease persists as a key cause for treatment failure. Recurrent disease is especially problematic in human papillomavirus (HPV)-unrelated SCCHN.

Early induction strategies sought to select chemoresponsive patients and capitalize on laryngeal organ preservation in head and neck cancer [1,2]. Decades later we have learned that a taxane-platinum-5-fluorouracil (TPF) combination is the preferred induction regimen, but it is not without significant toxicity [3]. A neoadjuvant approach (defined as systemic therapy prior to surgery) to induction using TPF has been explored in resectable oral cavity cancers and failed to demonstrate superior survival compared with an upfront surgical approach [4–6]. However, subgroup analysis showed that patients with bilateral cervical nodal involvement may benefit [6]. For now, the primacy of surgical resection remains the mainstay of definitive therapy in locoregionally advanced SCCHN involving the oral cavity, with post-operative concomitant CRT improving locoregional control and survival in patients with high-risk pathologic features [7,8]. Similarly, CRT with platinum-based regimens in combination with definitive radiation remains the standard for non-surgical disease.

More recently, a neoadjuvant approach has been revisited in several cancer types in an attempt to integrate immunotherapeutics into the upfront setting. Here we provide a rationale for these approaches including preclinical data, current neoadjuvant trial designs and implications for future management in SCCHN. Governed by the principle that tumors can evade immune detection, immunotherapies in clinical development aim to activate immunologic effector mechanisms to kill cancer cells. As one example, immune checkpoint receptors exist on the surface of immune cells that bind their cognate ligands on tumor or other immune cells. The ligand programmed cell death-1 (PD-L1) is one such moiety that can bind PD-1 on T cells, leading to T cell exhaustion, and ultimately promotes immune escape [9,10]. Immune checkpoint receptor blockade has demonstrated efficacy in platinum-refractory, advanced SCCHN patients leading to the recent approval of pembrolizumab and nivolumab (both anti-PD-1 antibodies) in this disease [11,12]. With response rates approaching 20% in this setting, identifying biomarkers predictive of response or resistance to these agents is of strong interest. Recognizing their clinical benefit and favorable toxicity profile in SCCHN, an exciting next step will be to investigate neoadjuvant approaches to treatment that evaluate immune-based therapies. Here we aim to: (1) review the rationale for neoadjuvant

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strategies using immunotherapy in SCCHN from both a therapeutic and discovery standpoint, (2) review preclinical data to support a neoadjuvant immunotherapeutic approach, and (3) discuss emerging trial designs incorporating neoadjuvant immunotherapy in SCCHN.

Therapeutic considerations

The potential therapeutic benefits of neoadjuvant treatment incorporating immunotherapy primarily include early selection of treatment responders and cytoreduction to minimize the degree of oncologic resection in patients requiring definitive surgery – which may have important functional and cosmetic implications. Similarly, pre-operative cytoreduction may reduce the likelihood of a positive resection margin and could facilitate de-escalation of adjuvant post-operative radiation and/or chemotherapy in surgical patients. Data from pre-clinical models suggests that priming an immune response may also be superior in the neoadjuvant setting [13], which leads to speculation about early targeting of immune mechanisms in treatment naïve patients. Additionally, neoadjuvant immunotherapy may downstage previously unresectable disease to become resectable disease and has the potential to provide early systemic therapy to address the risk of distant metastatic spread – a notion of particular concern in HPV-associated disease where distant relapse is the most common type of disease recurrence, and can occur late [14].

Discovery considerations

Aside from therapeutic benefits, neoadjuvant trials offer the opportunity for research and biomarker discovery (Fig. 1). Using immunotherapy after biopsy confirmation of disease, but prior to definitive surgery, offers a window phase of treatment in which to deliver therapy and assess clinicoradiologic and biologic response. Sequential biopsies allow for correlative studies aimed at understanding changes in tumor-immune metrics and permits correlation with response. Multiparametric flow cytometry, immunohistochemistry, and multiplexed immunofluorescence can be performed to quantify immune cells and immune checkpoint receptor expression patterns while the latter can provide insight about spatial tumor-immune cell interactions. Whole-exome and RNA sequencing platforms can be applied to understand genomic determinants of immune cell function, facilitating neoantigen prediction modeling and protein expression analysis. Additionally, T cell receptor (TCR) clonotyping can determine unique gene rearrangement sequences that arise in response to antigen presentation in the lymphocytes infiltrating an individual tumor, and extra- or intracellular cytokine levels can be quantified to understand immune cell signaling. These methods can be interpreted together to understand the dynamic and complex tumor immune network and how it changes in response to administration of immunotherapy.

Potential limitations of neoadjuvant immunotherapy

Despite the potential benefits highlighted above, the limitations of a novel, neoadjuvant approach using immunotherapy must be considered: administering neoadjuvant therapy of any kind prior to definitive surgical resection is not without some risk, as immune-mediated toxicity can be severe with the concern of delaying curative surgery. Of particular interest has been the notion of hyperprogression, where patients experience acceleration of tumor growth kinetics following anti-PD-1/L1 exposure [15]. The impact of changes in the tumor immune microenvironment on hemostatic effects after immunotherapy exposure are unknown. In addition, immunomodulation could have implications with regards to post-operative wound healing. While these latter concerns remain largely speculative and early studies show that neoadjuvant immunotherapy is safe [16], these are important considerations nonetheless.

Preclinical rationale to support neoadjuvant immunotherapeutic approaches

SCCHN is often considered an immunosuppressive disease, with an imbalance in both the composition and function of effector immune cells. Studies have shown that a decrease in tumor-infiltrating lymphocytes limits antigen-specific targeting of cancer cells, and along with increased suppressive T regulatory cells (Tregs) can promote tumor evasion [17,18], while disruptions in natural killer (NK) cell function and antigen presenting activity represent examples of impaired immune cell function [19,20]. Strategies to enhance anti-tumor immune activity focus on promoting an effector response mediated by cytotoxic T cells and NK cells or inhibiting suppressive signals facilitated by tumor-associated macrophages and myeloid-derived suppressor cells [21]. Clinical experience with patients who are immunosuppressed with SCCHN suggests higher rates of recurrence, emphasizing the importance of immune mechanisms to moderate cancer control [22]. High mutational burden among certain cancer types (including non-HPV SCCHN tumors, particularly in smokers) is thought to correlate with a larger neoantigen burden to facilitate T cell-specific responses and ultimately promote tumor regression [23]. Additionally, differences in immune cell expression signatures have been observed among SCCHN subtypes [24]. It is these observations combined with patterns of immune checkpoint receptor expression that provide a general preclinical rationale supporting investigation of immunotherapeutic approaches in the early treatment setting.

Preclinical data to support neoadjuvant immunotherapy-based approaches to cancer treatment started with observations in the adjuvant setting for other cancer types. Kwon et al. demonstrated that adjuvant cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody treatment immediately following prostate tumor resection in mouse models

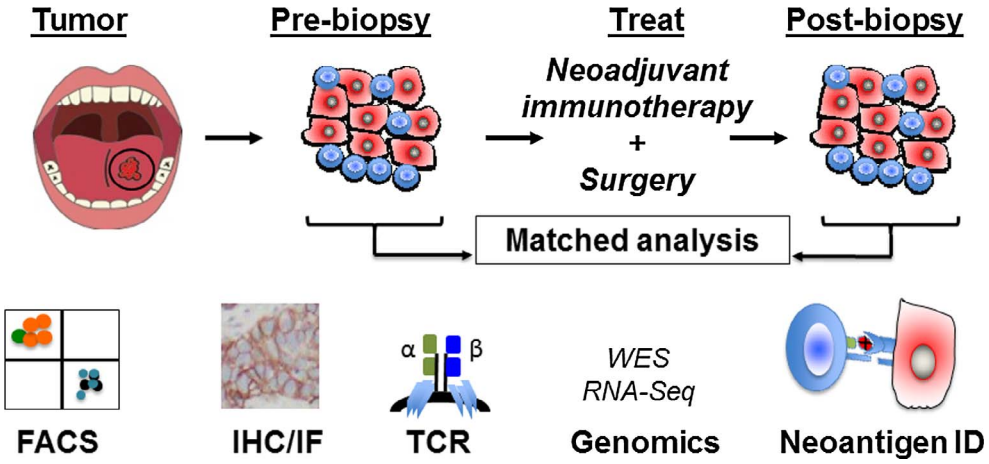

Fig. 1. Discovery considerations of neoadjuvant approaches using immunotherapy in resectable head and neck cancer. FACS = fluorescence-activated cell sorting, IHC = immunohistochemistry, IF = immunofluorescence, TCR = Tcell receptor, WES = whole-exome sequencing, ID = identification.