The Puzzle of Predicting Response to Immune Checkpoint Blockade

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Immunotherapy has opened a new chapter in cancer therapy. Recent introduction of CTLA-4 and PD-1/PD-L1 blockade therapy has proven to be a successful approach in a number of cancers, particularly those associated with chronic carcinogen exposure or deficiencies in mismatch repair. Metastatic melanoma, which is notoriously chemotherapy resistant, was the first cancer in which immune checkpoint blockade was shown to be an effective therapy in a subset of responders who achieved durable remissions. Immune checkpoint blockade has now become an option for first line therapy in cancers such as metastatic melanoma, metastatic non-small-cell lung cancer in combination with chemotherapy, and in patients with bladder cancer who are not candidates for platinum-based therapy. Nonetheless, response rates remain relatively low, ranging from 15 to 40% depending on cancer type and development of secondary resistance with disease progression is common. Immunotherapy clinical trials have typically included an experimental biomarker for sensitivity, such as PD-L1 expression by tumor cells or infiltrating immune cells, but to date, none have been highly sensitive or specific in predicting response. Thus, development of predictive biomarkers for sensitivity and, conversely, primary resistance remain an active area of research.

Multiple studies have been performed and are currently ongoing to establish predictive factors for response to immune checkpoint blockade. These studies are important for several reasons. First, defining predictive markers would guide treatment choices in patients who might benefit more from effective chemotherapy regimens or, in the case of neoadjuvant checkpoint blockade, from timely local control with surgery or radiation. Second, though checkpoint blockade therapies are generally thought of as having fewer side effects than cytotoxic chemotherapy, significant toxicities still occur. Grade 3–4 adverse events are seen in more than half of the patients treated with a combination of anti-CTLA-4 and anti-PD-1/PD-L1 for melanoma [1]. Autoimmune toxicities due to immunotherapy are also less predictable than chemo toxicities and not always reversible. Lastly, and probably most importantly, these studies seek not only to identify predictive markers but to uncover mechanisms of primary and secondary resistance to checkpoint blockade therapy to provide insights in how to overcome resistance.

Over the past decade, several predictive markers have been proposed and studied. PD-L1 expression on cancer cells, tumor stromal cells, and infiltrating immune cells has been well-studied. In fact, PD-L1 expression must be demonstrated in some cancer types to qualify for immunotherapy in the first-line setting, notably for lung and urothelial cancers [2,3]. Other markers include: overall mutational tumor burden, frequency of insertion-deletion mutations (which are considered particularly immunogenic), the presence of tumor infiltrating lymphocytes, 4-1BB (CD 137) expression on CD8+ T-cells [4], IDO expression [5], macrophage density [6], and others.

It is interesting to note that predictive factors that have been validated in one type of cancer type do not necessarily have predictive value in other solid malignancies. For example, PD-L1 expression in lung cancer is correlated with response, but it is not a marker of response for melanoma. It is also important to note that failure of predictive biomarkers in the metastatic setting might be due to sampling error of metastatic foci. Tumors are heterogeneous, and immunohistochemistry of sampled tissue might not be representative of the tumor as a whole.

Understanding the underlying biology of immune resistance by utilizing high-throughput techniques may provide insights for predictive and prognostic markers. Wenjing et al. [7] compiled and studied publicly-available multi-omic data on metastatic melanoma tumors from patients after exposure to ipilimumab, including 368 tumors from Tumor Cancer Genome Atlas (TCGA) and 110 from the Van Allen cohort. They analyzed specifically the predictive value of TP53 mutations for response to ipilimumab treatment. The authors looked at the overall mutational status of the TP53 gene, not necessarily loss of function mutations. TP53 is well-known for its role in cytotoxic T-cell-induced apoptosis; its loss is common to multiple types of cancer and is generally associated with a poor prognosis. TP53 mutation status was associated with higher tumor mutational burden in their analysis, which could theoretically increase tumor immunogenicity, but TP53 loss was not associated with higher response to anti-CTLA-4 therapy. A similar study in lung cancer patients treated with PD-1 blockade demonstrated the opposite results: TP53 mutation was associated with an increase in immune-related gene expression and prolonged progression-free survival in response to PD-1 blockade [8]. Wenjing et al. did not observe increased immune-related gene expression in melanoma, but did find a lower level of FAS expression in TP53-mutated melanoma patients, which they speculated to be the underlying mechanism of poor response to anti-CTLA-4 therapy. They also did not observe an association between insertion-deletion mutation burden and TP53 mutation in melanoma samples, which they hypothesize could be another explanation for poor response to CTLA-4 blockade. Further studies are needed to investigate interactions of TP53 function and immune response.
It is worth noting that a minority of cancers have a single dominant driving mutation that can be used as predictive marker for the therapy designed to target that mutation. In the majority of cancers, a diverse combination of key mutations leads to tumorigenesis. The ability of the immune system to detect novel tumor antigens and eliminate cancer cells makes it a universal and adaptive anti-cancer tool. Checkpoint blockade therapies cannot be called targeted cancer therapies per se, even though monoclonal antibody drugs are designed to disrupt certain immune inhibitory pathways. It may not be possible to develop a single ideal marker to predict response to checkpoint blockade in all tumors, but they are worth the hunt. Multiple combination therapies with checkpoint inhibitors are in clinical trials currently, and follow up analyses may reveal responding patient subgroups that may further lead to predictive marker development.

Disclosure

The author declares no conflicts of interest.

References

[1] Wolchok JD, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 2013 Jul 11;369(2):122–33.
[2] Yu H, Boyle TA, Zhou C, Rimm DL, Hirsch FR. PD-L1 expression in lung Cancer. J Thorac Oncol 2016 Jul;11(7):964–75.
[3] Bellmunt J, Powles T, Vogelzang NJ. A review on the evolution of PD-1/PD-L1 immunotherapy for bladder cancer: the future is now. Cancer Treat Rev 2017 Mar;54:58–67.
[4] Jacquenet N, et al. Predictors of responses to immune checkpoint blockade in advanced melanoma. Nat Commun 2017 Sep 19;8(1):592.
[5] Holmgaard RB, et al. Tumor-expressed IDO recruits and activates MDSCs in a Treg-dependent manner. Cell Rep 2015;13:412–24.
[6] Kridel R, et al. The prognostic impact of CD163-positive macrophages in follicular lymphoma: a study from the BC cancer agency and the lymphoma study association. Clin Cancer Res 2015;21:3428–35.
[7] Xiao Wenjing, et al. TP53 mutation as potential negative predictor for response of anti-CTLA-4 therapy in metastatic melanoma; 2018. https://doi.org/10.1016/j.ebiom.2018.05.019.
[8] Dong ZY, et al. Potential predictive value of TP53 and KRAS mutation status for response to PD-1 blockade immunotherapy in lung adenocarcinoma. Clin Cancer Res 2017;23:3012–24.