Better Late than Early: FDG-PET Imaging in Metastatic Renal Cell Carcinoma

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Sunitinib treatment benefits patients with metastatic renal cell carcinoma (mRCC), but response duration can vary widely and resistance is not predicted by standard measures. [18F]fluoro-2-deoxy-2-D-glucose positron emission tomography (FDG-PET) uptake is variable in mRCC, but changes in FDG-PET uptake may be useful in monitoring disease progression. Further work is needed to personalize treatment for patients with mRCC. Clin Cancer Res; 17(18); 5841-3. ©2011 AACR.

In this issue of Clinical Cancer Research, Kayani and colleagues report in a cohort of 44 metastatic renal cell carcinoma (mRCC) patients treated with sunitinib that a metabolic response by sequential [18F]fluoro-2-deoxy-2-D-glucose (FDG) positron emission tomography (PET) at 4 weeks did not correlate with outcomes, whereas metabolic progression at 16 weeks was predictive of inferior survival (1). Historically, FDG-PET imaging was not thought to be particularly useful in kidney cancer. Most radiotracers, including FDG, are eliminated by the kidneys and primary renal cell carcinoma tumors seemed to have relatively low glucose uptake (2). FDG-PET did not seem to add anything to conventional imaging for the characterization of renal masses. Previously, data were scant on the role of FDG-PET for treatment monitoring of mRCC (3, 4).

Kidney cancer is a heterogeneous disease. Consequently, prognostic models have been developed in the era of VEGF-targeted therapy based on clinical variables to classify patients into risk groups (5). Such classifications are especially important for patient counseling and risk-directed therapy, as well as for clinical trial design. The finding by Kayani and colleagues that the maximum standardized uptake value (SUVmax) correlated with decreased survival (1) is important, and SUVmax should be considered as a criterion for incorporation in future prognostic models. Despite the success of newer targeted therapies such as sunitinib in improving outcomes, essentially all patients experience progression, although the duration can vary widely (6). With an increasing number of treatment options for patients with mRCC, it is essential to develop predictive biomarkers for clinical benefit to sunitinib treatment, so that patients benefiting will stay on therapy, whereas those who are not may be considered for alternative approaches.

Standard anatomic radiographic imaging does not seem to do well in predicting mRCC patients who may benefit from sunitinib treatment (7). Functional molecular imaging, like PET, may provide additional information about tumor biology when used sequentially as a kind of "noninvasive biopsy." As such, Kayani and colleagues prospectively explored the prognostic and predictive significance of sequential FDG-PET. Clinically, at least 3 distinct patterns of resistance to sunitinib therapy are recognized, as observable by standard radiographic imaging. Some patients will not have any measurable tumor regression and will progress rapidly (intrinsic nonresponsiveness). Others will have a minor measurable tumor regression followed by disease progression. Still others will have remarkable, sustained tumor responses, with slow, perhaps mixed, progression to a lower tumor burden than that observed prior to therapy. Ideally, we would like a tool that discriminates among these phenotypes early in the treatment course and more accurately than standard imaging, to optimize treatment decisions in individual patients and better define patient populations for subsequent clinical studies.

FDG-PET imaging in cancer takes advantage of 2 general principles: (i) cancer cells tend to have elevated rates of glucose uptake and glycolysis compared with normal cells, and (ii) once the FDG radiotracer is taken up by cells and phosphorylated, it becomes trapped intracellularly. The reprogramming of energy metabolism is now considered a hallmark of cancer (8), in addition to the original paradigms of aberrant growth signaling, tissue invasion and metastasis, limitless replicative potential, sustained angiogenesis, and evasion of apoptosis. The capability of cancer cells to undergo "aerobic glycolysis" by limiting their energy metabolism largely to glycolysis, avoiding oxidative phosphorylation even under aerobic conditions (Fig. 1A), was first described by Otto Warburg (9). The glucose...
analogue FDG is moved into cancer cells by glucose transporters and phosphorylated by hexokinase to FDG-6-phosphate (Fig. 1B). Tissue FDG accumulation can be expressed semiquantitatively by the SUV, which normalizes the concentration of tissue radioactivity to the dose of the injected radiotracer and the patient’s body weight. Although the SUVmax is most often used in the clinic, several different SUV parameters have been defined (Fig. 1C).

Kayani and colleagues report that although 57% of patients had a metabolic response in the SUVmax metastatic lesion at week 4 (a 20% or greater decrease in SUVmax), this was not associated with improved progression-free survival (PFS) or overall survival (OS). This contrasts with the finding that PFS correlated with week 4 metabolic response in sunitinib-treated gastrointestinal stromal tumors (GIST; ref. 10). One key difference in the 2 studies is that the latter measured SUV in a 2-cm³ volume (i.e., SUVpeak) for each of the 3 most metabolically active lesions at baseline, which were then averaged and reevaluated at week 4. This discrepancy may reflect the inherent biological differences between mRCC and GIST or the dynamic nature of mRCC tumors, as the authors suggest (1). One alternative explanation is that the single most FDG-avid voxel (Fig. 1C), chosen from the median 6.5 FDG-avid sites per patient, may not by itself be reflective of treatment changes. To put it another way, the response to therapy by a patient’s disease might not be able to be boiled down to 1 number, calculated from just 1 point reflecting relative SUVmax within 1 of a patient’s many tumors. Finally, it is possible that other aspects of tumor biology in addition to increased glucose metabolism become dominant in response to treatment and, thus, drive outcomes.

So, how do we make sense of the findings that metabolic response at 4 weeks was not predictive, but metabolic
progression (i.e., increase in SUV\textsubscript{max}) at week 16 did correlate with inferior outcomes (1)? The authors’ explanation is that timing FDG-PET in week 4 may have been too early in mRCC to predict resistance, especially given that 82% of metabolic progressors at week 16 (n = 12) had a response at week 4. An alternative might be that when one evaluates at a point of maximal activity, attenuation is necessary, but not sufficient, to portend outcome. In other words, the SUV\textsubscript{max} is just the tip of the iceberg. When it disappears below the surface of the water, it does not give us any information about what may be going on beneath the surface, but when it continues to rise higher above the surface of the water, it may be more reflective of changes going on below the surface. In some respects, it is remarkable that an increase in SUV\textsubscript{max} on FDG-PET from a single selected lesion provides any insight into patient outcome, because it is not a direct measure of other biological changes simultaneously going on within the tumor involving growth signaling and/or proliferation, hypoxia and blood vessel formation, or programmed cell death.

Kayani and colleagues should be commended for incorporating an elegantly designed secondary analysis into a prospective treatment trial, shedding light on the role of treatment monitoring with FDG-PET in mRCC patients treated with sunitinib. However, more work remains to be done. Liu and colleagues have evaluated early changes in proliferation after sunitinib treatment in mRCC using a thymidine analogue (11). Additional PET radiotracers, perhaps in combination, and SUV parameters, should continue to be evaluated to obtain the best biological readout. Other functional imaging modalities should also be evaluated. For example, a recent study compared microbubble ultrasound, dynamic contrast-enhanced MRI, and dynamic contrast-enhanced computed tomography for assessment of vascular responses (12). Although more research is needed to translate these findings to clinical treatment monitoring for the benefit of patients, the work by Kayani and colleagues provides seminal insights into the biology and timing for biomarkers of sunitinib treatment response in mRCC patients.

Disclosure of Potential Conflicts of Interest

D. George: commercial research support, Novartis, Pfizer, Bristol-Myers Squibb, GlaxoSmithKline; honoraria, Novartis, Pfizer, and Genentech, consultant, Novartis, Pfizer, and Genentech. M. Harrison: honorarium, Novartis.

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