Imaging after one week on pembrolizumab may predict treatment response in advanced melanoma

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Imaging the tumors of patients with advanced melanoma receiving pembrolizumab (Keytruda) after only one week—rather than the

standard of around three months—identified metabolic changes that corresponded with treatment response and progression-free survival (PFS). These study results were published in *Clinical Cancer Research* on Jan. 24.

Cancer immunotherapy has helped transform the standard of care for many malignancies, but not all patients respond to therapy, and the treatment can cause severe adverse events. Typically, immunotherapy patients are imaged around three months after starting treatment to monitor their progress, with some more recent trials exploring the value of performing scans after three to six weeks, and in some cases closer to two weeks.

But Dr. Michael D. Farwell, Associate Professor of Radiology at the Hospital of the University of Pennsylvania, designed a study to explore if results could be observed even sooner. The goal was to identify a noninvasive imaging biomarker that could guide the management of patients on these therapies and avoid toxicity in patients not likely to benefit.

Farwell and his colleagues hypothesized that by using ^{18}F-fluorodeoxyglucose (FDG) PET/CT, which is one of the most common and readily available ways to test for cancer, they could see if patients experienced metabolic changes in tumors after a week on therapy.

When a patient responds to immunotherapy, activated immune cells infiltrate into the tumor, so the scans are expected to first show an increase in FDG activity, which Farwell calls a metabolic flare (MF).

Then, as the tumor responds to therapy, the tumor cells die and pass back through a stable metabolism phase and ultimately end at a metabolic response (MR), indicated by a decrease in FDG activity. In contrast, the tumors of non-responding patients are expected to maintain

stable metabolism.

"If you're imaging after three weeks, you're unlikely to catch this flare, because response to immunotherapy happens so quickly and, in some cases, it's already done—there's no tumor left," Farwell explained.

"The other nice thing about imaging at a week is we are looking at this response curve over a pretty short interval. If you wait to monitor progress over longer intervals, it means the tumor has more time to grow in non-responders, which can complicate the analysis."

To test their hypothesis, the researchers recruited 21 patients with advanced melanoma scheduled to initiate pembrolizumab. As part of the trial, patients were required to have at least one measurable lesion and could not have received previous anti-PD-1 or anti-PD-L1 therapies.

FDG PET/CT imaging was performed on each patient within four weeks prior to their start of therapy and then at about one week after the first dose of pembrolizumab. Two patients did not complete both scans, so their results were excluded.

FDG activity for each lesion was measured using the maximum standardized uptake value (SUV_{MAX}). For the purposes of this study, an MF was defined as a greater than 70% increase in tumor SUV_{MAX} and an MR as a greater than 30% decrease in tumor SUV_{MAX}.

An MF or MR was identified in 55% of the patients who responded to treatment (6 out of 11) and 0% of patients who did not respond (0 of 8). An MF or MR also correlated with longer survival, with 83% of the MF-MR group seeing an overall survival of three years compared to 62% in the group with stable metabolism. Additionally, median PFS was greater than 38 months in the MF-MR group and 2.8 months in the group with stable metabolism.

Farwell said they not only observed heterogeneity in the kinetics of response between patients, they also observed heterogeneity among lesions in the same patient. That is a challenge Farwell hopes to address in future studies. Further, because tumors pass through a stable metabolism phase between MF and MR responses, it will be key to identify if a tumor with stable metabolism is in fact responding but is in between reaction phases.

Farwell says some potential solutions for that include layering on companion studies such as blood tests, a CD8 PET scan, or serial FDG PET/CT imaging to better plot out the change over time.

"While the results need to be validated, this has the potential to be broadly applicable and offer physicians the ability to deescalate therapy or avoid surgery in patients who are responding, identify nonresponders who may need an escalation of therapy, and to be used in phase I clinical trials to test if a therapy is working," Farwell explained.

Limitations of the study include a relatively small sample size from a single institution, which did not include patients with stable disease. Also, there were variable intervals between a patient's first scan prior to therapy initiation and their scan after therapy initiation. Additionally, four different PET/CT scanners were used, which could have caused variability in SUV measurements.

More information: Thomas M. Anderson et al, FDG PET/CT Imaging 1 Week after a Single Dose of Pembrolizumab Predicts Treatment Response in Patients with Advanced Melanoma, *Clinical Cancer Research* (2024). DOI: 10.1158/1078-0432.CCR-23-2390

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