Journal of Nuclear Medicine, published on February 21, 2020 as doi:10.2967/jnumed.119.236158

Hot topics

Imaging responses to immunotherapy with novel PET tracers

AN Niemeijer[1], OS Hoekstra[2], EF Smit[3], AJ de Langen[3]

1. Dept of Pulmonary Diseases, Amsterdam UMC, location Vrije Universiteit Amsterdam, De Boelelaan 1117, 1081 HV, Amsterdam, The Netherlands.
2. Dept of Radiology and Nuclear Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, De Boelelaan 1117, 1081 HV, Amsterdam, The Netherlands.
3. Dept of Thoracic Oncology, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX, Amsterdam, The Netherlands.

Corresponding author: AJ de Langen. Dept of Thoracic Oncology, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX, Amsterdam, The Netherlands. j.d.langen@nki.nl

Immunotherapy has changed the treatment paradigm of many cancers. Monoclonal antibodies (mAb's) targeting specific immune checkpoints, in particular the programmed-death 1 (PD-1), programmed death ligand 1 (PD-L1) and cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) receptors, are active against a wide range of solid and hematological cancers. Durable responses that can last for years are now seen for disease settings that were treatment refractory before the era of immunotherapy. However, despite the success of immune checkpoint inhibitors (ICIs), only a subset of patients benefit and to a variable extent. Primary as well as acquired resistance limit their efficacy The underlying mechanisms of primary and acquired resistance are actively being analyzed and numerous trials designed to target these mechanisms. In melanoma for example, the response rate to nivolumab (PD-1 mAb) and ipilimumab (CTLA-4 mAb) was 58%[1] and the 5-year progression-free survival (PFS) 36%[2]. For most solid cancers these numbers are even lower. Therefore there is an urgent need to a priori discriminate responders from non-responders as well as to identify those patients that will develop acquired resistance, despite having experienced an initial good response to ICI therapy.

Biomarker development aims to select the optimal treatment strategy for the individual patient. Already during drug development, biomarkers can provide essential feedback of target inhibition and intended tumor micro-environmental changes that are associated with drug efficacy. The amount of clinical trials being designed to evaluate the large number of possible ICI drug combinations exceeds the number of patients eligible for enrollment. Pharmacodynamic biomarkers can help to speed up the development of high-potential drugs and halt the development of less potent drugs at an early stage, thereby limiting the number of large scale phase III studies with negative results.

In this "hot topics" we will discuss the opportunities of positron emission tomography as imaging biomarker in the field of ICI therapy.

Response prediction to ICI therapy: PD-L1 expression quantification

The most widely used biomarker for patient selection in the clinical setting is PD-L1 immunohistochemistry (IHC). Patients with high tumor membrane PD-L1 expression generally have a higher chance of obtaining a response to PD-(L)1 mAb therapy. However, this biomarker is certainly not optimal. NSCLC patients whose tumor show ≥50% PD-L1 expression have a response rate of 45% to PD-1 directed treatment[3], while patients without tumor PD-L1 expression still have a 10% chance of obtaining

a response[4,5]. The limited positive predictive value of PD-L1 IHC might be caused by treatment resistance mechanisms involving pathways beyond the PD-1 – PD-L1 axis, such as insufficient tumor antigenicity, impaired antigen presentation or an immunosuppressive micro-environment. The limited negative predictive value of PD-L1 IHC might be caused by PD-L1 expression heterogeneity within tumors[6,7].
Whole body PET-CT with radiolabeled PD-L1 tracers enables the visualization and quantification of PD-L1 throughout the body, albeit at a lower resolution than IHC performed on a tumor sample.
Three PD-L1 PET tracers have made it to the clinic so far. In summary these studies show that PD-L1 tracer uptake is heterogenous between patients, as well as within patients between different tumor lesions and that tracer uptake correlates with tumor PD-L1 expression, measured by IHC[8-10]. Intriguingly, Bensch et al reported that tracer uptake correlated better with treatment response than PD-L1 IHC[10]. Together these studies show that whole body PD-L1 PET-CT reveals, and can partially overcome, the limitations of PD-L1 quantification on a small biopsy. However, larger sized studies are required to validate the observations made in these pilot studies. Also, signal interpretation might differ between small molecule and full mAb PD-L1 tracers as tracer uptake is a result of tumor perfusion, interstitial pressure, aspecific tissue distribution and the nature of target binding (reversible vs irreversible).

Challenges of response evaluation and new promising PET tracers

Response monitoring during ICI therapy is complex due to a phenomenon that's called pseudoprogression. As a result of a massive immune cell influx, tumors can initially increase in size as a result of treatment efficacy. Therefore size based response criteria may underestimate treatment efficacy[11,12]. Receptor blockade by antagonistic mAb's of inhibitory immune checkpoint receptors such as PD-1 and CTLA-4 or receptor activation by agonistic mAb's of activating immune checkpoint receptors such as OX-40 and GITR aim to activate $CD8^+$ T cells and shift the immune micro-environment in tumors from an immunosuppressive state to an immune-activated one. These biological effects occur early during ICI therapy and precede volumetric changes. ^{18}F-FDG, the most widely used tracer in the clinic, is hampered by its inability to discriminate between high metabolism of tumor cells and immune cells[13,14]. The early phase of an immune response is characterized by a mixture of tumor cell kill (i.e. decrease of ^{18}F-FDG accumulation) and activation and influx of immune cells (i.e. increase of ^{18}F-FDG accumulation) and therefore it is unlikely that ^{18}F-FDG will be suitable for early response evaluation during ICI treatment. A different approach would be to monitor $CD8^+$ T cell changes. Two T-cell PET tracers have entered the clinical arena so for. Pandit-Taskar et al imaged 6 patients with solid malignancies with ^{89}Zr-Df-IAB22M2C, an anti-CD8 minibody, PET-CT[15], while Colevas et al imaged five patients with head and neck cancer in a study with ^{18}F-AraG PET-CT[16]. This tracer is an ^{18}F-labeled analogue of arabinofuranosyl guanine (AraG), a compound that shows selective accumulation in activated $CD8^+$ T cells. Preliminary results of both studies show that tracer injection is safe and biodistribution suggests successful targeting of benign and malignant $CD8^+$ T cell-rich tissues.
In contrast to early response evaluation, ^{18}F-FDG PET-CT seems to be an accurate biomarker to identify patients that are at risk of disease relapse despite having obtained an initial good response. In a retrospective analysis of 104 melanoma patients that were evaluated after one year of ICI treatment, only 28% had a complete response on CT, while 75% had a complete metabolic response (CMR). In the group of patients that obtained a partial response on CT, ^{18}F-FDG PET-CT was able to identify patients with a high risk of disease progression: patients with residual ^{18}F-FDG uptake had a PFS rate of 48%,

while those with a CMR had a PFS rate of 93%. In other words, a late stage ^{18}F-FDG PET-CT can be used to select patients for treatment intensification.

Opportunities of PET-CT to aid ICI drug development

PD-(L)1 and CTLA-4 checkpoint inhibitor therapy are able to induce long-term responses in a proportion of patients with late stage treatment refractory cancers such as melanoma and NSCLC. The ultimate goal of engaging the immune system against tumors is to provide a cure for patients with (currently) treatment-refractory cancers. Our understanding of tumor and immune biology and their interaction fuels therapeutic advances and drug development. PET-CT may facilitate this process. It has unique features that allows for non-invasive monitoring of virtually every biological pathway in a whole body fashion and it can be repeated over time to monitor changes without influencing the tumor. By radiolabeling intact drugs in an inert way, biodistribution can be visualized and quantified. During drug combination therapy, drug-drug interactions that can lead to changes in drug delivery to the tumor or immune organs can be monitored[17].

ICI-ICI combination studies should be smart-designed. Timing of different immune modulators is critical in order to stimulate immune activating cells and inhibit immune suppressive cells in an optimal way. Messenheimer et al for example showed that sequential instead of concurrent OX-40 agonist and PD-1 antagonist treatment resulted in better immune cell activation against tumor cells[18]. Treatment with the OX-40 agonist provided an initial boost in PD-1$^+$ CD4$^+$ and PD-1$^+$ CD8$^+$ antitumor T-cells that was at its maximum after 13 days of OX-40 treatment and only subsequent treatment with a PD-1 mAb extended this. Serial PET-CT would be an ideal way to monitor these changes and to prevent the necessity of repeated biopsies.

Conclusion

PET-CT using novel immune tracers can help to monitor and develop ICI therapy. The biomarker is in its early stage of development where validation and qualification are ongoing. Larger scale molecular imaging studies with adequate data modeling and feedback from tissue analysis and outcome on treatment are required to evaluate the full potential of PET-CT in the field of ICI therapy.

References

1. Larkin J, Chiarion-Sileni V, Gonzalez R, et al: Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 373:23-34, 2015
2. Larkin J, Chiarion-Sileni V, Gonzalez R, et al: Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med 381:1535-1546, 2019
3. Reck M, Rodriguez-Abreu D, Robinson AG, et al: Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 375:1823-1833, 2016
4. Borghaei H, Paz-Ares L, Horn L, et al: Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 373:1627-39, 2015
5. Rittmeyer A, Barlesi F, Waterkamp D, et al: Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 389:255-265, 2017
6. Li C, Huang C, Mok TS, et al: Comparison of 22C3 PD-L1 Expression between Surgically Resected Specimens and Paired Tissue Microarrays in Non-Small Cell Lung Cancer. J Thorac Oncol 12:1536-1543, 2017
7. McLaughlin J, Han G, Schalper KA, et al: Quantitative Assessment of the Heterogeneity of PD-L1 Expression in Non-Small-Cell Lung Cancer. JAMA Oncol 2:46-54, 2016
8. Niemeijer AN, Leung D, Huisman MC, et al: Whole body PD-1 and PD-L1 positron emission tomography in patients with non-small-cell lung cancer. Nat Commun 9:4664, 2018
9. Xing Y, Chand G, Liu C, et al: Early Phase I Study of a (99m)Tc-Labeled Anti-Programmed Death Ligand-1 (PD-L1) Single-Domain Antibody in SPECT/CT Assessment of PD-L1 Expression in Non-Small Cell Lung Cancer. J Nucl Med 60:1213-1220, 2019
10. Bensch F, van der Veen EL, Lub-de Hooge MN, et al: (89)Zr-atezolizumab imaging as a non-invasive approach to assess clinical response to PD-L1 blockade in cancer. Nat Med 24:1852-1858, 2018
11. Hodi FS, Hwu WJ, Kefford R, et al: Evaluation of Immune-Related Response Criteria and RECIST v1.1 in Patients With Advanced Melanoma Treated With Pembrolizumab. J Clin Oncol 34:1510-7, 2016
12. Tazdait M, Mezquita L, Lahmar J, et al: Patterns of responses in metastatic NSCLC during PD-1 or PDL-1 inhibitor therapy: Comparison of RECIST 1.1, irRECIST and iRECIST criteria. Eur J Cancer 88:38-47, 2018
13. Humbert O, Cadour N, Paquet M, et al: (18)FDG PET/CT in the early assessment of non-small cell lung cancer response to immunotherapy: frequency and clinical significance of atypical evolutive patterns. Eur J Nucl Med Mol Imaging, 2019
14. Rossi G, Bauckneht M, Genova C, et al: Comparison between 18F-FDG-PET- and CT-based criteria in non-small cell lung cancer (NSCLC) patients treated with Nivolumab. J Nucl Med, 2019
15. Pandit-Taskar N, Postow M, Hellmann M, et al: First-in-human imaging with (89)Zr-Df-IAB22M2C anti-CD8 minibody in patients with solid malignancies: preliminary pharmacokinetics, biodistribution, and lesion targeting. J Nucl Med, 2019
16. Colevas AD, Bedi N, Chang S, et al: A study to evaluate immunological response to PD-1 inhibition in squamous cell carcinoma of the head and neck (SCCHN) using novel PET imaging with [18F]F-AraG. 36:6050-6050, 2018
17. Van der Veldt AA, Lubberink M, Bahce I, et al: Rapid decrease in delivery of chemotherapy to tumors after anti-VEGF therapy: implications for scheduling of anti-angiogenic drugs. Cancer Cell 21:82-91, 2012
18. Messenheimer DJ, Jensen SM, Afentoulis ME, et al: Timing of PD-1 Blockade Is Critical to Effective Combination Immunotherapy with Anti-OX40. Clin Cancer Res 23:6165-6177, 2017