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IMAGE OF THE MONTH

A theranostic approach of [^{68}Ga]Ga-DOTA.SA.FAPi PET/CT-guided [^{177}Lu]Lu-DOTA.SA.FAPi radionuclide therapy in an end-stage breast cancer patient: new frontier in targeted radionuclide therapy

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A 31-year-young female was diagnosed with breast cancer in September 2019. The histopathology revealed atypical cells arranged cords and tubules in the fibrotic stroma suggestive of invasive ductal carcinoma of the breast and the immunohistochemistry reported cells immunopositive for Her2neu, while negative for ER and PR (Fig. 1a). The patient underwent all the standard lines of treatment; however, during treatment, she experienced a new onset of headaches and seizures. A follow-up [^{18}F]F-FDG PET/CT was performed (Fig. 1b) on a dedicated GE Discovery 710* 128 Slice PET/CT Scanner, in which the maximum-intensity projection image (MIP) (Fig. 1b) revealed evidence of extensive involvement of disease in known sites, namely, the loco-regional, lungs, liver and bones. However, due to the detection of a new brain lesion, the patient was classified as having a progressive disease (Fig. 1b).

Based on the small molecule FAP inhibitor (4-quinolinoyl)glycyl-2-cyano-4,4-difluoropyrrolidine, referred to as UAMC1110 [1], a new class of radiopharmaceuticals such as FAPi-02 and FAPi-04 [2, 3] represented highly promising molecular targeting probes when labelled with gallium-68. Recently, another new FAPi agent with further improvised structural features, namely DOTA.SA.FAPi (Fig. 1c), has been designed such that the same molecules can be used for diagnosis and therapy when labelled with the radionuclides gallium-68 and lutetium-177 or actinium-225, respectively [4].

As the patient had depleted all approved therapy options, she was counselled for [^{68}Ga]Ga-DOTA.SA.FAPi exploratory PET/CT scan (GE Discovery 710* 128 Slice PET/CT Scanner). Interestingly, there were one-to-one intense matching lesion uptakes seen in [^{18}F]FDG PET/CT scan MIP and trans-axial fused PET/CT images (yellow box) (Fig. 1b) and [^{68}Ga]Ga-DOTA.SA.FAPi images (MIP, and trans-axial fused PET/CT images (Fig. 1d, red box)). Brain metastasis was confirmed on the magnetic resonance imaging of the brain (Fig. 1d, T2-weighted, axial, turbo spin-echo sequence) which demonstrates hyperintense lesion in the adjacent frontal lobe parenchyma with underlying moderate white matter oedema.

On compassionate grounds, the patient was considered for [^{177}Lu]Lu-DOTA.SA.FAPi treatment. The radiolabelling of [^{177}Lu]Lu-DOTA.SA.FAPi involved heating the reaction vessel containing the mixture of $^{177}LuCl_3$, DOTA.SA.FAPi and 1 M ammonium acetate buffer (pH 5) at 95 °C for 10 min. The radiochemical purity of the labelled product was ~95%. The patient was administered a single cycle of 3.2 GBq (86 mCi) of [^{177}Lu]Lu-DOTA.SA.FAPi, which was diluted in 30 mL normal saline and administered through slow intravenous infusion over a time span of 10 min under steroid coverage. The 24-h post-therapeutic whole-body and SPECT/CT scans (Fig. 1e, green box) were acquired on an Infinia GE Hawkeye dual detector SPECT/CT imaging system. Physiological radiotracer uptake of [^{177}Lu]Lu-DOTA.SA.FAPi (Fig. 1e) was observed in the liver, kidneys,

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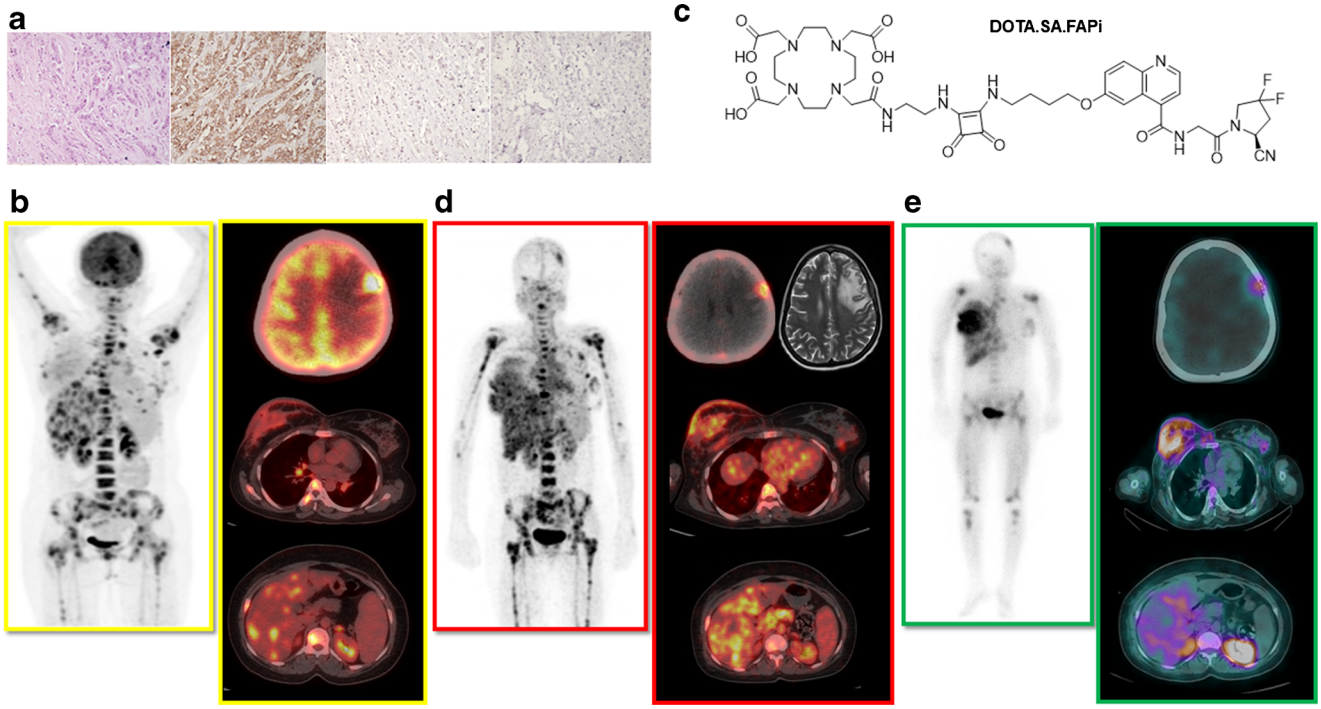

pancreas and background muscle uptake and an intense radiotracer accumulation was noted in all the lesions in concordance to [^{68}Ga]Ga-DOTA.SA.FAPi PET/CT scans (Fig. 1d). In this patient, the dosimetry revealed an approximate absorbed tumour dose of 1.48E mGy/MBq and 3.46 mGy/MBq of [^{177}Lu]Lu-DOTA.SA.FAPi to the primary tumour and the brain metastasis, respectively. However, different cancers demonstrate various uptake patterns of [^{68}Ga]Ga/[^{177}Lu]Lu-DOTA.SA.FAPi radiotracers and hence, the results should be interpreted with caution.

Dosimetric analysis in a larger number of patients with different types of cancers must be studied to standardise the biodistribution, pharmacokinetics and mean absorbed dose estimate of [^{177}Lu]Lu-DOTA.SA.FAPi. Post-treatment, the patient experienced a decrease in the intensity of headaches. Post-treatment 4-week laboratory parameters were well within the normal range and no treatment-related adverse events were observed.

The exact mechanism of action of radiolabelled DOTA.SA.FAPi is not known; however, preliminary information shows that the CAFs help tumour cells to survive and grow in hostile microenvironment by overexpressing fibroblast activation protein (FAP) which in turn is involved in the angiogenesis via the cleavage products of its substrates. Besides these activities, CAFs also secrete a variety of molecules, mostly growth factors and cytokines, namely, the transforming growth factor β (TGFβ). The overexpression of TGFβ has been shown to induce an increased expression of a variety of proteins known as mesenchymal markers including fibronectin, vimentin and matrix metalloproteinases. Thus, the alpha/beta-labelled FAP inhibitors shall deliver a sufficient absorbed radiation dose to kill the tumour cell that constitutes 10% of total tumour mass by bystander effects [5].

Hence, [^{68}Ga]Ga-DOTA.SA.FAPi PET/CT-guided [^{177}Lu]Lu-DOTA.SA.FAPi therapy may open up a new opportunity in breast cancer therapy, particularly for the patients refractory to conventional treatment options. This radio-ligand therapy could be a new milestone in precision oncology. Though the pharmacokinetics and dosimetry data are in the pipeline, this is a feasibility and a proof-of-concept preliminary report.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical clearance Ref. No IECPG-22/2020 for the clinical use of [^{68}Ga]Ga-DOTA.SA.FAPi and Ref. No. IEC/1054/5/2020 for the clinical use of [^{177}Lu]Lu-DOTA.SA.FAPi.

Informed consent Written informed consent from the patient was obtained before the conduction of imaging and therapy.

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