PD-L1 is a positive prognostic factor in squamous cell carcinoma of the nasal vestibule*

Domenic Vital[1], David Holzmann[1], Gerhard F. Huber[1], Holger Moch[2], Grégoire B. Morand[1], Kristian Ikenberg[2]

[1] Department of Otorhinolaryngology, Head and Neck Surgery, Zurich University Hospital and University of Zurich, Zurich, Switzerland

[2] Department of Pathology and Molecular Pathology; Zurich University Hospital and University of Zurich, Zurich, Switzerland

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Background: Aim was to analyse the role of PD-L1 in squamous cell carcinomas of the nasal vestibule. Advanced squamous cell carcinoma of the nasal vestibule is a highly aggressive tumour. The role of PD-L1 expression is unclear in this tumour type.

Methodology: Forty-six patients diagnosed between 1995 and 2014 were analyzed. Baseline characteristics and outcome were correlated to immunohistochemical staining of PD-L1. PD-L1 positivity of tumour cells and tumour infiltrating immune cells (TIIC) was defined by any staining of more than 1% of the tumour cells.

Results: PD-L1 expression was interpretable in 31 of 46 patients (67.4%). PD-L1 positivity was present in 14 (45.2%) patient's tumour cells and 17 (54.8%) patient's TIIC. PD-L1 positivity of tumour cells was associated with a favourable disease free survival (p=0.019).

Conclusions: Positivity for PD-L1 in tumour cells is a prognostic factor in squamous cell carcinoma of the nasal vestibule and might enable a patient-tailored treatment.

Key words: squamous cell carcinoma, nasal vestibule, PD-L1, immune check point, prognosis

Introduction

Squamous cell carcinoma of the nasal vestibule (NV-SCC) are rare malignant skin tumours similar to cutaneous squamous cell carcinomas (SCC), accounting for <1% of all head and neck cancers and 3.8% of all nasal skin tumours[1-5]. While early NV-SCC (e.g. T1 or T2 tumours) can be cured with high success rates (either by surgery, radiotherapy or combined modalities), advanced lesion with invasion of bone and/or cartilage show loco-regional failure of therapy in almost 50% of the cases[6]. The staging system, however, remains controversial for NV-SCC with authors using the UICC TNM classification for non-melanoma skin cancer, the UICC TNM nasoethmoid complex system and the Wang's staging system[5-7]. Although the UICC TNM system for non-melanoma skin cancers might not be beyond any doubt for staging NV-SCC due to the anatomic complexity of the NV, it seems to be the most appropriate staging system for our series as published previously[6].

It is known that in non-operable loco-regional or metastatic head and neck SCC, conventional chemotherapeutic regimens have limited capacities regarding tumour control and lead to a median survival of 8-10 months[8-10]. Therefore, new therapeutic strategies are needed. While traditional anti-tumoural monoclonal antibodies mediate cytotoxicity primarily by targeting molecules on the cell surface (e.g. cetuximab towards EGFR), new classes not necessarily target the tumour directly, but interfere with pathways enhancing tumour immunity[9, 11-14]. The most prominent antibodies of the latter category are probably PD-L1 inhibitors (e.g. pembrolizumab, atezolizumab). Among others, PD-L1 is expressed on T- and B-lymphocytes, myeloid dendritic cells, tissue macrophages, some epithelial (e.g. tonsils) and tumour cells[9, 12, 15]. Its interaction with the PD-1 receptor in the tumour microenvironment protects cancer by induction of a functional anergy of T-cells, tumour immuntolerance, protection from apoptosis and inhibition of immune response[9, 12, 16-21].

The prognostic value of PD-L1 as a biomarker is controversially discussed with evidence towards a rather predictive (i.e. with regard to response on therapy with PD-L1 inhibitors) than prognostic nature in some studies[9]. PD-L1 expression rates could become relevant, if immune checkpoint inhibition is introduced as a treatment option of NV-SCC. Therefore, this study aims to analyse the role of PD-L1 in NV-SCC.

Materials and methods

Patients

The study protocol obtained approval by the local ethics committee (KEK-ZH-No. 2015-0167). All patients with NV-SCC treated at our institution between 1995 and 2014 were included in this study. Patients with nasal SCC located outside the nasal vestibule, patients with tumours of the nasal vestibule other than SCC and patients with incomplete data sets or inadequate histology were excluded. The medical charts were retrospectively reviewed for age, gender, tumour localization, TNM classification, treatment modalities, recurrence and survival. Disease-free survival was defined as the length of time after primary treatment, in which as patients survived without any signs of cancer; disease-specific and overall survival as the period from the last day of primary therapy to last date of follow-up or death. The diagnostic workup included clinical examination, ultrasound examination of the neck with fine needle aspiration (FNA) of suspicious lymph nodes and imaging with computed tomography scans (CT) and/or magnetic resonance imaging (MRI) in patients with extended disease. Patients with large primary tumours or large recurrence of NV-SCC as well as patients with multiple lymph node metastases additionally underwent positron emission tomography (PET)-CT imaging. All patients were staged or re-staged, respectively, according to the UICC TNM classification for non-melanoma skin cancer (7th edition, 2009)[22]: T1 = tumour ≤ 2cm in greatest dimension; T2 = tumour > 2cm in greatest dimension; T3 = tumour invades extradermal structures (i.e., skeletal muscle, bone, cartilage, orbit); T4 = tumour invades skull base or axial skeleton (directly or via perineural spread).

Construction of human tissue microarray (TMA)

For the construction of the tissue microarray, formalin fixed and paraffin embedded (FFPE) tumour samples were carefully re-evaluated. Tumour tissue blocks were collected from the Department of Pathology and Molecular Pathology, University Hospital Zurich, Switzerland. Samples were selected based on availability, quality and size of tumour tissue. Region of interest for TMA construction was selected on freshly cut, H&E stained sections. For the construction of the tissue bearing TMA block, precisely orientated 0.6mm wide holes were set in the final recipient paraffin block in a semi-automated system with a guided X-Y coordinate system. From the region of interest on the donor block, a precisely fitting tissue core was punched out and transferred to the final recipient block. Each sample is represented by two tissue cores. After completing tissue transfer and final conditioning of the TMA block, freshly 3µm sections were cut for further analyses.

Immunohistochemistry

For immunohistochemical stainings, freshly cut consecutive 3µm section were used and staining procedure was performed according to the manufacturer's instructions on an automated staining system (Leica Bond-III, Leica Biosystems, Wetzlar Germany). Briefly for PD-L1: Pretreatment Buffer H1, rabbit monoclonal anti PD-L1 (SP142) antibody (Spring Bioscience, Pleasanton, CA, USA) [23].

Positivity for PD-L1 was defined as any unequivocal membranous staining of at least 1% of the tumour cells or the tumour infiltrating immune cells (TIIC)[24].

Statistical analysis

Descriptive statistics and cross-tabulation were used. Statistical differences among baseline characteristics were assessed using analysis of variance (ANOVA) and chi-square tests. The relationship between PD-L1 expression, the TNM classification, tumour grading, lymphatic-, blood vessel- or perineural invasion and the presence of lymph node metastases was analysed using cross-tabulation and chi-square tests. Kaplan-Meier estimates with calculation of log rank statistics were performed to compare RFS, DSS and OS. SPSS statistics (IBM), version 23 was used for statistical analyses. A p-value < 0.05 was considered to be significant.

Results

Forty-six patients with NV-SCC fulfilled the inclusion criteria of this study. The baseline characteristics of these patients are depicted in Table 1. Mean age of these patients was 63.8 ± 13.9% (range 27.9 – 90.3 years). Female to male ratio was near 1:2 and the majority of the patients reported to be smokers (60.9%). The 1-, 3- and 5-year survival was 87.1%, 80.9& and 71.0% for the DFS and 97.6%, 92.0% and 92.0% for the DSS and 90.3%, 81.3% and 73.1% for the OS, respectively. Median follow-up was 38 months (range 0 – 118 months).

Adequate (i.e. well preserved tumour tissue on actual slide) histological specimens to perform immunohistochemistry (IHC) for PD-L1 were available in 31 (67.4%) patients. Positivity for PD-L1 was present in 14 (45.2%) patient's tumour cells (Figure 1) and 17 (54.8%) patient's TIIC. PD-L1 positivity the patient's tumour cells did not show a significant relationship with PD-L1 positivity of TIIC. Characteristics like age, gender, smoking status such as TNM classification and tumour grading did not differ amongst PD-L1 positivity or negativity (Table 1). There were no correlations of patient's age, smoking habits, the presence of other tumours, the modality of therapy, the T classification and the tumour grading to PD-L1 positivity of tumour cells or TIIC

Table 1. Baseline data of patients with squamous cell carcinoma of the nasal vestibule among positivity or negativity for PD-L1 in tumour cells and tumour infiltrating lymphocytes (TIL).

PD-L1 expression in tumour cells and TIL (positivity defined as ≥ 1% of the cells with any staining)						
	Tumour cells			Tumour infiltrating lymphocytes		
	PD-L1 positive (n=14, 45%)	PD-L1 negative (n=17, 54.8%)	p-value	PD-L1 positive (n=17, 81.0%)	PD-L1 negative (n=4, 19.0%)	p-value
Gender			p=1.000			
• female	4 (28.6%)	6 (35.3%)				
• male	10 (71.4%)	11 (65.7%)				
Age (years)	62.3 ± 4.2	58.1 ± 2.8	p=0.408	59.0 ± 2.5	63.0 ± 4.6	p=0.484
Smoking	9 (64.3%)	11 (65.7%)	p=1.000	12 (70.6%)	2 (50%)	p=0.574
Other tumours	5 (35.7%)	5 (29.4%)	p=1.000	4 (23.5%)	2 (50%)	p=0.544
Therapy			p=0.201			p=0.124
• Sx	11 (78.6%)	8 (47.1%)		13 (76.4%)	1 (25%)	
• Sx + Rt	2 (14.3%)	6 (35.3%)		2 (11.8%)	2 (50%)	
• Rt	1 (7.1%)	3 (17.6%)		2 (11.8%)	1 (25%)	
T-classification			p=0.714			p=0.450
• T1	5 (35.7%)	6 (35.3%)		7 (41.2%)	2 (50%)	
• T2	2 (14.3%)	1 (5.9%)		1 (5.9%)	1 (25%)	
• T3	6 (42.9%)	7 (41.2%)		8 (47.1%)	1 (25%)	
• T4	0	1 (5.9%)		0	0	
• Tx	1 (7.1%)	2 (11.8%)		1 (5.9%)	0	
N-classification			p=1.000			p=1.000
• N0	13 (92.9%)	16 (94.1%)		16 (94.1%)	4 (100%)	
• N+	1 (7.1%)	1 (5.9%)		1 (5.9%)	0	
M-classification			p=1.000			p=1.000
• M0	14 (100%)	17 (100%)		17 (100%)	4 (100%)	
• M1	0	0		0	0	
Grading			p=0.296			p=0.769
• G1	5 (35.7%)	3 (17.6%)		4 (23.5%)	1 (25%)	
• G2	6 (42.9%)	12 (70.6%)		11 (65.7%)	3 (75%)	
• G3	3 (21.4%)	2 (11.8%)		2 (11.8%)	0	

Age (years): Mean ± standard deviation. Abbreviations: Sx = surgery, Rt = radiotherapy. A p-value <0.05 is considered significant.

(Table 1).

Patients with tumour positivity for PD-L1 showed a favourable DFS compared to their PD-L1 negative counterparts (mean DFS 79.9 months, 95% confidence interval (CI) 76.7 – 82.0 months vs. 52.7 months, 95% CI 32.0 – 73.4 month, p=0.019, Figure 2). There was no difference in DSS and OS among tumour positivity of PD-L1 and no influence on survival of PD-L1 status of TIIC.

Discussion

Our retrospective study on PD-L1 in squamous cell carcinoma of the nasal vestibule reports the following major findings:

- PD-L1 positivity (by means ≥ 1% of the cells with any staining) was present in the tumour cells of 45.2% of the patients and the TIIC of 54.8% of the patients.
- While PD-L1 positivity of the TIIC did not show any influence on outcome, PD-L1 positivity of the tumour cells was associated with a favourable DFS.

SCC of the nasal vestibule is localized in the transition zone between cutis and mucosa.

The rate of PD-L1 positive patients with head and neck cancer is reported to be approximately 25% for cutaneous SCC and about 50 to 100% for mucosal SCC.

PD-L1 expression rates have to be compared carefully between the different studies, since various assays have been used (different antibodies, use of fresh or paraffin embedded tissue) and tumour heterogeneity might not be adequately represented by the analysis of tissue microarrays (TMA), which is (of course) also true for biopsies during clinical routine[9, 10, 16, 25-29].

The correlation of the tumour cell's PD-L1 expression with clinical outcome data (i.e the prognostic implication of PD-L1 expression independently of the treatment with PD-L1 blockers) is discussed controversially[9, 10, 29, 30] and both favourable and unfavourable outcomes are reported in various malignancies[16, 26, 29, 31]. Given the fact that PD-L1 is regarded as an immunosup-

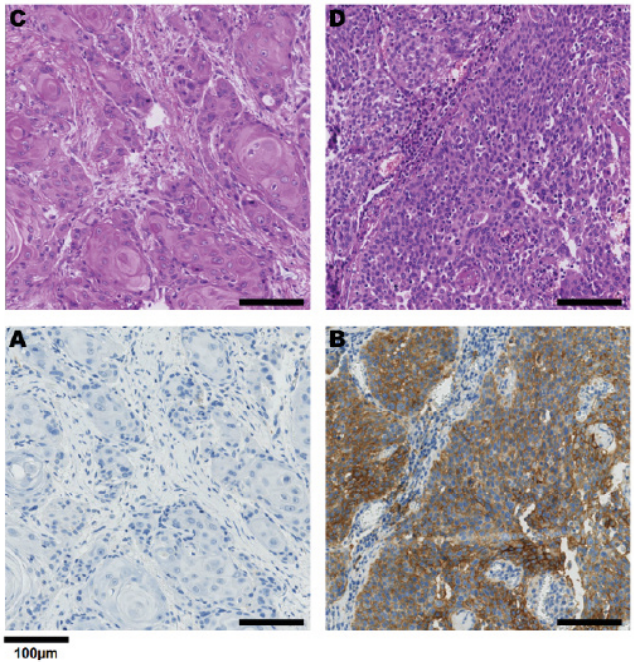

Figure 1. Representative immunohistochemical stainings of squamous cell carcinoma of the nasal vestibule demonstrating (A) negative and (B) positive staining for PD-L1 in tumour cells and (C + D) corresponding H&E stainings.

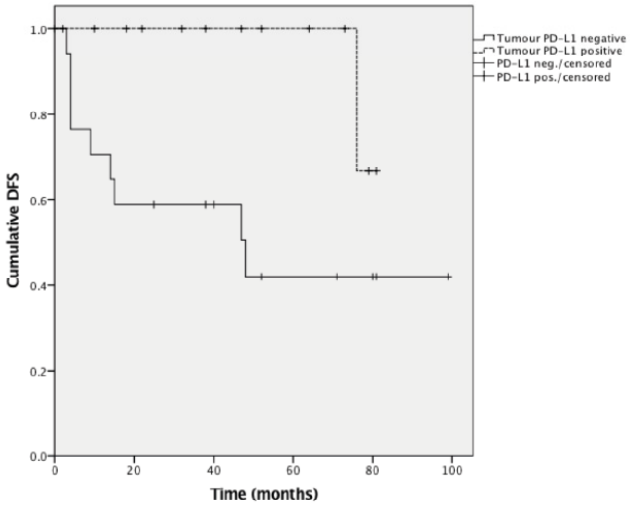

Figure 2. Patients demonstrating PD-L1 positivity in the tumour cells show a significantly better disease free survival (DFS) than their PD-L1 negative counterparts (p=0.019).

pressive molecule, which interaction with its PD-1 receptor leads to tumour protection or immunotolerance, respectively, most studies considering the role of PD-L1 in the head and neck area found its expression to be correlated with a worse outcome[30, 32-36]. This is in contrast not only to our results, but also to the findings of other authors analysing PD-L1 in Merkel cell carcinoma, malignant melanoma or laryngeal squamous cell carcinoma[37-39]. These findings might be explained by the upregulation of PD-L1 expression, which is not only a dominance of immunosuppression, but also a sign of an endogenous inflammatory immune response[39]. Thereafter, PD-L1 expression by tumour cells may induce a recruitment of immune cells to the tumour microenvironment, consequently leading to an antitumor response, which could explain the findings of a better outcome in tumours expressing PD-L1[38, 39]. Therefore, PD-L1 can also be regarded as a surrogate marker of endogenous antitumor response explaining potential associations with unexpected good prognosis and outcome as a result of the balance between the host's immune response and negative feedback inhibition of the antitumor immune reaction[31, 39].

In that context, authors like Fusi et al.[40] raise the question, which cells should be analysed best for PD-L1 expression with regard to predict outcome. Given the fact that PD-L1 expression in the immune infiltrate of tumours correlates with response to therapy with PD-L1 inhibitors, they conclude PD-L1 to have rather a predictive role and to be problematic as a prognostic biomarker[40]. Indeed, the link between PD-L1 expression in both tumour and immune cells was also described by other authors[38, 39] and roughly can be explained by interferon gamma, which is produced by the tumour infiltrating immune cells and is one of the triggers inducing PD-L1 expression[10, 37, 39]. The presence of PD-L1 expression in the TIIC of our patients, however, did neither correlate with baseline nor outcome characteristics and also did not show a correlation with PD-L1 expression of the tumour cells. However, these findings must be interpreted in the light of our small retrospective cohort and the relevance of PD-L1 in the TIIC in NV-SCC or head and neck cancer in general merits further investigation.

PD-L1 expression in tumour cells of squamous cell carcinoma of the nasal vestibule is a positive prognostic factor and correlates with a favourable disease-free survival. Consequently, it may be interpreted to act as a surrogate marker of endogenous antitumor immunity, explaining the unexpected association with good prognosis.
However, our data failed to correlate these findings with the expression of PD-L1 in the TIIC, what must be interpreted in the light of the small cohort and merits further investigation.

Our findings raise further questions, which might represent goals for further studies, especially

- if patients with extensive NV-SCC and PD-L1 positivity might be treated less aggressively, e.g. with less mutilating surgical procedures,
- if patients undergoing primary radiation treatment benefit from a concurrent immunotherapy with PD-L1 inhibitors and

- if patient with un-resectable primaries profit from a palliative systemic therapy with PD-L1 inhibitors.

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Authorship contribution

Study concept and design: DV and KI. Acquisition of data: DV, DH, GFH, KI. Analysis an interpretation of data: DV, DH, GFH, HM, GBM, KI. Drafting of the manuscript: DV, GBM, KI. Critical revision of the manuscript: DH, GFH, HM. Study supervision: DH, GFH, HM.

Conflict of interest

None.

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Dr. Domenic Vital, MD
Department of Otorhinolaryngology
Head and Neck Surgery
Zurich University Hospital and University of Zurich
Frauenklinikstrasse 24
CH-8091 Zurich
Switzerland

Tel: +41 44 255 11 11
Fax: +41 44 255 45 56
E-mail: domenic.vital@usz.ch