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Original Research

Comparative analysis of PD-L1 expression between primary and metastatic pulmonary adenocarcinomas

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Abstract Programmed death-ligand 1 (PD-L1) expression in pulmonary adenocarcinomas (pADCs) was implicated in predicting anti-PD-1/PD-L1 therapy efficacy. However, the differential expression of PD-L1 between primary and metastatic pADC remains unclear. Thus, we addressed this issue. In total, 161 paired primary and metastatic tumour tissues from 146 patients with pADC were collected. Most of the cases had regional nodal metastasis (134/161, 83.2%). PD-L1 expression was categorised based on the proportion of immunostained tumour cells using cutoff values of 1%, 5%, 10% and 50%. In primary tumours, PD-L1 positivity was observed in 28.1% (41/146), 27.4% (40/146), 22.6% (33/146) and 13.0% (19/146) of cases using cutoff values of 1%, 5%, 10% and 50%, respectively. The overall concordance rate for PD-L1

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expression between primary and metastatic tumours was 75.2% (121/161). The concordance rate in primary tumours expressing PD-L1 in <1% or ≥50% of tumour cells was 87.2% (102/117) or 70% (14/20), respectively. In contrast, the concordance rate in tumours expressing PD-L1 in ≥1% to <50% of cells was only 20.8% (5/24). After dichotomising the cases using cutoff values of 1% and 50%, the concordance rate increased to 80.1% (129/161) and 90.7% (146/161) in all paired cases and to 70.4% (19/27) and 85.2% (23/27) in cases with distant metastases, respectively. This study demonstrates that the concordance of PD-L1 expression between primary and metastatic pADC is high when using cutoff values of 1% and 50%. Thus, evaluation of PD-L1 in either primary or metastatic tumours would be helpful for guiding anti–PD-1/PD-L1 immunotherapy in patients with advanced pADC.

1. Introduction

Non-small-cell lung cancer (NSCLC) is the most common cause of cancer-related death worldwide [1]. More than 65% of patients with NSCLC present with locally advanced or metastatic disease [2]. NSCLC is a heterogeneous group of cancers comprising squamous cell carcinoma (SqCC), adenocarcinoma (ADC), and other cancers, which differ from each other in terms of aetiology, biological behaviour, genetic alterations and treatment modalities. Patients with distant metastasis or some patients with locally advanced disease are treated with chemotherapy and/or radiotherapy as a first-line or adjuvant therapy. Tyrosine kinase inhibitors are considered in patients with metastatic NSCLC harbouring *EGFR* mutations or *ALK* translocations [3,4]. However, patients without druggable genetic alterations or those with resistance to tyrosine kinase inhibitors are generally treated by cytotoxic chemotherapy [5].

Cancer utilises immune checkpoints to suppress antitumour immunity and evade immune surveillance, and this process includes the programmed cell death-1 (PD-1)/programmed cell death-ligands (PD-Ls) pathway [6]. Recently, the cancer immunotherapy targeting the PD-1/PD-Ls pathway has emerged as a promising therapeutic strategy for NSCLC [7–12]. However, the response rate to PD-1 or PD-L1 blockade is approximately 30% in NSCLC, indicating the need for a predictive biomarker [7,9,10].

PD-1 blockades have shown clinical efficacy in patients with NSCLC, including both SqCC and non-SqCC [8–11]. Nivolumab showed better clinical outcomes compared with cytotoxic chemotherapy in patients with SqCC, regardless of PD-L1 expression [8], but it has a higher efficacy in patients with non-SqCC when the tumours are expressing PD-L1 [9]. In addition, responsiveness to pembrolizumab and PD-L1 blockade in patients with NSCLC was correlated with PD-L1 expression in tumours [10,12]. PD-L1 expression in at least 50% of tumour cells predicted significantly prolonged survival in patients with NSCLC treated with pembrolizumab compared with cytotoxic chemotherapy [10,11]. Nivolumab was approved by the US Food and Drug Administration (FDA) for the treatment of patients with metastatic SqCC, and subsequently for patients with non-SqCC with complementary PD-L1 evaluation [13]. In contrast, pembrolizumab was approved by the US FDA for the treatment of patients with metastatic PD-L1–positive NSCLC [14]. Thus, PD-L1 testing is important for determining the efficacy of PD-1/PD-L1–targeted immunotherapy in patients with pulmonary ADC (pADC). In clinical practice, PD-L1 expression is estimated in either primary or metastatic pADC tissues from an individual patient, typically to evaluate the potential applicability of PD-1/PD-L1–targeted immunotherapy.

PD-L1 expression in tumour cells is induced by various mechanisms, including endogenously via oncogenic signalling and adaptively via cytokines secreted from tumour-infiltrating immune cells [6]. This suggests that PD-L1 expression in primary and metastatic pADCs may be modulated in different ways, resulting in discrepancies in PD-L1 expression between primary and metastatic lesions. Therefore, a comprehensive understanding of PD-L1 expression in primary and metastatic pADCs may help establish guidelines to estimate PD-L1 expression in patients. However, little is known about the consistency of PD-L1 expression in primary versus metastatic pADCs. We addressed this issue here.

2. Materials and methods

2.1. Patients and samples

In total, 161 paired primary and metastatic tumour tissues from 146 patients who underwent surgical resection for pADC at Seoul National University Hospital (SNUH) from 2002 to 2015 were included. The features of each primary and metastatic tumour pair are schematically illustrated in Supplementary Fig. S1. Briefly, patients developed metastases synchronously ($N = 127$) or metachronously ($N = 34$). Synchronous and metachronous metastatic tumour samples were available for 12 patients. A total of 15 patients had multiple metastatic tumour samples. All primary tumour samples were taken from resected specimens and the 15 metastatic tumour samples