Editorial

Immunotherapy's new challenge: identification of predictive biomarkers for tumor response

Charlotte Domblides[1,2], Anne-Marie Ruppert[1,2], Martine Antoine[1,2], Marie Wislez[1,2]

[1]Sorbonne Universités, UPMC Univ Paris 06, GRC n(o) 04, Theranoscan, F-75252, Paris, France; [2]AP-HP, GH HUEP, Hôpital Tenon, Service de Pneumologie, F-75970, Paris, France

Correspondence to: Marie Wislez, MD, PhD. AP-HP, GH HUEP, Hôpital Tenon, Service de Pneumologie, F-75970, Paris, France.
Email: marie.wislez@aphp.fr.

Comment on: Parra ER, Behrens C, Rodriguez-Canales J, *et al.* Image Analysis-based Assessment of PD-L1 and Tumor-Associated Immune Cells Density Supports Distinct Intratumoral Microenvironment Groups in Non-small Cell Lung Carcinoma Patients. Clin Cancer Res 2016;22:6278-89.

Submitted Feb 28, 2017. Accepted for publication Mar 01, 2017.
doi: 10.21037/tcr.2017.03.04
View this article at: http://dx.doi.org/10.21037/tcr.2017.03.04

Immune checkpoint inhibitors (ICI) targeting programmed cell death protein 1 (PD-1)/ programmed cell death protein ligand 1 (PD-L1) pathway are a promising therapeutic option in patients with non-small cell lung cancer (NSCLC) (1). However, PD-L1 immunohistochemistry (IHC) assessment has a non-optimal predictive value of response. Main reasons are tumor heterogeneity, no standardized staining assessment with different primary antibodies, variable positive thresholds and interobserver variability. A major challenge for these immunotherapies is to improve patient selection. PD-L1 expression does not seem to be sufficient, and other immunologic or non-immunologic markers may influence responses to ICI.

Parra *et al.* have recently described in Clinical Cancer Research tumour-associated immune cell (TAIC) infiltration in a large cohort of 254 surgically resected NSCLC (adenocarcinomas or squamous-cell carcinomas (SCC)) treated at the MD Anderson Center between 1997 and 2012 (2). They assessed expression of PD-1 and PD-L1, CD4, CD8, CD45RO, CD57, CD68, granzyme B, CD45RO, FOXP3 immune markers by IHC. Patients treated by neoadjuvant chemotherapy were excluded (3). All immune markers were studied in peritumoral and intratumoral compartments, and were correlated with clinical features. In this study, 23% of adenocarcinomas and 31% of SCC expressed PD-L1 with a cut-off of 5%, and more TAIC were detected in the peritumoral than within the tumour compartment. In adenocarcinomas, they identified positive correlations between PD-L1 expression, TAIC density and clinical features such as solid histology pattern, smoking history, and airflow limitation. They demonstrated in SCC that high peritumoral CD57+ infiltration was correlated with better recurrence-free survival (P=0.0236; HR, 0.457) and overall survival (P=0.0261; HR, 0.481). In adenocarcinoma, high intratumoral CD68+ infiltration, was correlated with better recurrence-free survival (P=0.0436; HR, 0.553). There was no correlation between PD-L1 expression alone (*H*-score or percentage of expression) and patient's outcome. However, the combination of high PD-L1 *H*-score and low CD4+, CD8+ and CD68+ cell density was associated with a poor prognosis (RFS: P=0.036; HR, 4.299; OS: P=0.00034; HR, 5.632) in a subset of adenocarcinomas. Furthermore, they identified 4 patterns of tumour microenvironments, already described by Teng *et al.*, which could allow to better stratify patients for ICI treatments (4).

In this study, assessment of histologic biomarkers was done by a quantitative image analysis system. This computer-based analysis has been demonstrated to be more reproducible because of an automatized count (5). Furthermore, quantitative image analysis is a time saving method for pathologists, with an increased number of immune markers that could be analysed, and reduced intraobserver and interobserver variabilities.

© Translational Cancer Research. All rights reserved.

The challenge of ICI is to find biological and/or histological parameters, which improved the predictive and prognostic values of PD-L1 expression. The authors highlighted the crucial role of TAIC on patient outcomes. They showed that cancer relapse was associated with low CD3+ T cells, CD8+ cytotoxic T cells, CD45RO memory T cells and granzyme B tumour infiltration. In lung cancer, TAIC had already been shown to be associated with survival (6-8), with a crucial positive role for CD8+ cytotoxic T cells and CD45RO memory T cells (9). Furthermore, in colorectal cancer, type, density and location of immune infiltration were more prognostic than TNM staging (6,10). In this study, infiltration in the peritumoral compartment was also higher than in intratumoral in both adenocarcinomas and SCC, as already reported by Bindea *et al.* (11). It could be because of high stroma density within the tumour, with thick collagen fibres, inhibiting migration into the tumour, which is then protected from immune response.

Parra *et al.* showed that TAIC were strongly associated with tumour PD-L1 expression in both histologies. Indeed, PD-L1 is not expressed in normal lung tissue, and is induced by inflammatory cytokines such as interferon gamma. In Parra's study, 19% of adenocarcinomas and 24% of SCC had high PD-L1 expression and high TAIC density. This pattern is called adaptive immune resistance, and is correlated to responses to ICI (4,12). However, the most represented group in their cohort had low PD-L1 expression and high TAIC (48% of adenocarcinomas and 43% of SCC). This pattern is associated with immune resistance, linked to others immunosuppressive pathways (CTLA-4, TIM-3, LAG-3…), or others immune cells such as regulatory T cells, myeloid-derived suppressor cells or M2 macrophages. These patients could benefit from targeting these pathways alone or in combination with anti-PD-1/anti-PD-L1. Finally, tumours without TAIC infiltration or PD-L1 expression represented in Parra's study 29% of adenocarcinomas and 26% of SCC. These tumours are so-called "cold tumours" and need T-cell priming to benefit from immunotherapies because of the absence of target cells for ICI. The aim will be to recruit immune cells in the tumour or its invasive margins, using combination with an anti-CTLA4.

Assessment of TAIC density and PD-L1 expression need to be associated to predict ICI responses. Parra *et al.* generated a new immunoscore combining both innate (CD68+) and adaptive immune markers (CD4+, CD8+) with PD-L1 expression. However, CD68+ macrophages are very plastic cells, and the lack of specific markers for the distinction of the different phenotypes, antitumoral M1/protumoral M2, is a problem. Nevertheless, an interesting point is that these cells are characterized by interferon-γ secretion under activation. Several recent studies have also found an important value of interferon-γ signature in different subtypes of cancer, probably because of its functional value (13). Interferon-γ signature seems to outperform PD-L1 IHC alone for the prediction of ICI response in head and neck cancers (14). This signature is actually assessed as predictive biomarker in pembrolizumab trials.

All these data underlie the important need to assess TAIC density in association with PD-L1 expression to better select patients for ICI therapies. Cytotoxic cell infiltration and their functional profile seem to be key factors for response to anti-PD-1/PD-L1therapies. The available tissue could limit TAIC density assessment. ICI are actually delivered only in locally advanced or metastatic NSCLC. In these patients, diagnosis is mostly performed on small biopsies provided by bronchoscopy, or transthoracic needle biopsy. Mutational status for EGFR or ALK is mandatory. Analysis of the immune infiltration could be unfeasible because of lack of tissue. A recent study presented at the WCLC 2016, showed above 75% of false-negative PD-L1 staining for biopsies, versus only 25% for matched surgically resected tumours (15).

In conclusion, more biomarkers are needed to improve prognostic and predictive values of PD-L1 expression assessed by IHC. Several parameters are under study (interferon-γ signature, mutational importance, TCR clonality…), but the most promising parameter seems to be the composition and localisation of TAIC infiltration.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Yi-Jiu Ren (Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2017.03.04). The authors have no conflicts

© Translational Cancer Research. All rights reserved.

of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References

1. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366:2455-65.
2. Parra ER, Behrens C, Rodriguez-Canales J, et al. Image Analysis-based Assessment of PD-L1 and Tumor-Associated Immune Cells Density Supports Distinct Intratumoral Microenvironment Groups in Non-small Cell Lung Carcinoma Patients. Clin Cancer Res 2016;22:6278-89.
3. Parra E, Rodriguez-Canales J, Behrens C, et al. OA20.05 The Influence of Neoadjuvant Chemotherapy, on Immune Response Profile in Non-Small Cell Lung Carcinomas. J Thorac Oncol 2017;12:S323-4.
4. Teng MW, Ngiow SF, Ribas A, et al. Classifying Cancers Based on T-cell Infiltration and PD-L1. Cancer Res 2015;75:2139-45.
5. Väyrynen JP, Vornanen JO, Sajanti S, et al. An improved image analysis method for cell counting lends credibility to the prognostic significance of T cells in colorectal cancer. Virchows Arch 2012;460:455-65.
6. Galon J, Costes A, Sanchez-Cabo F, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science 2006;313:1960-4.
7. Pagès F, Galon J, Dieu-Nosjean MC, et al. Immune infiltration in human tumors: a prognostic factor that should not be ignored. Oncogene 2010;29:1093-102.
8. Fridman WH, Pagès F, Sautès-Fridman C, et al. The immune contexture in human tumours: impact on clinical outcome. Nat Rev Cancer 2012;12:298-306.
9. Pagès F, Berger A, Camus M, et al. Effector memory T cells, early metastasis, and survival in colorectal cancer. N Engl J Med 2005;353:2654-66.
10. Galon J, Mlecnik B, Marliot F, et al. Validation of the Immunoscore (IM) as a prognostic marker in stage I/II/III colon cancer: Results of a worldwide consortium-based analysis of 1,336 patients. J Clin Oncol 2016;34:abstr 3500.
11. Bindea G, Mlecnik B, Tosolini M, et al. Spatiotemporal dynamics of intratumoral immune cells reveal the immune landscape in human cancer. Immunity 2013;39:782-95.
12. Tumeh PC, Harview CL, Yearley JH, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature 2014;515:568-71.
13. Chow LQM, Mehra R, Haddad RI, et al. Biomarkers and response to pembrolizumab (pembro) in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). J Clin Oncol 2016;34:abstr 6010.
14. Seiwert TY, Burtness B, Weiss J, et al. Inflamed-phenotype gene expression signatures to predict benefit from the anti-PD-1 antibody pembrolizumab in PD-L1+ head and neck cancer patients. J Clin Oncol 2015;33:abstr 6017.
15. Ilie M, Long-Mira E, Bence C, et al. Comparative study of the PD-L1 status between surgically resected specimens and matched biopsies of NSCLC patients reveal major discordances: a potential issue for anti-PD-L1 therapeutic strategies. Ann Oncol 2016;27:147-53.

Cite this article as: Domblides C, Ruppert AM, Antoine M, Wislez M. Immunotherapy's new challenge: identification of predictive biomarkers for tumor response. Transl Cancer Res 2017;6(Suppl 2):S306-S308. doi: 10.21037/tcr.2017.03.04

© Translational Cancer Research. All rights reserved.