Submitted: 27.12.2021
Accepted: 10.03.2022
Early publication date: 18.07.2022

Endokrynologia Polska
DOI: 10.5603/EP.a2022.0060
ISSN 0423–104X, e-ISSN 2299–8306
Volume/Tom 73; Number/Numer 5/2022

Disseminated medullary thyroid cancer — an alternative therapeutic approach

Maja Wilczyńska[1], Mateusz Suchmiel[1], Grzegorz Sokołowski[2], Alicja Hubalewska-Dydejczyk[2], Małgorzata Trofimiuk-Müldner[2]

[1]*Students' Scientific Group of Endocrinology at the Department of Endocrinology, Jagiellonian University Medical College, Krakow, Poland*
[2]*Chair and Department of Endocrinology, Jagiellonian University Medical College, Krakow, Poland*

Key words: *medullary thyroid cancer; vandetanib; lanreotide; PRRT; targeted radiotherapy*

There is no established medical therapy for advanced medullary thyroid carcinoma (MTC). The tyrosine kinase inhibitors (TKIs) vandetanib and cabozantinib are currently recognized as the preferred systemic therapy resulting in partial response (vandetanib 45%, cabozantinib 28%) or stable disease (vandetanib 87%, cabozantinib not estimated) [1]. Unfortunately, adverse events, such as diarrhoea, rash, and palmar-plantar erythrodysesthesia are seen in 10–63% of patients and may result in drug withdrawal [1]. In the case of TKI treatment failure, other therapeutic modalities, with lesser evidence, may be offered. Herein, we present a case of an MTC patient treated with radiolabelled and cold somatostatin analogues.

A 78-year-old female underwent a complete thyroidectomy with a middle neck compartment and a modified left lateral neck lymphadenectomy due to sporadic medullary thyroid cancer (MTC) of the left thyroid lobe (cT3N1b) in July 2017. Concurrently, she was treated surgically for breast cancer (lumpectomy, followed by right mastectomy in November 2017). Her medical history also revealed type 2 diabetes, hypertension, hypercholesterolaemia, meningioma, and glaucoma.

Due to markedly elevated calcitonin concentration (Fig. 1), the patient was scheduled for PET/CT with [^{68}Ga] Ga-DOTATOC, which revealed somatostatin receptor expressing MTC metastases to the liver, mediastinal lymph nodes, and lungs (Fig. 2A). In March 2018, therapy with vandetanib (300 mg daily) was initiated. The treatment was discontinued after two weeks due to side effects, such as rapid kidney function deterioration [creatinine 109–131 μmol/L, urea 9.3–10.7 mmol/L, glomerular filtration rate (GFR): 36–45 mL/min/1.73 m^2], weakness, hypoglycaemia, diarrhoea, and loss of appetite. The symptoms resolved within one week after therapy withdrawal.

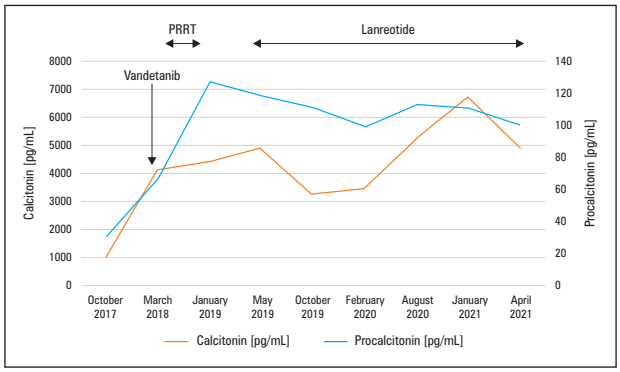

Figure 1. *Calcitonin (normal range 0–10 pg/mL) and procalcitonin (normal range < 0.1 ng/mL) concentrations during the patient's treatment. PRRT — peptide receptor radionuclide therapy*

The patient was subsequently qualified for peptide receptor radionuclide therapy (PRRT) and received 3 cycles of 100 mCi of [^{177}Lu]Lu-DOTA-TATE in July, October, and December 2018. As progression of the disease was noted (both biochemical and on imaging) (Fig. 1, Fig. 2B), the therapy with cold somatostatin analogue (lanreotide autogel 120 mg) was started in April 2019. The therapy resulted in the initial stabilization of the disease on imaging (Fig. 2C). Due to an increase of calcitonin levels since mid-2020 (Fig. 1), as well as progression on imaging (Fig. 2D), the therapy was discontinued in April 2021. The patient was offered cabozantinib treatment in July 2021, but she opted against therapy with TKI.

Małgorzata Trofimiuk-Müldner, Chair and Department of Endocrinology JUMC, ul. Jakubowskiego 2, 30–688 Kraków, Poland, tel: +48 12 400 2332; e-mail: malgorzata.trofimiuk@uj.edu.pl

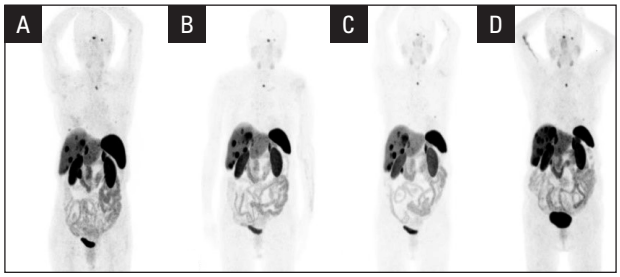

Figure 2. *^{68}Ga-DOTATE PET/CT MIP (maximum intensity projection) images:* **A.** *October 2017 — tracer uptake in liver metastases (Krenning score 3), vague lesions in the both lungs supradiaphragmally (Krenning score 1), mediastinal lymph node (Krenning score 2), as well as in the left-sided meningioma (Krenning score 2);* **B**. *April 2019 — progression of the liver metastases; no uptake in the lungs;* **C.** *December 2019 — stabilization of the liver metastases, faint uptake in the small metastasis in the left lung;* **D.** *April 2021 — progression of the liver metastases, still visible single lesion of faint tracer uptake in the left lung*

Because somatostatin receptor expression is frequently present in MTC, PRRT is an alternative treatment modality when TKIs are contraindicated or poorly tolerated. Currently there is insufficient evidence, but a review of studies claims that there is a potential benefit of using PRRT in MTC patients [objective response rate (ORR) in 7.31–11.64% and disease control rate (DCR) in 60.02–63.65% of MTC patients], with ^{177}Lu-based therapy showing better therapeutic effects than ^{90}Y-based therapy [2]. The presented patient, however, progressed shortly after PRRT had been completed.

MTC, as a neuroendocrine cancer, may be targeted with cold somatostatin analogues (SSAs). Cell line experiments suggest that in a subset of MTCs, SSAs may inhibit cell proliferation and tumour invasiveness, with little or no effect on calcitonin secretion [3]. The reports on effectiveness of SSAs in the management of advanced MTC are, however, contradictory. One study showed no reduction of carcinoembryonic antigen (CEA) and calcitonin concentrations in a long-term observation, and no structural response in 5 patients [4]. On the other hand, a case of a patient with asymptomatic metastatic MTC treated with lanreotide, who achieved a nearly 3.5-year remission after an 11-month treatment, has been reported [5]. In our patient, lanreotide therapy resulted in stabilization of the disease for approximately 1.5 years. Stabilization of procalcitonin concentration and a short-term decrease in calcitonin concentration could be explained by other, somatostatin receptor-dependent mechanisms regulating calcitonin secretion and cell proliferation.

Beneficial effects of a combination of SSAs with interferon (alleviation of symptoms and a reduction in calcitonin and CEA concentrations with no significant change in tumour lesions size in 6 patients, improvement of symptoms without major tumour regression in 7 patients) or recombinant interleukin 2 (IL-2) (partial response in 3 patients and stable disease in 3 patients) in MTC patients were also noted [4, 6].

Other, partly experimental, therapeutic methods for MTC including PRRT targeting CCK2 receptors, external beam radiotherapy (EBRT) for lung, bone, and brain metastases, and novel TKIs, particularly the RET inhibitor selpercatinib, recently approved by the Food and Drug Administration (FDA) for therapy of advanced or metastatic RET-mutant medullary thyroid cancer, are options, if available.

In conclusion, the optimal therapeutic approach to medullary thyroid cancer is still to be established. The rarity of the disease, particularly requiring systemic treatment, limits the possibility of large randomized controlled trials on different therapeutic modalities. The choice of and response to therapies may be influenced by the patients' age, comorbidities, and the molecular and genetic profile of the tumour (including driver mutations, receptors expression, or desensitization in the course of treatment). It seems that desensitization of somatostatin receptors is one of the causes of long-term SSAs treatment failure in MTC patients.

Conflict of interest

The authors declare that they have no conflicts of interest concerning this article. All authors have read and approved the final form of this article.

Funding

This study did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

References

1. Viola D, Elisei R. Management of Medullary Thyroid Cancer. Endocrinol Metab Clin North Am. 2019; 48(1): 285–301, doi: 10.1016/j.ecl.2018.11.006, indexed in Pubmed: 30717909.
2. Lee DY, Kim YI. Peptide Receptor Radionuclide Therapy in Patients With Differentiated Thyroid Cancer: A Meta-analysis. Clin Nucl Med. 2020; 45(8): 604–610, doi: 10.1097/RLU.0000000000003110, indexed in Pubmed: 32520503.
3. Giardino E, Catalano R, Mangili F, et al. Octreotide and pasireotide effects on medullary thyroid carcinoma (MTC) cells growth, migration and invasion. Mol Cell Endocrinol. 2021; 520: 111092, doi: 10.1016/j.mce.2020.111092, indexed in Pubmed: 33248230.
4. Díez JJ, Iglesias P. Somatostatin analogs in the treatment of medullary thyroid carcinoma. J Endocrinol Invest. 2002; 25(9): 773–778, doi: 10.1007/BF03345511, indexed in Pubmed: 12398235.
5. Cano JM, Galán R, López R. Recurrent Metastatic Medullary Thyroid Carcinoma: A Case of Sustained Response to Prolonged Treatment with Somatostatin Analogues. Thyroid. 2017; 27(11): 1450–1455, doi: 10.1089/thy.2016.0540, indexed in Pubmed: 28927353.
6. Vitale G, Lupoli G, Guarrasi R, et al. Interleukin-2 and lanreotide in the treatment of medullary thyroid cancer: in vitro and in vivo studies. J Clin Endocrinol Metab. 2013; 98(10): E1567–E1574, doi: 10.1210/jc.2013-1443, indexed in Pubmed: 23884781.