^{18}F-Fluciclovine (FACBC) and Its Potential Use for Breast Cancer Imaging

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Radiolabeled amino acids have been in use for oncologic imaging for more than 2 decades, and several amino acids have proven utility in neurooncology. More recently, a major focus in this field has been the development of ^{18}F-labeled amino acids targeting distinct transporter systems with different biologic and imaging properties and the assessment of these tracers in other solid tumors (*1*). The nonnatural amino acid *anti*-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid (FACBC, fluciclovine) has recently received U.S. Food and Drug Administration (FDA) approval for the detection and localization of biochemically recurrent prostate cancer. Because amino acid transport is upregulated in many types of cancer, ^{18}F-fluciclovine has potential application in multiple types of cancer. In this issue of *The Journal of Nuclear Medicine,* 2 groups report promising preliminary results for FACBC in women with breast cancer naïve to therapy (*2,3*). These studies demonstrated substantially higher uptake of ^{18}F-fluciclovine in primary and metastatic breast cancers than in benign breast lesions and normal breast tissue. Additionally, higher ^{18}F-fluciclovine uptake occurred in more aggressive breast cancers, and both groups observed higher uptake of ^{18}F-fluciclovine than ^{18}F-FDG by invasive lobular carcinoma (ILC). Although definitive conclusions regarding the clinical utility of ^{18}F-fluciclovine PET/CT in breast cancer are not possible from these small studies (39 patients collectively), further investigations of ^{18}F-fluciclovine in this population are clearly warranted. In addition to detecting and localizing breast cancer, ^{18}F-fluciclovine may provide a new tool for probing amino acid transport and metabolism in breast cancer.

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The report from the Emory group, by Tade et al. (*2*), evaluated ^{18}F-fluciclovine PET/CT in 12 women with malignant ($n = 13$) and benign ($n = 4$) breast lesions with histologic verification. In this study, patients underwent dynamic ^{18}F-fluciclovine PET/CT of the thorax for 45 min. The highest uptake of ^{18}F-fluciclovine in malignant lesions occurred within 5–10 min after tracer injection, with slow washout in most cases over the course of imaging. For example, at the 5-min time point the average of the maximum SUV measurements in malignant lesions was 6.2 ± 3.2 compared with 1.3 ± 0.6 in benign lesions. ^{18}F-fluciclovine also detected nodal and skeletal metastases but was less effective for hepatic metastases due to the high physiologic uptake of this tracer in liver parenchyma. The highest uptake of ^{18}F-fluciclovine occurred in Nottingham grade 3 cancers and triple-negative breast cancers, suggesting that ^{18}F-fluciclovine may have a role in identifying more aggressive malignancies. In the 4 patients in this study who also underwent clinical ^{18}F-FDG PET/CT, similar maximum SUVs were observed with ^{18}F-fluciclovine and ^{18}F-FDG for infiltrative ductal carcinomas. In contrast, the maximum SUVs with ^{18}F-fluciclovine were higher for ILC than with ^{18}F-FDG, although this difference in ILC did not reach clinical significance.

The report from the Memorial Sloan Kettering group, by Ulaner et al. (*3*), evaluated ^{18}F-fluciclovine PET/CT in 27 women with newly diagnosed, locally advanced breast cancer. Patients in this prospective study underwent dynamic ^{18}F-fluciclovine PET of the thorax for 30 min, and peak tumor uptake was observed at 5–10 min after tracer injection. The primary breast cancer was visualized in all patients, and ^{18}F-fluciclovine identified axillary lymph node metastases in 20 of 21 patients with pathologic confirmation. Comparison with ^{18}F-FDG PET/CT was possible for 14 of the 27 patients enrolled in this study. As with the Emory group, primary ILCs were observed to have higher maximum SUVs with ^{18}F-fluciclovine than ^{18}F-FDG. In 2 patients, ^{18}F-fluciclovine PET/CT detected previously unsuspected internal mammary lymph node metastases. The authors also observed weak concordance between ^{18}F-fluciclovine and ^{18}F-FDG SUVs whereas the tumor volumes defined by both tracers had strong concordance, consistent with the different mechanisms of uptake of these tracers by cancer cells.

The results of these studies are important for several reasons. First, the results show that ^{18}F-fluciclovine may have clinical utility in breast cancer and suggest that this tracer has higher uptake in more aggressive breast cancers and better imaging properties in ILC than ^{18}F-FDG. These properties of ^{18}F-fluciclovine may make it more useful than ^{18}F-FDG for the evaluation of primary breast cancer, particularly ILC, with positron emission mammography and PET/MR imaging systems. Additionally, these results suggest that amino acid transport and metabolism are different in histologic subtypes of breast cancer, which may be relevant to therapies targeting cancer metabolism. Second, ^{18}F-fluciclovine has recently been approved by the FDA for the detection of recurrent prostate cancer. These initial results in breast cancer patients along with studies in patients with gliomas and with lung cancer suggest that

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^{18}F-fluciclovine may have clinical value for a range of solid tumors (*4–7*). A wider range of applications would help differentiate ^{18}F-fluciclovine from more targeted approaches to prostate cancer imaging, particularly radiolabeled prostate-specific membrane antigen ligands and increase the likelihood of widespread availability and commercial viability of ^{18}F-fluciclovine. Finally, a major mechanism of ^{18}F-fluciclovine uptake by cancer cells is the neutral amino acid transport, ASC transporter type 2 (ASCT2, SLC1A5) (*8,9*). ASCT2 is a key mediator of glutamine uptake by many cancers, and thus ^{18}F-fluciclovine has the potential to provide a new tool for noninvasively studying glutamine biology in cancer and for use with therapies that target glutamine metabolism.

Part of the significance of these studies derives from the biologic properties of ^{18}F-fluciclovine and the roles of amino acid transporters in cancer biology (*10*). ^{18}F-fluciclovine is a nonnatural alicyclic amino acid containing a 4-membered ring that was originally developed as a leucine analog for brain tumor imaging by Mark Goodman et al. at Emory University (*5,11*). The mechanism of uptake of ^{18}F-fluciclovine differs from other radiolabeled amino acids that have been widely used for human oncologic imaging. There are more than 20 mammalian amino acid transporter families, and specific transporters including the system L large neutral amino acid transporter type 1 (LAT1, SLC7A5) and ASCT2 play key roles in cancer metabolism (*12*). Mechanistic studies of ^{18}F-fluciclovine uptake by prostate cancer cells demonstrate that the amino acid transporter ASCT2 is the major mediator of uptake of this tracer, with LAT1 and the system A amino acid transporter type 2 (SNAT2, SLC38A2) also contributing to cellular uptake (*8,9*). Uptake via ASTC2 differentiates ^{18}F-fluciclovine from the system L amino acid transport substrates that have been used extensively for brain tumor imaging, including L-^{11}C-methionine, *O*-(2-^{18}F-fluoroethyl)-L-tyrosine, and 3,4-dihydroxy-6-^{18}F-fluoro-L-phenylalanine. Because ASCT2 plays an important role in glutamine transport by many cancers, ^{18}F-fluciclovine may be able to provide metabolic information not available with other PET tracers. The alicyclic structure of ^{18}F-fluciclovine provides in vivo metabolic stability and facilitates kinetic modeling of amino acid transport unlike ^{11}C- and ^{18}F-labeled glutamine analogs that are metabolized and in some cases incorporated into proteins in vivo.

Although these results are promising, there are several important limitations and unanswered questions that remain. An obvious limitation is the small sample size in both studies, and additional studies in larger patient populations are needed to confirm these initial observations in breast cancer. Both studies also limited imaging to the thorax, and thus the clinical utility of ^{18}F-fluciclovine for whole-body staging was not assessed. These studies were not designed to compare the diagnostic yield of ^{18}F-fluciclovine PET/CT with conventional imaging and diagnostic evaluation for the detection of primary breast cancers or the staging of axillary nodal and distant metastases. These types of studies will be critical for determining the clinical value of ^{18}F-fluciclovine in newly diagnosed breast cancer. High physiologic liver uptake will likely limit the detection of hepatic metastases with ^{18}F-fluciclovine. The washout over time of ^{18}F-fluciclovine is expected given that the amino acid transporters ASCT2 and LAT1 are reversible and can mediate both the uptake and the efflux of their substrates by cells. This washout phenomenon must be taken into consideration when designing imaging protocols with ^{18}F-fluciclovine and may affect quantitation and lesion detection, particularly at later time points after tracer injection. Correlation of ^{18}F-fluciclovine with the presence of specific amino acid transporters, including ASCT2 and LAT1, as well as with the metabolomics is needed to establish the biologic significance of ^{18}F-fluciclovine uptake in breast cancer and other malignancies. These correlations may explain the differences in ^{18}F-fluciclovine uptake between infiltrative ductal carcinomas and ILC and the higher uptake of ^{18}F-fluciclovine than ^{18}F-FDG in breast cancer with ILC histology. Given the initial encouraging results with ^{18}F-fluciclovine in breast cancer, further studies to answer these clinical and research questions are warranted.

DISCLOSURE

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