Imaging of Prostate Cancer Using Fluciclovine

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KEYWORDS

• FACBC • Fluciclovine • Axumin • CT • PET • Prostate

KEY POINTS

- Functional molecular imaging with PET improves the ability to detect prostate cancer.
- Fluciclovine is beneficial for the localization of recurrent prostate disease when conventional imaging is negative.
- When interpreted with knowledge of radiotracer biodistribution and normal variants, fluciclovine PET is highly specific for extraprostatic metastasis but has lower specificity for disease within intact or treated prostate.
- Less data are available on the performance of fluciclovine in bone metastases; therefore, skeletal-specific imaging is recommended for suspected bone involvement if fluciclovine PET is unrevealing.

RADIOLABELED AMINO ACIDS AS PET RADIOTRACERS FOR PROSTATE CANCER IMAGING

Amino acids play a central role in cell metabolism and are the building blocks of proteins. Transmembrane amino acid transporters are upregulated in cancer cells to provide nutrients for tumor cell growth.[1,2] Certain amino acids such as leucine and glutamine are key components in the mammalian target of rapamycin cancer signaling pathway.[3] Because this upregulation of amino acid transport also occurs in prostate cancer cells, using an amino acid–based radiotracer can localize prostate cancer as well.[4]

Many amino acid transporter systems are overexpressed in prostate cancer, predominantly large neutral amino acid transporters (systems L: LAT1, LAT3, and LAT4) and alanine-serine-cysteine transporters (systems ASC: ASCT1, ASCT2).[1,3,5–14] Of these transporters, LAT1 and ASCT2 are particularly associated with more aggressive tumor behavior.[7,15–17] Both ASCT2 and LAT3 expression are stimulated by androgen signaling in androgen-dependent prostate cancer cells.[18]

Prostate cancer may be imaged using both radiolabeled natural and synthetic amino acids. Naturally occurring amino acids such as C-11-methionine are not optimal for imaging because

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of accumulation of metabolites in nontarget organs, whereas radiolabeled synthetic, nonmetabolized amino acid analogues are preferred due to simpler kinetics and the ability to radiolabel with longer-lived radionuclides.[1]

Anti-1-amino-3-F-18-fluorocyclobutane-1-carboxylic acid (FACBC or fluciclovine) is a nonnaturally occurring amino acid analogue for which the most comprehensive clinical studies for prostate cancer have been performed to date.[10,17,19–26] Fluciclovine is predominantly transported via ASCT2 and LAT1. Because these transporters mediate both influx and efflux of amino acids, peak uptake in tumors occurs at 5 to 20 minutes after injection with variable washout.[17,22,27]

FLUCICLOVINE FROM DEVELOPMENT TO US FOOD AND DRUG ADMINISTRATION APPROVAL

The development of C-11 aminocyclobutane arboxylic acid (ACBC) was first described in 1978 by Washburn and colleagues.[28] ACBC was structurally modified from 1-aminocyclopentanecarboxylic acid. Subsequently, ACBC was radiolabeled with Carbon-11 and found to have potential for imaging soft tissue tumors in humans.[29] However, C-11 has a half-life of 20 minutes, which requires an on-site cyclotron for production. In 1995, Dr Mark Goodman and coworkers described the synthesis of fluorine-18 (half-life 109.8 minutes) labeled anti-1-amino-3-fluorocyclobutane-1-carboxylic acid, 3-FACBC. In 1999, they reported the evaluation of 3-FACBC in gliomas.[30] In 2002, the synthesis of the 3-FACBC labeling precursor and 3-FACBC were improved for routine production for clinical use.[31,32]

Early work suggested that fluciclovine was transported into the cell most like leucine via system L, especially LAT1.[31,33] Subsequent in vitro studies found that the ASC transporter system, specifically ASCT2, plays the largest role in fluciclovine transport, whereas LAT1 transport may become elevated in an acidic tumor environment or with castration-resistant cells.[10,16–18] Thus, it is currently thought that fluciclovine transport more closely mirrors that of glutamine rather than leucine.[34] When compared with methionine, glutamine, choline, and acetate, uptake of fluciclovine in prostate cancer cell lines has also been noted to be higher.[17] Experiments with a rat orthotopic prostate cancer model compared the uptake of fluciclovine with that of fludeoxyglucose (FDG). It was found that target-to-background ratio was higher for fluciclovine with only minimal bladder accumulation.[33]

In human clinical studies, fluciclovine was initially developed for the evaluation of cerebral gliomas.[30] Further evaluation in human dosimetry studies demonstrated physiologic highest tracer uptake by the liver and pancreas, with less intense heterogeneous uptake within the marrow, salivary glands, lymphoid tissue, and pituitary gland, and only minimal brain and kidney uptake. Variable activity was noted in the bowel[27] (**Fig. 1**). When compared with FDG, fluciclovine is only minimally eliminated by the kidneys during the typical imaging time course. Hence, evaluation of fluciclovine for imaging of renal and pelvic malignancies seemed promising.

Fluciclovine was next evaluated for staging of patients with renal cancer. Although no highly promising data from renal mass evaluation were observed, an important incidental finding was reported in a patient with intense uptake within retroperitoneal lymphadenopathy and subsequent biopsy-proven metastatic prostate cancer.[35] Evaluation of fluciclovine for prostate cancer imaging took priority, and in 2007, Schuster and colleagues[22] described the first experience with fluciclovine for the evaluation of 9 patients with primary and 6 patients with recurrent prostate cancer. Early results reported promising correlation between biopsy-proven disease and fluciclovine uptake. Further human studies with fluciclovine, which will be detailed in later discussion, demonstrated the potential to detect local and distant recurrent prostate cancer.

A New Drug Application was subsequently accepted in December 2015 by the US Food and Drug Administration (FDA) as filed by Blue Earth Diagnostics, Ltd for priority review based on data collected from 877 subjects, including 797 patients with prostate cancer in the United States and Europe, and approval was granted to fluciclovine (trade name: Axumin) on May 2016 for the clinical indication of suspected prostate cancer recurrence based on elevated prostate-specific antigen levels following prior treatment.[36]

FLUCICLOVINE IN THE EVALUATION OF PATIENTS WITH SUSPECTED RECURRENCE OF PROSTATE CANCER

Fluciclovine has been most extensively studied in relation to recurrent prostate cancer. Fluciclovine diagnostic performance has been reported to be significantly higher than that of In-111-capromab pendetide and computed tomography (CT) in the diagnosis of patients with suspected disease relapse.[21,24,37] A single-center study with 115