CASE REPORT

Clin Thyroidol 2020;32:39–42.

“Detecting the Undetectable”

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“Detecting the Undetectable”: Utility of ⁶⁸Ga DOTATATE in Medullary Thyroid Cancer

PRIOR to Cabozantinib

ON Cabozantinib

OFF Cabozantinib

6 Weeks

4 Months

- 55 year old man
- History of MTC 3 years ago
- Rising calcitonin & CEA
- Unable to localize by CT or MRI

⁶⁸Ga-DOTATATE PET/CT was effective in both localizing the recurrent MTC and monitoring response to systemic therapy

Brown SJ, Waguespack SG, Chuang HH, Murphy WA, Hu MI. *Clinical Thyroidology*, January 2020

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Patient 1

A 55-year-old man with a history of medullary thyroid cancer (MTC) (*HRAS* G13R+) had been successfully treated with radiotherapy for recurrent disease in bone and liver 3 years earlier. However, owing to newly increasing serum calcitonin (Ctn) and carcinoembryonic (CEA) levels, MRI of the spine and CT of the chest/abdomen were performed, but these failed to show any localizing lesions. A ⁶⁸Ga-DOTATATE PET/CT (Ga-DOTA) then confirmed recurrent metastatic foci in several bony sites, pleura, and the liver. Cabozantinib therapy was begun; 6 weeks later, repeat Ga-DOTA imaging showed notable decreases of the metastatic foci and decreased serum Ctn (from 2962 pg/ml to 1933 pg/ml) and stable CEA concentrations (Figure 1, Panel A-D). Cabozantinib was then discontinued due to medication intolerance and a worsening sacral decubitus ulcer. Off of therapy, repeat Ga-DOTA imaging showed progression of the disease with concurrent uptrending of the serum Ctn to 6171 pg/ml and CEA from 7.0 ng/ml to 207.1 ng/ml.

Patient 2

A 75-year-old woman with MTC (*RET* M918T+) who had undergone total thyroidectomy 4 years earlier was noted at diagnosis to have a new supraclavicular mass. CT of the neck, chest, and abdomen did not show obvious lesions, but Ga-DOTA was able to demonstrate extensive multifocal bone metastases that were also seen with MRI of the spine

and pelvis, but less conspicuously. Denosumab and lanreotide therapy was begun. Repeat Ga-DOTA imaging 6 months later showed a subtle increase in DOTA-avidity of some bony lesions (Figure 1, Panel E-H, page 41) and an MRI 9 months later confirmed slight progression of the bone metastases. The serum Ctn increased from 4999 pg/ml to 6484 pg/ml, corroborating progression despite the systemic therapy, and she was ultimately switched to other FDA-approved systemic therapies.

Patient 3

An 82-year-old man with MTC (*KRAS* Q61R+) who had undergone total thyroidectomy was seen for rising tumor markers 2 years after diagnosis. Staging images with a CT of the neck and chest suggested that the disease was stable in the right supraclavicular region. However, Ga-DOTA imaging showed that the disease had progressed, with involvement at the right supraclavicular, paratracheal, and mediastinal lymph nodes. Vandetanib was begun, and because the patient had chronic kidney disease, Ga-DOTA was used for monitoring while he was on this therapy. After 9 months of vandetanib use, there was gradual progression of disease, as shown by interval increases of the DOTA-avid cervical and superior mediastinal lesions and confirmed by increased serum tumor marker concentrations (Figure 1, Panel I-L). Vandetanib was stopped and the patient was switched to lanreotide therapy.

DISCUSSION

Monitoring of medullary thyroid cancer remains a challenge. A combination of conventional imaging methods is required to obtain an accurate picture of disease burden; even then, the detection of disease recurrence remains around 40% (4). ⁶⁸Ga-DOTATATE PET/CT is increasingly recognized as a useful tool

to identify tumors of neuroendocrine-cell lineage, such as MTCs (3). The high affinity of ⁶⁸Ga to human somatostatin receptor 2 (hSSTR2), in conjunction with PET imaging, allows high-resolution imaging of MTC metastases, which commonly express hSSTR2 (2,3,4).

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Results of recent studies assessing the utility of Ga-DOTA imaging in detecting MTC metastases have been inconsistent, with some studies suggesting its superiority to other imaging methods while others suggest that its performance is similar or inferior to that of standard imaging (1,4,5,6). Overall,

however, Ga-DOTA does appear to be particularly useful in detecting small bone lesions and is more sensitive with higher serum Ctn and CEA levels (1,4, 6). However, the use of Ga-DOTA imaging in monitoring patients with MTC who are on systemic therapy has not been well characterized.

Figure 1. Patient 1’s small bone lesions, such as this right pelvic bone metastasis, were difficult to appreciate on CT (panel A) as compared with Ga-DOTA (panel B). After 6 weeks of systemic therapy, sclerotic changes were visualized in the right ischium on CT (panel C), while decreased activity was seen on Ga-DOTA (panel D). Patient 2’s bone metastases, as demonstrated in the right sacral ala, were also better appreciated on Ga-DOTA (panel F) as compared with CT (panel E). Follow-up imaging after 6 months on lanreotide and denosumab showed sclerotic changes on CT (panel G). Increased activity on Ga-DOTA (panel H) was consistent with disease progression. Patient 3’s CT (panel I) and Ga-DOTA (panel J) reveal anatomically consistent paratracheal disease, though uptake on Ga-DOTA helps to identify active disease. Follow-up imaging after 9 months on systemic therapy revealed increased activity on Ga-DOTA (panel L), supporting that there is disease progression that is not readily discernible on CT (panel K).

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In the three patients presented here, Ga-DOTA imaging demonstrated better detection of metastatic lesions—especially the smaller lesions in bony sites and the pleura—as compared with standard imaging methods such as CT and MRI. Additionally, with Ga-DOTA imaging, metastatic disease was often apparent earlier as compared with imaging methods such as CT, and it helped to identify active/progressive disease versus regression; this impacted initiation of and changes in therapy. For example, the bone lesions seen on CT imaging in Patients 1 and 2 showed sclerotic changes on follow-up imaging while the patient was taking systemic therapy, but this represented regression in Patient 1 and progression in Patient 2 on the basis of Ga-DOTA uptake intensity and serum tumor marker trends. More

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subtle progression of lymph node disease was better appreciated with this imaging method in Patient 3; serial CT imaging had suggested stable lymph node disease, but Ga-DOTA uptake instead demonstrated progression in the paratracheal and mediastinal nodes. Ultimately, the progression of MTC as shown on Ga-DOTA imaging helped direct management of systemic therapy in all three of our patients.

These cases underscore the potential value of Ga-DOTA imaging not only in staging select patients with MTC, in whom DOTATATE-avid lesions may not be readily apparent on other more conventional cross-sectional imaging methods, but also highlight its use in evaluating the response to systemic therapies.

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