A comparative analysis of PD-L1 distribution in primary NSCLC and metastatic tumors to the lung

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Abstract (updated)

Introduction: Expression of programmed death-1 ligand (PD-L1, CD274) in non-small cell lung cancer (NSCLC) is associated with a benefit to PD-1/PD-L1 blockade targeted therapy. Expression of PD-L1 is believed to be an immune surveillance evasion mechanism, and in the present study we investigated expression of PD-L1 on tumor cells (TC) and inflammatory (immune) cells (IC) in metastatic tumors to the lung and compared it with the NSCLC's.

Materials and Methods: 257 formalin-fixed paraffin-embedded tissue samples (81 NSCLC and 176 metastatic tumors) that were stained against PD-L1 (clone: SP142, Spring Biosciences) using immunohistochemistry. PD-L1 positivity was defined as membranous expression 2+ intensity at ≥5% in TCs and ICs. All cases were stratified into 4 categories based on the presence or absence of PD-L1 expression on TCs or ICs.

Results: PD-L1 TCs positivity in primary NSCLC was significantly higher than in metastatic carcinomas (28% vs. 10%, p<0.009). In contrast, PD-L1 expression in inflammatory cells was significantly higher in metastatic carcinomas than in the primary NSCLC (31% vs. 0%, p<0.001). No significant difference in PD-L1 expression was observed within the NSCLC histologic subgroups and within the metastatic tumors types. When stratified on the basis of combined PD-L1 distribution (tumor microenvironment TME) primary and metastatic tumors exhibited significantly different patterns (p<0.001) (Table 1).

Conclusions: PD-L1 distribution differs significantly between the primary (NSCLC) and metastatic tumors to the lung with predominance of PD-L1 expression on neoplastic cells (TC) in NSCLC and on immune cells (IC) in metastatic tumors to the lung. Further clinical studies should elucidate the therapeutic relevance (response rates) of these observations.

Introduction

The clinical development and use of the immune checkpoint inhibitors has opened new avenues in the cancer treatment (1). Despite the impressive therapeutic effects in several malignancies (e.g. melanoma, non-small cell lung cancer [NSCLC], renal cell carcinoma, bladder carcinoma, classical Hodgkin lymphoma), there is still an unmet need to optimize the predictive biomarkers and their thresholds (1).
Programmed death 1 (PD-1) or B7-1, expressed on activated T-lymphocytes and other immune cells and its ligands PD-L1 and

Introduction (Continued)

PD-L2, represent a major immunosuppression mechanism in the tumor microenvironment (2). Inhibition of this axis may reactivate T-cell function and induce their antineoplastic activity (2, 3). PD-L1 expression (by immunohistochemistry) in both tumor and inflammatory cells (IC) has been described in various malignancies and PD-1/PD-L1 blockade had remarkable survival benefits in these patients (2, 4). Despite it, a subset of PD-L1-negative tumors may still respond to the PD-1/PD-L1 blockade while failure to the therapy has been observed in some PD-L1 positive cancers (1). Therefore, substantial efforts have been invested in identifying additional biomarkers that would predict which patients would respond best to the immune checkpoint inhibition. This might be particularly relevant for the over-treated patients with metastatic cancers having limited therapeutic options (5).
In the present study, we comparatively analyzed distribution of PD-L1 in both tumor and inflammatory cells a cohort of primary (NSCLC) and metastatic tumors to the lung (carcinomas, sarcomas, melanomas).

Methods

Samples and Immunohistochemistry (IHC)
257 formalin-fixed paraffin-embedded tissue samples (81 NSCLC and 176 metastatic tumors to the lung) were profiled at the CLIA-certified laboratory, Caris Life Sciences (Phoenix, AZ, USA). Histologic diagnosis for all cases was confirmed by a board certified pathologist.
FFPE tissue sections were stained for PD-L1 (anti-PD-L1 clone, SP142 antibody, Ventana) using automated procedures. PD-L1 positivity was defined as expression of 2+ intensity at ≥5% in tumor (TC) or inflammatory cells (IC) as suggested earlier. Due to the overall low PD-L1 expression in IC, we dichotomized PD-L1 IC variable into two categories (<1% and ≥1%).

Results (updated)

- PD-L1 TC positivity in primary NSCLC was 23/81 (28%) while in metastatic tumors it was 24/176 (14%)
- PD-L1 expression in IC was low although we observed significantly higher PD-L1 expression in IC in metastatic carcinomas in comparison with the NSCLCs (28% vs. 0%)
- No significant difference in PD-L1 expression was observed within the primary NSCLC subgroups (adenocarcinoma vs. squamous cell carcinoma9) whereas significant differences were seen among the metastatic carcinomas (from 0% positivity in pancreatic to 40% positivity in head and neck carcinomas, Table 1).

Results (Continued)

Histotype	PD-L1 expression in tumor cells		Total
	[<5%]	[≥5%]	
NSCLC	**58 (72%)**	**23 (28%)**	**81**
Adenocarcinoma	44 (72%)	17 (28%)	61
Squamous cell carcinoma	11 (73%)	4 (27%)	15
Other NSCLC	3 (60%)	2 (40%)	5
Metastatic carcinomas	**113 (90%)**	**13 (10%)**	**126**
Colorectal carcinoma	49 (96%)	2 (4%)	51
Gynecologic carcinomas	21 (95%)	1 (5%)	22
Breast carcinoma	18 (86%)	3 (14%)	21
Head and neck carcinomas	9 (60%)	6 (40%)	15
Pancreatic carcinoma	10 (100%)	0 (0%)	10
Renal cell carcinoma	6 (86%)	1 (14%)	7
Other metastatic tumors	**39 (78%)**	**11 (22%)**	**50**
Soft tissue tumors	12 (80%)	3 (20%)	15
Malignant melanoma	7 (64%)	4 (36%)	11
Other cancers	20 (83%)	4 (17%)	24
Total	**210**	**47**	**257**
Histotype	**PD-L1 expression in inflammatory cells**		**Total**
	[<1%]	[≥1%]	
NSCLC	**81 (0%)**	**0 (100%)**	**81**
Adenocarcinoma	61 (100%)	0 (0%)	61
Squamous cell carcinoma	15 (100%)	0 (0%)	15
Other NSCLC	5 (100%)	0 (0%)	5
Metastatic carcinomas	**87 (69%)**	**39 (31%)**	**126**
Colorectal carcinoma	32 (63%)	19 (37%)	51
Gynecologic carcinomas	16 (73%)	6 (27%)	22
Breast carcinomas	13 (62%)	8 (38%)	21
Head and neck carcinomas	12 (80%)	3 (20%)	15
Pancreatic carcinoma	7 (70%)	3 (30%)	10
Renal cell carcinoma	7 (100%)	0 (100%)	7
Other metastatic tumors	**40 (81%)**	**10 (19%)**	**50**
Soft tissue tumors	13 (87%)	2 (13%)	15
Malignant melanoma	7 (64%)	4 (36%)	11
Other cancers	20 (80%)	4 (20%)	24
Total	**208**	**49**	**257**

Table 1. PD-L1 expression in tumor cells was significantly higher in NSCLC compared with the metastatic carcinomas (p=0.003) while IC within metastatic tumors exhibited significantly higher PD-L1 expression (p<0.001).

Histotypes	TME categories (PD-L1 expression)				Total
	TC+/IC+	TC-/IC-	TC+/IC-	TC-/IC+	
NSCLC	0 (0%)	58 (72%)	23 (28%)	0 (0%)	81
Metastatic	8 (5%)	111 (63%)	16 (9%)	41 (23%)	176
Total	8	169	39	41	257

TC = tumor cells; IC = inflammatory (immune cells); TME = tumor microenvironment; NSCLC = non-small cell lung cancer.

Table 2. Significantly different TME categories between NSCLC and metastatic carcinomas to the lung (p<0.001)

Results (Continued)

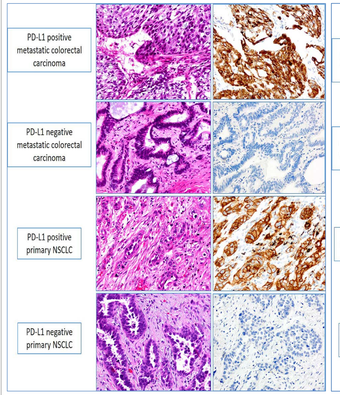

Figure 1. PD-L1 expression in tumor cells in primary (NSCLC) and metastatic tumor to the lung (colorectal carcinoma)

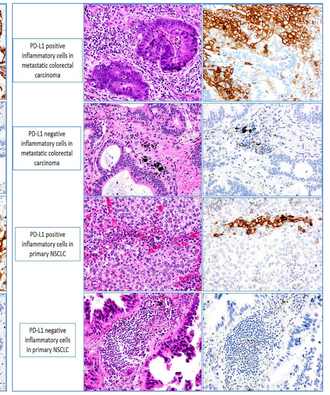

Figure 2. PD-L1 expression in inflammatory (immune) cells in primary (NSCLC) and metastatic tumor to the lung (colorectal carcinoma)

Conclusions

- A significant differences observed in PD-L1 expression between the primary (NSCLC) and metastatic tumors to the lung with predominance of PD-L1 expression on neoplastic cells in NSCLC and on inflammatory (immune) cells in metastatic tumors to the lung.
- Clinical studies should elucidate the therapeutic relevance (response rates) of these observations.

References

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