HHS Public Access

Author manuscript

Clin Transl Imaging. Author manuscript; available in PMC 2018 August 01.

Published in final edited form as:

Clin Transl Imaging. 2017 August ; 5(4): 299–301. doi:10.1007/s40336-017-0241-z.

The new era of cancer immunotherapy: what can molecular imaging do to help?

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Cancer immunotherapy and targets for immunotherapy

Homeostasis of the immune system is regulated by a complex network of signals including multiple checkpoints that prevent uncontrolled harmful immune responses and maintain self-tolerance. Cancer cells are self-derived tissues and may take advantage of these checkpoints to escape detection by the innate immune system. Blockade of these immune checkpoint pathways has shown remarkable efficacy in the treatment of many cancers, including Hodgkin lymphoma, non–small-cell lung cancer, melanoma, and others [1]. Some of these checkpoints, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) and programmed cell death protein 1 (PD-1), have been extensively studied as targets for more efficacious and precise cancer immunotherapy.

CTLA4 counteracts the activity of the T cell co-stimulatory receptor CD28 and actively delivers inhibitory signals to the T cell, with the final downregulation of T cell activation through several mechanisms (e.g., increasing the T cell activation threshold and attenuation of clonal expansion). In addition to its expression on T cells, CTLA4 may also be expressed by many tumor types, such as non-small-cell lung cancer, although the biological consequences remain to be elucidated. CTLA4-targeted antibodies have shown efficacy in the treatment of many cancers, and many of these antibodies have been approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for clinical use [1]. However, despite the therapeutic benefits, anti-CTLA4 treatments can also lead to severe adverse effects [1].

PD-1 has two endogenous ligands, PD-1 ligand 1 (PD-L1) and PD-L2, and their inhibitory effect is accomplished through a dual mechanism of promoting apoptosis by antigen-specific T cells in lymph nodes while simultaneously reducing apoptosis for regulatory T cells (i.e.,

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Authors' contributions LE: literature search, manuscript writing and editing; MJ: manuscript writing and editing; SV: manuscript writing and editing; WC: manuscript writing, editing and content planning.

Conflict of interest None.

suppressor T cells). Immunotherapy strategies that interfere with the PD-1 checkpoint have shown enhanced anticancer activity in the clinical setting. In contrast to PD-1, which is primarily expressed on T cells and pro-B cells, PD-L1 is naturally expressed on several tissues, including some tumor cells, vascular endothelium, hepatocytes, mesenchymal stem cells, T and B cells, macrophages, and mast cells. In general, PD-1-targeted treatments have shown fewer adverse effects than therapy targeting the CTLA4 pathway.

Besides these commonly studied targets (i.e., PD-1/PD-L1 and CTLA4), there are at least a dozen immune checkpoint receptors, all of which could be potential therapeutic targets. However, most of these play a secondary role in T cell responses to tumors, such as Lag-3, T-cell immunoglobulin and Tim-3, and T-cell immunoglobulin and ITIM domain (TIGIT). Since these targets are usually co-expressed with PD-1 on exhausted T cells, targeting any of these in combination with PD-1 blockade could be effective and/or synergistic for cancer therapy. Many preclinical studies using such combination therapy have been reported and a number of related clinical studies are ongoing, aiming at reinvigorating T cells to kill tumor cells.

To date, the US FDA has approved several immune checkpoint inhibitors for the treatment of cancer, such as nivolumab (target: PD-1) for melanoma, lung cancer, and renal cell cancer; pembrolizumab (target: PD-1) for melanoma and lung cancer; and ipilumumab (target: CTLA4) for melanoma. A large number of phase II/III clinical trials are currently ongoing and many are expected to lead to approval over the next few years. In addition, other immunotherapeutic agents, such as atelizumab (target: PD-L1) and tremelizumab (target: CTLA4) are been tested in phase I–II clinical trials [1].

How to evaluate the response to immunotherapy?

To date, few strategies are available in clinical practice to test the efficacy of immunotherapy [2-4]. As previously reported, evaluation of tumor response to immunotherapy should provide a surrogate end point for prediction of clinical outcome in patients treated with these novel targeted agents and should allow discontinuation of therapy in refractory patients avoiding useless side effects. Morphological imaging and functional imaging are often used for these purposes, by employing Response Criteria in Solid Tumors (RECIST), Immune Related Response Criteria (irRC), PET Response Criteria in Solid Tumors (PERCIST) or European Organization for Research and Treatment of Cancer (EORTC) criteria [2]. However, all these strategies have demonstrated not just advantages but also limitations in assessing the response to immunotherapeutic drugs. RECIST performs reasonably well in predicting survival for cytotoxic therapies, including most conventional chemotherapy and radiotherapy regimens that lead to cell death and subsequent regression of tumor lesions, but is less helpful in situations where inhibition of cell proliferation is the most common mechanism of response [3]. The irRC were developed to overcome the limitations of RECIST in patients treated with immunotherapy [4, 5]. These criteria are based on two-dimensional tumor measurements (in contrast to RECIST, which is based on one-dimensional tumor measurement), thus incorporating measurable new lesions into the total tumor burden, and description of additional patterns of tumor response that can occur after initial increases in tumor burden [5].

PERCIST and EORTC are applied in patients undergoing ^{18}F-FDG PET/CT, in order to assess the metabolic response to therapy [2]. In this respect, it is worth noting that ^{18}F-FDG is able to monitor changes in glucose metabolism not only in tumor cells but also in inflammatory infiltrates. As known, immunotherapy elicits a natural inflammatory response and therefore traditional PET imaging using ^{18}F-FDG has proven inadequate in examining responses to immunotherapy. Only very limited data are available for the evaluation of immunotherapy by means of ^{18}F-FDG-PET. Two clinical experiences have been made in 49 patients [6, 7], demonstrating the inability of ^{18}F-FDG PET/CT make a differential diagnosis between patients with pseudo-progression (due to inflammatory infiltrate) from those with a real progression, during immunotherapy. In fact, it has been reported that the initial increase in tumor size, later followed by tumor volume reduction in part of the patients treated with immune checkpoint inhibitors, is due to inflammatory cell infiltrates [2, 6, 7].

Conversely, ^{18}F-FDG PET/CT seems useful in monitoring the response to BRAF and MEK inhibitors, because the down-regulation of extra-cellular signal-regulated kinase (ERK), the terminal mediator gene of the MAPK pathway, suppresses glycolysis via a network of transcriptional regulators of glycolysis. Furthermore, some authors have observed presumed immune responses on ^{18}F-FDG PET with BRAF and MEK inhibition [8]. As reported by Wong et al. [8], patterns of immune-related inflammatory responses may be visualized on ^{18}F-FDG PET/CT and include a symmetrical hilar and mediastinal nodal uptake, similar to sarcoidosis; a reactive nodal uptake in the drainage basin of metastases; and a diffuse splenic uptake. In the experience of these authors inflammatory changes, which could be considered an immune flare response, are significantly more frequently observed with anti-CTLA4 than with anti-PD1 agents, congruent with the higher incidence of autoimmune side effects seen with anti-CTLA4 agents.

Molecular imaging of immunotherapy targets

Molecular imaging can provide nearly real-time information about target/receptor expression levels, potentially allowing physicians to predict which patients may benefit from immunotherapy and accounting for different responses in individual patients. For example, whole-body scanning with radiolabeled antibodies before initiation of therapy can not only spare patients ineffective therapy and potential adverse effects but also may have economic implications, as cancer therapy, especially with monoclonal antibodies, remains very costly and time intensive [1]. Similarly, PET scans during therapy can be helpful for an early monitoring of response to drugs, thus sparing further unnecessary immunotherapy cycles.

Because immune checkpoint inhibitors rely on adequate target expression levels, rather than using ^{18}F-FDG PET/CT, alternative noninvasive imaging strategies to detect PD-1/PD-L1 and/or CTLA4 may improve patient identification, stratification, and the early assessment of therapeutic response [2]. To date, preclinical imaging of these targets with PET (using ^{64}Cu or ^{89}Zr as the radiolabel) and SPECT (e.g. using ^{111}In) have been investigated [1]; however, no data in the clinical setting are available yet.

Immunotherapy treatments may also benefit from molecular imaging of targets not directly involved in the checkpoint blockade itself. For instance, CD3/CD8-targeted imaging agents, in addition to those targeting PD-1 or CTLA4, may be able to trace T-cell infiltration occurring during immunotherapy. Furthermore, PET imaging of activated lymphocytes using radiolabeled IL-2 has been performed in preclinical and clinical settings [9] and some clinical trials are now available on http://www.clinicaltrial.gov, suggesting a promising future impact on day-to-day cancer patient management.

Since molecularly specific imaging agents for the evaluation of responses to cancer immunotherapy have been tested in preclinical studies, several issues need to be addressed for successful clinical translation. First, most of the agents in these studies are murine antibodies and may not display specificity for human antigens; thus, human or humanized antibodies are required for clinical translation. Second, imaging of these immune checkpoint pathways may also be limited by external conditions, including previous therapeutic interventions and some viral or bacterial infections that may perturb the immune system. Third, the expression of the immune checkpoint pathway-related targets is heterogeneous and dynamic, further complicating the potential imaging strategies. Fourth, establishing and validating more clinically relevant animal models to test radiolabeled clinically used antibodies (e.g., ^{89}Zr-labeled pembrolizumab) will facilitate future clinical translation. Humanized mouse models of cancer can play very important roles in this regard. Lastly, the absence of specific criteria for the accurate assessment of response to immunotherapeutic agents can make procedure standardization a real challenge.

In conclusion, significant future efforts should be made by preclinical and clinical imaging specialists and oncologists to develop new strategies for better selection of cancer patients for immunotherapy, more accurate definition of an early response to immunotherapy, and as prevention of potential adverse effects related to these drugs. The extremely promising and exciting preclinical/clinical data that have been reported to date for cancer immunotherapy are unprecedented. With the continued development and optimization of innovative tools for patient selection and effective monitoring of the therapeutic responses, such as molecular imaging techniques and various ex vivo assays, the era of precision medicine has dawned.

Acknowledgments

Funding None.

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