CLINICAL IMAGE

Innovative radioisotope therapy for patients with neuroendocrine tumors using an α (^{225}Ac) emitter labeled somatostatin analog: octreotate

A promising new treatment for advanced progressive neuroendocrine neoplasms

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Neuroendocrine neoplasms (NENs) constitute a diverse group of solid tumors of various locations, and they account for approximately 2% of all malignancies. In 30% of cases, NENs occur in locations other than the gastrointestinal tract, that is, the lungs, bronchi, thymus, thyroid, or ovaries. The current average incidence rate for these diseases is approximately 35 cases per 100 000 inhabitants.[1] However, epidemiological studies show a significant increase in their occurrence. The current recommendations for the treatment of neuroendocrine tumors include surgery, therapy with long-acting somatostatin analogs, somatostatin analogs labeled with β emitters, and locoregional therapies such as radioembolization, radiofrequency ablation, and chemoembolization. The most promising therapy of nonresectable metastatic changes, especially when other available treatment methods are ineffective, is a peptide receptor radionuclide therapy based on somatostatin analogs conjugated with β emitters ^{90}Y[2,3] and ^{177}Lu.[4] Unfortunately, in the cases of tumor recurrence, neoplastic lesions usually show resistance to β radiation, despite the retained increased expression of somatostatin receptors. First trials with another ^{225}Ac-labeled somatostatin analog DOTA-D-Phe1-Tyr3-octreotide (DOTATOC) showed excellent results during the 5-year period of clinical observation.[5] Therefore, a novel study using DOTA-Tyr3-octreotate (DOTATATE) bioconjugate labeled with the α emitter ^{225}Ac was conducted to develop a more effective and safe therapy. In this paper, we report on the therapy with the α emitter ^{225}Ac, which to our knowledge has been so far unprecedented in Poland.

We present preliminary treatment results for a 66-year-old patient with a pancreatic neuroendocrine tumor of G1, according to the World Health Organization criteria, with unresectable liver metastases, after distal pancreatectomy and splenectomy on August 18, 2009. Since April 2015, the patient has been treated with a long-acting somatostatin analog. Due to the progression of the disease found on the computed tomography (CT) scan on August 28, 2019, additional treatment with everolimus under a therapeutic program of the National Health Fund in Poland was started on September 10, 2019. The treatment under the drug program was discontinued in March 2021 due to the disease progression in the form of significant enlargement of the target liver lesions visualized on CT scan on March 22, 2021, and significant increase in serum chromogranin A level.

Due to the progression of the disease, the patient was qualified for the treatment with ^{225}Ac-DOTATATE as part of an experimental rescue therapy (FIGURE 1A–1D).

After the patient had signed an informed consent, the radiopharmaceutical was administered in accordance with the principles of the Helsinki Declaration (Unproven Intervention in Clinical Practice) and the Ethics Committee Agreement (73/2019, issued on June 5, 20219). The patient received 2 cycles of ^{225}Ac-DOTATATE, with an 8-week interval, with the activity of 16.4 and 14.3 MBq, respectively. The observed treatment tolerance was very good. After 2 cycles of the therapy with ^{225}Ac-DOTATATE, an excellent metabolic and structural response visible

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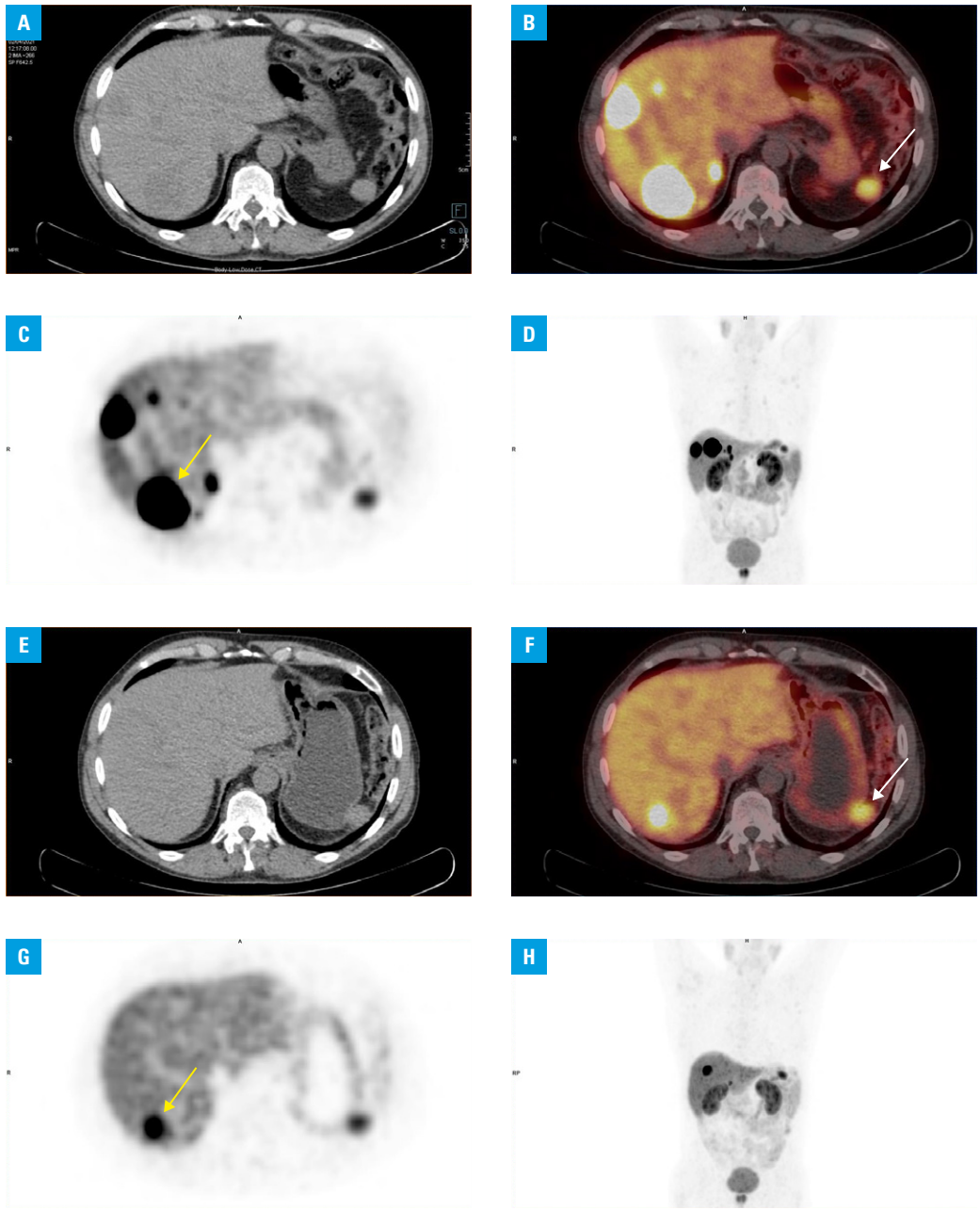

FIGURE 1 **A–D** – somatostatin receptor scintigraphy with ^{68}Ga positron emission tomography/computed tomography (^{68}Ga-PET/CT) scans show increased expression of somatostatin receptors in the liver metastases, seen in panels: **B** – fusion, **C** – transaxial PET, and **D** – maximum intensity projection, which corresponds with hypodense lesions on the transaxial CT in panel **A**. Maximum standardized uptake value body weight (SUV Max-bw) of 73.80 in the dominant tumor, indicated by a yellow arrow in panel **C**, and SUV Max-bw of 10.82 in the accessory spleen indicated by a white arrow in panel **B**. **E–H** – somatostatin receptor scintigraphy with ^{68}Ga-PET/CT. Images show significantly reduced somatostatin receptor expression in the liver lesions in comparison with the baseline, seen in panels: **F** – fusion, **G** – transaxial PET, and **H** – maximum intensity projection, corresponding with the reduced size of the hypodense foci seen on the transaxial CT in panel **E**. SUV Max-bw of 17.5 in the dominant tumor is indicated by a yellow arrow in panel **G**. The visualized location of the accessory spleen indicated by a white arrow in panel **F** shows the same level of somatostatin receptor expression as baseline.

on the control ^{68}Ga-DOTATATE positron emission tomography / CT (FIGURE 1E–1H) was found. In addition, laboratory tests showed a significant reduction of chromogranin A from 851.3 ng/ml to 123.1 ng/ml (reference range 27–94 ng/dl).

Laboratory tests revealed normal values of morphological parameters, hepatic, and renal indices. The patient was qualified to continue the treatment according to the protocol.

To summarize, the innovative therapy with ^{225}Ac-DOTATATE radiopharmaceutical was well-tolerated at this very early stage of treatment, without significant attributable adverse events. The potential long-term toxicity, in particular kidney toxicity, will be monitored. After 2 doses of the targeted α therapy, we found an excellent positive response. Nevertheless, further studies are required to develop optimal time of treatment

and optimal doses of the new radiopharmaceutical to get the best possible treatment response in advanced progressive NEN.

ARTICLE INFORMATION

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