About the Editor

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Foreword

Current therapies for HNC: why is immunotherapy not yet in the forefront?

Theresa L. Whiteside

Despite substantial, even impressive, recent advances in the detection and therapy of head and neck cancer (HNC), morbidity and mortality attributable to this disease remain high throughout the world. Today, head and neck squamous cell carcinomas are the sixth cause of cancer deaths worldwide [1]. In the USA, more than 52,000 new cases of head and neck squamous cell carcinomas are reported per year, with approximately 12,000 deaths [101]. Locoregional recurrence is the main cause of treatment failure; however, distant metastases arise in approximately 10–15% of cases and are associated with very poor prognosis [2]. There is an urgent need for improvements, and while surgery, chemotherapy and/or radiotherapy remain the major therapeutic strategies, a variety of novel approaches to diagnosis, prognosis and treatment of HNC have been introduced. This book attempts to present these various approaches, emphasizing that the rationale for their implementation is based on recent progress in our understanding of the biology of HNC and of molecular mechanisms involved in its progression.

Perhaps two most important findings that have had a considerable translational impact on therapy of HNC concern its genetic instability and its unique host–tumor interactions. The former has focused attention on the identification and classification of various genetic abnormalities in HNC, including the advantages these genetic changes provide to the growing tumor. This has opened the way for selective administration of drugs that could inhibit the molecular mechanisms responsible for tumor progression.

doi:10.2217/EBO.12.495

However, this initially effective treatment sooner or later becomes ineffective, as drug resistance enforces the need for alternative therapies. The second conceptual advance in HNC redirects attention from the tumor to the host and is highlighted by the emergence of recognition that the hosts' health status, including nutritional, virological and immunological factors, can influence outcome and may even serve as a guide for selection of alternative novel therapies. To a certain extent, both these developments are reflected in the narrative of this book. Chapters covering aspects of HNC biology, diagnosis and prevention, and those summarizing therapies available today for HNC patients, adequately relate the advances made in the field. However, one developmental aspect that has been relatively neglected in this book, and in HNC in general, is immunotherapy. In view of the recent emergence of immune therapies used as potentially effective adjuncts to conventional therapeutics in a variety of other human solid tumors [3,4], the apparent lack of immune interventions in HNC is striking and disappointing. With the notable exception of anti-EGF receptor antibody therapy covered in **Chapters 5 & 6** of this book, immunotherapy of HNC has lagged behind relative to other solid tumors, where biologic strategies have been embraced with a much greater enthusiasm and some notable recent successes [5].

One reason for this slow and reluctant use of immune interventions in HNC may reside in a perception that HNCs are strongly immunosuppressive and exceptionally successful in escaping from the host immune surveillance [6,7]. Indeed, a substantial body of accumulated evidence points to the numerous mechanisms that HNCs employ to engineer escape from the host immune defenses [8]. These broadly range from a rapid turnover and demise of effector lymphocytes in the peripheral circulation; accumulation of Tregs and myeloid-derived suppressor cells or immature neutrophils in the tumor; the ability of HNCs to produce quantities of tumor-derived exosomes carrying membrane-bound cell ligands (e.g., FasL or PD-L1); to secretion by the tumor of immunosuppressive factors such as TGF-β1, arginase or IL-10 [9,10]. The microenvironment of HNCs is thus dominated by the tumor, which effectively disarms immune cells preventing host attempts at tumor rejection. Immunosuppressive effects of the tumor extend to the periphery, where changes in the frequency and function of antitumor effector cells are also compromised [10]. While the mechanisms and extent of immune suppression are unique characteristics of every tumor, and may be, in part, responsible for strikingly different aggressiveness of HNCs exhibiting the same clinicopathologic features, it is now clear that HNC progression is accompanied by increasingly potent immune suppression of host antitumor responses. The argument could be advanced that fixing the failed immune system is not only difficult but counterintuitive, especially in advanced disease.

Evidence also suggests that HNCs are immunogenic: these tumors are able to induce and often maintain antitumor immune responses. The presence of anti-EGF receptor antibodies in the patients' circulation [11], oligoclonal and monoclonal expansions of T cells with specificity for tumor-associated antigens in the blood [12], and the ability of tumor-infiltrating lymphocytes isolated from HNCs to proliferate and kill tumor cells [13] all serve to remind us that the patients' immune system recognizes the tumor. These manifestations of antitumor immunity are often weak but could potentially be enhanced to assume a more significant role in preventing tumor progression. Human papillomavirus-positive HNCs have a better prognosis and respond better to therapies [14], perhaps because of the fact that viral antigens are strongly immunologic and serve as a kind of adjuvant for antitumor responses. HNCs developing at or in the proximity of mucosal surfaces are in continually close contact with bacterial flora, and signaling via the Toll-like receptors expressed by HNC provides stimuli for production of cytokines/chemokines [15] and creating an inflammatory milieu that is enriched in immune cells and may influence prognosis [16].

How are we to reconcile these opposing effects of the host immune system with regard to the growing tumor? The optimal solution would be to achieve the balance necessary for keeping immune suppression at bay while favoring immune activation. However, before attempting to achieve this balance, it may be advisable to enquire whether the immune system activities matter for the disease outcome. That the immune system matters in HNC can be demonstrated by establishing a robust correlation between antitumor immune responses and prognosis or response to therapy. Unfortunately, this type of correlative data has been difficult to obtain in HNC, largely because of inadequate or incomplete immune monitoring of patients in prospective studies. Lately, however, with improved monitoring tools and greater insights into assay selection, it has been possible to begin linking HNC recurrence and outcome to immune responses in HNC patients, as illustrated below. The frequency of $CD8^+CCR7^+$ T cells (>28%) in the blood of HNC patients tested at diagnosis and prior to any therapy in a recent study, was shown to positively and significantly correlate with recurrence-free survival. Despite the small number of HNC patients enroled (n = 25) in the study, this report suggested that a simple flow cytometry-based blood test at diagnosis discriminated HNC patients with better recurrence-free survival regardless of subsequent therapy received [17]. In another study that measured the frequency of circulating Treg after definitive therapy, HNC patients with no evident disease segregated into those with a significant persistently high Treg frequency versus those whose Treg frequency normalized after therapy. The hypothesis was suggested that

patients with elevated Treg are likely to experience early recurrence, and serial blood samples are being collected to test the hypothesis in a prospective nontherapeutic clinical study [Whiteside TL, Unpublished Data]. These two examples offer support for an increasingly growing body of evidence that successful outcome in HNC may depend on the strength and health of the host immune system.

Having established in principle that the host immune system plays an important role in HNC progression, the question arises as to the best strategy to adopt for its mobilization. There are many such strategies available today, which can be divided into two general categories of [18]:

- Blocking the inhibitor
- Upregulating existing antitumor immunity

In the first category, the recent checkpoint blockade with antibodies such as ipilimunab (specific for CTLA-4) or PDL-1 antibodies represents a particularly apt example. Ongoing clinical trials in patients with solid tumors indicate efficacy with mild toxicities and are highly promising for HNC patients who often suffer from profound immune suppression. In the second category, antitumor vaccines, for example, employing newly developed technologies for making better vaccines and utilizing powerful adjuvants are available [18], as are *ex vivo* preconditioned immune cells for adoptive transfers. Multiple other clinically applicable strategies for increasing antitumor immune responses including arrays of various pharmacologic agents and cytokines targeting distinct immune pathways exist as previously reviewed [18]. Recent progress in our understanding of cellular and molecular mechanisms operating in cancer and of the possibilities to therapeutically manipulate these pathways has placed immune therapies among desirable, albeit still experimental, approaches available to the oncologic community. As these therapies become more widely evaluated and are clinically applied, their beneficial effects on antitumor responses even in patients with advanced disease are being recognized; for example, objective and durable clinical responses seen with two cancer therapeutic agents, anti-PD-1 and anti-PD-L1 antibodies, in early clinical trials were reported in substantial proportions of patients with metastatic melanoma, renal cell carcinoma or non-small-cell lung cancer [19]. There is reason to hope that these and other biologic therapies will exert similarly promising effects in patients with HNC.

Immune therapies have been delivered to patients with cancer for over three decades with remarkably infrequent serious adverse events. Some of these therapies have induced durable clinical benefits. This is in contrast to either chemo- or radio-therapy, both of which are known to be associated

with often severe and debilitating toxicities and a poor quality of life. While the promising results of recent clinical trials with various immunotherapies have created hope and enthusiasm, it now appears that combination therapies rather than immunotherapy alone will have the greatest impact on improving patient survival. Combinations of two or more immunotherapeutic agents are being evaluated, as are interventions combining conventional cancer therapy with immunotherapy. In HNC, the field is wide open for implementation of these novel therapies, especially those combining immune therapy with a molecularly targeted agent, and especially, when such an agent is known to target a tumor-specific pathway. Since the strong rationale for usefulness of immunotherapy in HNC exists and the agents/tools necessary for its delivery to patients are available, it is only the matter of time before immunotherapy alone or in various combinations will become a widely accepted paradigm for treatment of HNC. Therefore, the author has devoted the introductory foreword to making the readers of this book aware of the impending changes that will soon bring HNC therapy into the more modern and, hopefully, more efficacious arena.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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