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Anti-Tumour Treatment

Innovative perspectives of immunotherapy in head and neck cancer. From relevant scientific rationale to effective clinical practice

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ABSTRACT

It is now well established that head and neck cancer carcinogenesis is characterized by genetic instability and several immune defects, leading to unique host–tumor interactions. In such condition, recent improved comprehension and relevant findings could lead to identification of innovative molecular therapeutic targets, achieving considerable clinical and translational research. This review aims to summarize and to highlight most recent and relevant scientific rationale in this era of immunotherapy revival, and to correlate it to the near future clinical practice for the management of this challenging disease.

Introduction

Head and neck cancer (HNC) is the sixth most common type of malignanacy in developed countries, representing approximately 6% of all cases with a world annual incidence of approximately 650,000 cases, and accounting for 350,000 cancer-related deaths worldwide every year [1,2]. Head and neck squamous cell carcinomas (HNSCC) is accounting for nearly 90–95% of HNC tumors. Primary HNSCC is a complex and heterogeneous group of aggressive diseases, associated with a poor prognosis (5-year survival rate around 40–60%), with only modest improvement achieved over the past two decades, despite intensive multimodality therapeutic strategies [3–5].

For recurrent or metastatic disease (R/M HNSCC), cytotoxic-based chemotherapy remains the standard therapeutic option, yielding very slow progress [6–10]. The median survival for these patients treated with palliative chemotherapy alone is only 6–10 months. The prognosis for those patients who are not candidates for chemotherapy or present with progressive disease after platinum-based therapy is even worse, with a median overall survival ranging from 3 to 6 months, and less than 5% of these patients being alive at 1 year [11].

To date, Cetuximab remains the only targeted therapy approved by the FDA for managing R/M HNSCC [12]. As with great variety of malignancies, such monoclonal antibody-based therapy is currently the most widely used form of immunotherapy. Beyond the well-known blockade of cytoplasmic transduction signals from epidermal growth factor receptor (EGFR) signaling interfering with tumor growth, this monoclonal antibody has indeed a number of clinically important innate and adaptive immune mechanisms, including triggering of the antibody-dependent cellular cytotoxicity (ADCC), IFN-c secretion by activated natural killer (NK) cells and activation of the FccR IIIa on NK cells. This will result in up-regulation of antigen presentation in dendritic cells (DCs), and finally stimulation of tumor antigen-specific cytotoxic T lymphocytes (CTLs) [13,14].

Beyond first-line, clinical efficacy of several systemic therapies either as single agents or in combination with other treatment modalities, have been extensively studied, including drugs targeting growth factors and receptors such as EGFR, vascular endothelial growth factor (VEGF), and various tyrosine kinases interfering with known molecular pathways activated in HNSCC. Whilst use of these new modalities has resulted in modest improvement in response rates, only few and limited benefit has been seen in terms of survival improvements [15–20], without effective therapeutic breakthroughs. Therefore, there is an urgent need to develop new therapeutic approaches to improve R/M HNSCC outcomes.

HPV and HNSCC

Besides the usual risk factors of tobacco and alcohol addiction, an increasing proportion of oropharyngeal squamous cell carcinoma (OPSCC) is related to oncogenic human papilloma virus

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(HPV), accounting for 40–80% of cases in the western world [21–26], with a continuous rising of incidence. This group reveals unique risk factors, tumor biology and clinical characteristics when compared to HPV-negative tumors. Despite late stage presentation at initial diagnosis, HPV+ tumors have a much better prognosis, with improved long-term survival and a 60–80% reduced risk of death when compared with matched stage HPV- OPSCC [27–30]. Even if not fully understood, some factors have been proposed to explain this specific clinical behavior, including retained expression of wild-type p53 (TP53) and retinoblastoma 1 (Rb1) tumor suppressor genes, but also the absence of field cancerization with a lower risk of developing secondary primary tumors. In addition, HPV status inversely correlates with biomarkers of poor prognosis such as EGFR overexpression. Nevertheless, other studies failed to demonstrate any association between HPV positivity and patient prognosis [31–35], whereas others even suggested that the HPV positive subgroup even could be correlated with an increased risk of recurrence or developing a second primary tumor [36–38].

Moreover, the increased incidence of HPV+ cases is increasingly important in terms of total HNSCC mortality, with the need to develop adapted therapeutic strategies in this specific entity [39,40]. Interestingly, improved survival of HPV+ OPSCC patients appears to be independent of considered treatment modalities, raising the possibility that some of these patients might be "over-treated", with potentially useless acute and late toxicities [41]. Based on these observations, various clinical trials are currently testing treatment de-escalation attitudes, in order to reduce such therapy-related toxicity and morbidity. However, at present, HPV infection status is not routinely used to direct strategies for treatment decisions. Such procedure should be exclusively considered into clinical trials.

It is also known that a portion of HPV+ OPSCC patients will respond poorly to conventional treatments, leading to an unexpected poor prognosis. There is currently no widely accepted strategy and no single clinical or morphological feature for identifying those HPV+ OPSCC patients who will have poor disease outcome [42]. It has been suggested that future clinical investigations should focus on this specific patient group, in order to improve outcome and to avoid potential deleterious treatment de-intensification in this setting.

Interplay between tumor immune infiltration and HPV status in HNSCC

In a normally functioning immune system, CTLs are activated by binding of its cell receptor (TCR) to a matching antigen packaged onto major histo-compatibility complex proteins (MHC). To avoid auto-immunity, along with the MHC/TCR binding, there are co-stimulatory and co-inhibitory receptors signaling by DCs and CD4+ helper T cells, as well as freedom from suppression by CD4 + regulatory T cells (Treg). The balance between these co-stimulatory and co-inhibitory receptors determines whether the T-cell is activated or becomes anergic to the specific antigen displayed on the MHC molecule.

As a major watch guard, the immune system plays a crucial role in tumor surveillance by targeting unique neo-antigens presented on the cancer cell surface [43]. This process of immune-editing of antigens expressed by tumors occurs spontaneously during cancer development. Activated CD8+ CTLs are among the critical effectors of adaptive antitumor immunity. Because of their intrinsic genomic instability, cancer cells can escape CTLs recognition by mutation or down-regulation of these antigens, just as they usually develop resistance to cytotoxic agents and molecular-based systemic therapies [44–46].

Tumors, such colorectal cancer with the highest degree of genomic instability (e.g. Microsatellite Instability; MSI), often also display a more prominent lymphocytic infiltrate [47,48], and tumors with an immune-active microenvironment are more likely to respond to immunotherapy agents targeting key immunosuppressive pathways [49]. Several mechanisms have been proposed regarding tumor-immune interaction in response to cancer treatment in malignant tumors [50,51]. These investigations have hypothesized that the pretreatment of host immune response may increase the potential of cancer therapies to eradicate cancer cells.

Tumor-infiltrating lymphocytes (TILs) have been identified in many tumor types and often have prognostic value. Even if high numbers of TILs have been considered as a good prognostic factor for HNSCC patients, it seems also well established that all subtypes of these lymphocytes are not associated with a good prognosis. Although TILs abundance is associated with improved clinical outcomes in a number of other tumor types, their role in HNC is not fully understood and documented [52], but emerging interesting data must be considered for potential future clinical applications.

The CD4/CD8 ratio of infiltrating cells among specimens of surgically treated patients with advanced oral cavity cancers ($n = 52$) tended to be higher in patients with better overall ($p = 0.08$) and disease specific survival ($p = 0.10$). Moreover, the CD4/ CD8 ratio significantly predicted disease specific survival, which added prognostic significance after extra-capsular spread was considered. Mean TIL levels for CD4, CD8, and FoxP3 were higher in surviving patients [53]. However, the authors highlighted the lack of correlation of individual T lymphocyte subset tumor infiltrates with overall prognosis, needing further analysis.

In HNSCC, the role of Tregs remains controversial as mixed and ambiguous findings have been reported, with regard to disease progression and survival outcomes, leading to some conflicting reports over whether presence of Tregs are associated with better loco-regional control, negative prognosis or of no relevance at all [54–59]. Both the nature of underlying malignancy and/or the documented functional heterogeneity of Tregs may probably largely explain such conflicting and confusing data. There could also be a role of Tregs in reducing tumor-specific immune-mediated inflammation which has been shown to drive the progression of tumors in certain cases. Finally, the discrepancies happen in part because of the multiple markers that are used to identify the Treg population, but also potentially because of differences in patient cohorts where a variety of anatomical sub-sites were analyzed.

Heterogeneous Treg subsets in the peripheral circulation of HNSCC patients have been observed, using detection of CD45, Forkhead Box Protein P3 (FoxP3) and CD25 markers has allowed determination in the circulation of HNSCC patients with various tumor stage and nodal status. Frequency of CD45RA−FoxP3 high Tregs and CD45RA−FoxP3low CD4+ T cells in patients with HNSCC developing from different subsites was higher than in healthy donors ($p < 0.0001$), whereas the frequency of CD45RA+ Foxp3low Tregs was lower than in healthy donors ($p < 0.0001$). A significant increase of the subset CD45RA−FoxP3high Tregs has been observed in the peripheral circulation of HNSCC patient subgroups, and could be positively correlated with tumor stage ($p < 0.0001$) and nodal status ($p < 0.0001$) [60]. These data suggest that identification of distinct Treg subsets rather than the whole population of Tregs should be considered, requiring further clarification about the potential prognostic or therapeutic that might be gained when considering analysis of such specific T cell population.

Beside such functional heterogeneity of Tregs, another attempt to explain their paradoxical role in HNSCC may come from a possible role of the translocation of microbial flora from the oropharynx to HNSCC tissues. Such hypothesis is largely based on what has been suggested for colorectal malignancies, with a promotion of cancer growth mediated by T-cell-mediated antimicrobial