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^{18}F-DOPA: the versatile radiopharmaceutical

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Sir,

Neuroendocrine tumors (NET) typically have a good outcome despite the dismal prognosis of highly aggressive forms. Their clinical and therapeutic management largely depends on their embryological origin, stage, degree of differentiation, proliferation status, hormonal activity, and location. Nuclear medicine has a central role in managing these patients, aiding in the diagnostic localization, and staging of the disease. Nuclear imaging also provides prognostic information particularly by assessing tumor differentiation using specific radiopharmaceuticals such as ^{68}Ga-labeled somatostatin analogs (^{68}Ga-DOTA-SSA) for gastroenteropancreatic NETs and chromaffin cell tumors [1]. Tumor aggressiveness and various cellular events (e.g. apoptosis, hypoxia, etc.) can also be assessed using ^{18}F-FDG [2] and other radiopharmaceuticals, respectively. Recognition of the imaging, molecular, and cellular pathology or functional correlations has underpinned the concept of imaging biomarkers. A similar approach based on the use of imaging prognosticators is already widely used in the assessment of thyroid cancers of follicular origin by radioiodine and ^{18}F-FDG. Compared to the use of these radiopharmaceuticals for phenotypic characterization of tumors, ^{18}F-FDOPA appears as a versatile imaging tool for NETs. The prognostic information provided by ^{18}F-FDOPA is largely unknown. ^{18}F-FDOPA seems to be positioned between a radiotracer for tumor differentiation and ^{18}F-FDG. In our opinion, this means that ^{18}F-FDOPA provides potential information that we are unable to fully understand with our current knowledge of the biology of these tumors.

^{18}F-FDOPA is a fluorinated analog of a naturally occurring amino acid, L-DOPA. It is widely accepted that ^{18}F-FDOPA enters the cells via the large-type amino acid transporters (mainly LAT-1 and LAT-2). LAT transporters require another cell surface glycoprotein, heavy chain (CD98hc), for their functional expression, as a heteromeric complex at the membrane. Therefore, ^{18}F-FDOPA uptake by target cells depends primarily on the

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expression of the LAT1-2/CD98hc heterodimer. The retention of the tracer is probably more dependent on the expression and activity of the aromatic L-amino acid decarboxylase (AADC) that converts ^{18}F-FDOPA into ^{18}F-dopamine, and the concentration of ^{18}F-dopamine in synaptic vesicles via vesicular monoamine transporters. This probably explains the prolonged retention of ^{18}F-FDOPA in tumors that secrete serotonin and catecholamines.

Beyond their role in neurosecretion, the LATs allow the constant supply of amino acids necessary for cellular growth, metabolism, and signaling. However, these transporters have a lower affinity for L-DOPA than other larger amino acids such as leucine, which is a major activator of mTOR kinase, enabling continuous protein synthesis, cell cycle progression, and inhibition of autophagy induction. Therefore, these nutritional transporters are not specific to NETs and can be overexpressed in a variety of tumors that rely on them for growth, migration, and invasiveness [3]. For example, there is a correlation between higher ^{18}F-FDOPA uptake and histological grade in gliomas. Another element adding to the complexity of these amino acid transporters is related to their mode of function. In fact, LATs are sodium-independent exchangers of amino acids. This means that ^{18}F-FDOPA enters the cells via an obligatory efflux of certain amino acids. Therefore, ^{18}F-FDOPA uptake could be dependent on the overall intracellular concentration of amino acids. Finally, another influencing factor could be the phenomenon of competitive cellular entry between ^{18}F-FDOPA and other amino acids.

What can be highlighted through publications and clinical observations? First, ^{18}F-FDOPA is an exceptional radiopharmaceutical in the evaluation of NETs of the ileum [4, 5] and sporadic pheochromocytoma/paraganglioma (PHEO/PGL). Second, uptake in pancreatic NETs is variable from one patient to another regardless of the secretory profile [6-8]. Third, medullary thyroid cancers usually have moderate uptake of ^{18}F-FDOPA with an often low, but unpredictable retention rate pattern [9]. The behavioral model of PHEOs/PGLs highlights the complexity of this radiotracer and its relationship to molecular genetics. Based on our longstanding experience in the imaging of PHEOs/PGLs, it appears that the major phenotypic determinant of ^{18}F-FDOPA-based imaging is the genetic component of these tumors [10, 11]. Indeed, findings are almost always false-negatives in tumors associated with succinate dehydrogenase (mitochondrial complex II) deficiency. It is now well established that these tumors exhibit tricarboxylic acid cycle (Krebs cycle) dysfunction with highly elevated accumulation of succinate [12] acting as an oncometabolite, deficiency in certain amino acids such as glutamate, aberration of catecholamine metabolism, a DNA hypermethylation phenotype [13], and accelerated angiogenesis. We have also observed differences in ^{18}F-FDOPA uptake/retention between different tumors in the same patient.

We still do not know what mechanisms are involved in the dysregulation of the ^{8}F-FDOPA transport and storage machinery and cannot explain the interpatient and intrapatient differences. It is probable that these relationships between genotype and the phenotype found on imaging could play an important role in the pathogenesis and clinical behavior of other NETs. Thus, it may be worth pursuing further studies seeking to correlate the ^{18}F-FDOPA phenotype with the molecular biology, genetics, and clinical behavior of various NETs. The addition of sophisticated tools in the quantification of ^{18}F-FDOPA uptake would be particularly interesting in these exploratory approaches. Due to the relationship between

these amino acid transporters and the mTOR signaling pathway, the evaluation of therapeutic responses to mTOR inhibitors using ^{18}F-FDOPA PET is worth particular consideration.

In conclusion, ^{18}F-FDOPA is the most versatile radiotracer for NETs, rendering it clinically very sensitive for tumor localization in the era of ^{68}Ga-DOTA-SSA and theranostic approaches with peptide receptor radionuclide therapy. However, a better understanding of this tracer will without doubt have major implications in the metabolic phenotyping of these tumors. LAT-based imaging by PET also enables the evaluation of specific LAT family inhibitors/modulators as emerging tools for mTOR inhibition.

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