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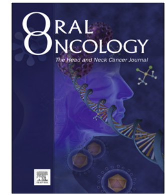

Review

Turning the tide: Clinical utility of PD-L1 expression in squamous cell carcinoma of the head and neck

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ABSTRACT

The use of cytotoxic and/or targeted agents is the gold standard in first- and second-line treatment of metastatic head and neck cancer. Currently the focus of oncologic research is shifting to the implementation of immune checkpoint inhibitor regimens. Many trials are being performed evaluating the survival benefit of various PD-1/PD-L1 blocking antibodies in both solid and haematological malignancies. Also, evaluation of the predictive value of PD-L1 expression on tumour cells and immune cells is being explored.

We first review the current knowledge and possible pitfalls for PD-L1 expression in squamous cell carcinoma of the head and neck. Next, we provide an update on the therapeutic use of PD-1/PD-L1 blocking antibodies as treatment modality for patients with squamous cell carcinoma of the head and neck and we assess the predictive value of tumour PD-L1 positivity. Finally, we elaborate on other promising predictive biomarkers of interest in this patient population.

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Introduction

Squamous cell carcinoma of the head and neck (SCCHN) groups a number of tumours arising from distinct locations in the upper aerodigestive tractus, including nasal and oral cavity, pharynx and larynx [1]. Its association with tobacco and alcohol has been investigated and confirmed in various trials [2,3]. Moreover a number of cases of SCCHN, in particular tumours arising from the oropharynx, are linked to human papillomavirus (HPV) infection [4–6].

Local (=stage I/II) disease is treated by surgery or radiotherapy whereas locoregionally advanced (=stage III/IV) disease requires a multimodal approach combining surgery, radiotherapy and systemic therapy [7,8]. Survival rates for SCCHN have not improved over the last decades [7] hence there is an urgent need for new therapeutics with safer and more specific profiles.

Programmed cell death protein 1 (PD-1) is a 50–55 kDa type I transmembrane receptor expressed by activated T and B cells, as well as by monocytes and dendritic cells (DCs) [9,10]. It has two binding partners, PD-L1 (= B7-H1 or CD274) and PD-L2 (=B7-H2 or CD273), members of the B7-CD28 superfamily, each specific for various tissue types and with specific expression patterns. PD-L1 is found on activated T cells, DCs and monocytes whereas expression of PD-L2 is restricted to DCs and monocytes [10,11]. An overview of the B7-CD28 superfamily members with their effect on the T cell immune response is depicted in Fig. 1. In addition, PD-L1 is expressed in the context of T cell exhaustion during chronic viral infections (e.g. HPV infection) and by tumour cells (TCs) [12–14]. The expression of PD-L1 on TCs is induced by interferon gamma (IFNγ) produced by T cells. As a consequence, TCs upregulate PD-L1 as an adaptive immune resistance mechanism against the host IFNγ mediated immune response [15,16]. Other mechanisms such as hypoxia or toll like receptor signalling can also induce PD-L1 expression on TCs. Besides these extrinsic stimuli, different intrinsic alterations such as *epidermal growth factor receptor* (*EGFR*) mutations in lung cancer and *phosphatase and tensin homolog* (*PTEN*) deletions in glioblastoma are responsible for PD-L1 upregulation (oncogene-driven constitutive expression) [17,18].

The improved understanding of the mechanism of PD-L1 expression has resulted in the development of new, promising

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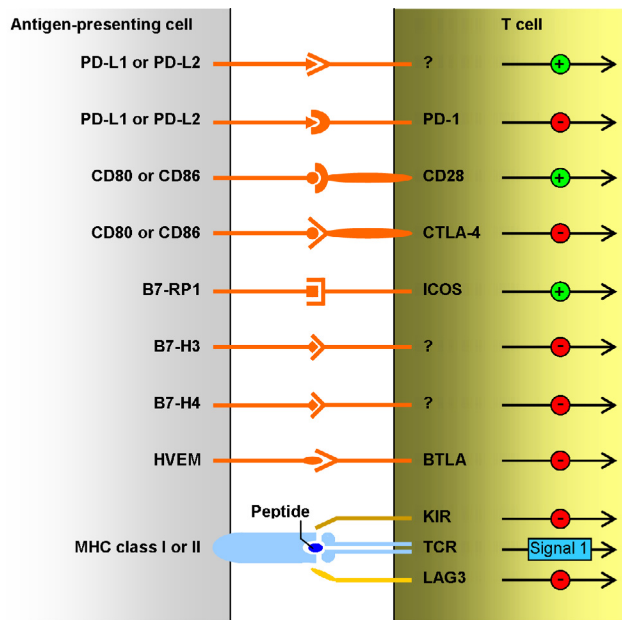

Fig. 1. Overview B7-CD28 superfamily. Receptors and respective ligands of the B7-CD28 superfamily and their impact on the T cell immune response, mediated through peptide – major histocompatibility complex [MHC] molecule complexes recognised by the T cell receptor [TCR], have been depicted. Abbreviations: B7-RP1, B7-related protein 1; BTLA, B and T lymphocyte attenuator; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; HVEM, herpesvirus entry mediator; ICOS, inducible T cell co-stimulator; KIR, killer cell immunoglobulin-like receptor; LAG3, lymphocyte activation gene 3.

immune checkpoint inhibitors (ICI). Blocking the interaction between PD-1 and PD-L1 can induce durable responses in metastatic disease. This has already been proven in several tumours such as bladder and lung cancer and may eventually change the therapeutic options and outcome for patients with SCCHN.

We review the current knowledge and possible pitfalls regarding PD-L1 expression in SCCHN. We also provide an overview on the therapeutic use of PD-1/PD-L1 blocking antibodies (Abs) in SCCHN and we discuss different predictive biomarkers of immune checkpoint inhibition.

PD-L1 in head and neck

Evaluation of PD-L1 status

PD-L1 status is usually determined by immunohistochemistry (IHC) and has recently emerged as a valuable biomarker to predict response to anti-PD-1/PD-L1 blocking treatment. Several studies report on the expression of PD-L1 in SCCHN, revealing positivity in a range from 18% up to 87% of TCs (Table 1) [19–28]. This high variability between studies, which is also observed in other tumour types, can partially be explained by technical difficulties.

First, no current standardisation exists for the evaluation of the PD-L1 status by IHC techniques. Several different pharmaceutical companies produce therapeutic Abs: pembrolizumab, nivolumab, atezolizumab and durvalumab. For each of these biologicals however, another IHC PD-L1 assay was trial-validated as complementary diagnostic, using different Ab clones and platforms: 22C3 and 28-8 (Dako platform) for pembrolizumab and nivolumab, respectively, and SP142 and SP263 (Ventana platform) for atezolizumab and durvalumab, respectively. More detailed information on the therapeutic and complementary diagnostic Abs is shown in Table 2. Different Abs target different epitopes of PD-L1 with diverse affinity thus yielding different staining patterns [29]. This is clearly visible when the same SCCHN tumour is stained with both the SP142 and 22C3 Ab (Fig. 2).

Second, various thresholds on different cell populations were used in the trials to determine PD-L1 positivity. It is therefore difficult to determine whether these companion diagnostics are equivalent to each other, both technically and as far as predictive value is concerned. To test the technical equivalence of PD-L1 assays, a FDA-regulated large scale comparative study (Blueprint) is now being conducted in non-small cell lung cancer (NSCLC) to determine the technical differences between the currently available Abs. This will allow to build an evidence base for PD-1/PD-L1 companion diagnostic characterisation. A study in 500 archival NSCLC samples was recently reported, comparing the Ventana SP263 assay with the Dako 28-8 and 22C3 assay. It demonstrated that all assays showed similar patterns of tumour membrane staining, with high correlation between percentage PD-L1 staining [30]. Similarly, a comparative study in SCCHN of the same Abs in 108 head and neck biopsy samples was also reported. At three different cut-offs ($\geq$1%, $\geq$10% and $\geq$25%), the overall percent agreement was more than 90% for all comparisons at all predefined cut-offs ($r \geq 0.9$). This indicates that the assays are comparable and can be used as predictive assay in SCCHN. Further validation is planned on a larger sample size ($n = 396$) [31].

Besides these technical and interpretative challenges, determining PD-L1 status by IHC is complicated by the heterogeneity of PD-L1 expression. Controversy on intra-patient tumour heterogeneity exists as different PD-L1 expression patterns between primary and metastatic lesions have been reported for renal cell carcinoma but not for NSCLC [32–34]. This explains why determining PD-L1 expression solely at diagnosis, progression or relapse may sometimes underestimate or overestimate the percentage PD-L1 expression induced on neoplastic cells [35,36]. In addition, systemic therapy and radiotherapy modulate PD-L1 expression over time in various tumour types, including SCCHN, due to the increased accumulation and activation of $CD8^{+}$ T cells [37–41]. Therefore it might be of interest to examine the level of PD-L1 at different time frames, e.g. at diagnosis, during therapy and at progression.

Moreover, most of the data on PD-L1 expression in SCCHN relies on studies using resection samples from patients with tumours arising from the oral cavity [19,22,24–26]. Primary tumour resection has proven a significant survival benefit and thus is the first choice of therapy for those patients. However, as many patients with SCCHN present with locoregionally advanced or metastatic disease, organ function-sparing approaches rather than large ablative primary surgery are preferred and for those patients only endoscopic biopsies will be available for biomarker testing. As changes in PD-L1 expression between biopsy specimens and resection material have been previously reported for patients with NSCLC [42], it remains unclear in what way intra-tumour heterogeneity affects PD-L1 evaluation in biopsy material and whether the determination of PD-L1 status in a biopsy has the same prognostic or predictive value as in resection specimens for patients with SCCHN.

Remarkably, only one study reports on the expression of PD-L1 on immune cells (ICs) in SCCHN (Table 1) [20]. In human, PD-L1 is expressed on T cells, DCs and monocytes and it is therefore intuitive to consider the immune infiltrate in the assessment of PD-L1 expression. Although inclusion of ICs in the scoring algorithm adds a certain level of complexity, it may be relevant for clinical trials. In fact, this variable might even be more important than PD-L1 expression on TCs [43].

Correlation with clinicopathological variables

Several investigators have looked for a possible correlation between PD-L1 expression and different clinicopathological features such as age, gender, tumour size, lymph node involvement

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