Case report

Hypothyroidism caused by cabozantinib therapy of clear cell renal cell carcinoma – case report, own experience

Agnieszka Buraczewska, Joanna Kardas, Beata Młot, Wojciech Solarek, Anna Waśko-Grabowska

Oncology Clinic of the Military Institute of Medicine

Correspondence:
Agnieszka Buraczewska
Oncology Clinic of the Military Institute of Medicine
04-141 Warsaw, ul. Szaserów 128
e-mail: aburaczewska@wim.mil.pl

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ABSTRACT

Cabozantinib, the latest available in Poland medication for the treatment of renal cell carcinoma, registered in this indication by the European Medicines Agency (EMA) in September 2016, has been available in several cancer centers in Poland since November 2016 as part of the expanded access program.

Primary hypothyroidism is a common complication during thyrosine kinase inhibitors (TKI) treatment, although there are few reports of its occurrence during treatment with cabozantinib, which belongs to this medication group.

We present a case of rapid development of clinically apparent hypothyroidism after cabozantinib treatment and report data on this complication in the group of our patients.

Key words: cabozantinib, renal cell carcinoma, hypothyroidism

INTRODUCTION

Cabozantinib, the latest available in Poland medication for the treatment of renal cell carcinoma, inhibits numerous tyrosine kinase receptors associated with tumor growth and angiogenesis, pathological bone remodeling, drug resistance and the process of cancer spreading. It is an inhibitor of MET (hepatocyte growth factor receptor protein) and VEGF (vascular endothelial growth factor), it also inhibits other tyrosine kinases, including GAS6 (AXL), RET, ROS1, TYRO3, MER, stem cell factor receptor (KIT), TRKB, fms-like tyrosine kinase 3 (FLT3) and TIE-2 [1].
In 2014 cabozantinib was registered in the treatment of adult patients with progressive, inoperable, locally advanced or metastatic medullary thyroid carcinoma. In September 2016, the European Commission under the central procedure issued a decision of new substance registration in the treatment of advanced renal cell carcinoma after previous anti-VEGF therapy.

In the III phase registration study METEOR, in which participated 658 patients in a good and very good performance status, from all prognostic MSKCC (Memorial Sloan Kettering Cancer Center score system) groups, a statistically significant improvement in PFS (progression free survival) was observed for cabozantinib (median survival 7.4 months) in comparison with everolimus (median survival 3.8 months).

In an interim OS (overall survival) analysis, statistically significant improvement was observed for patients randomized to the cabozantinib in comparison with everolimus (median survival 21.4 months vs. 16.5 months; HR = 0.66 [0.53–0.83], p = 0.0003) [2, 3].

From November 2016 cabozantinib is available in several oncology centers in Poland within the expanded access program.

Primary hypothyroidism (caused by thyroid damage) is a common phenomenon during the treatment with some tyrosine kinase inhibitors, especially frequent during the treatment with axitinib, sunitinib, imatinib, sorafenib, pazopanib, regorafenib [2, 4–7, 10, 17, 18]. In most cases hypothyroidism occurs during the first 8 weeks of treatment [6]. In the METEOR study, the prevalence of hypothyroidism in 1st and 2nd grade in the course of therapy with cabozantinib was 23% [2]. Because the medication is relatively new, there are only few reports of this [7].

The variable incidence associated with different TKIs is most likely related to certain differences in their mechanism of action. Next to hypothyroidism, hyperthyroidism may also occur with TKI, but it is much less frequent and transient [8]. The course of hypothyroidism is in most cases mild, however, unrecognized hypothyroidism can lead in the long run to serious, even fatal sequelae. Many authors suggest that beyond hypertension and hand–foot syndrome, hypothyroidism can be a biomarker of the effectiveness of treatment with one of the most widely used TKIs – sunitinib [9–11].

The mechanism of the rise of hypothyroidism during TKI therapy remains unknown, but there are several theories explaining this problem. VEGF is a signaling protein that stimulates the formation of new blood vessels, and the inhibition of VEGF reduces the blood flow through the tumor and the formation of new blood vessels within it. But yet, regression of capillary vessels is also observed in healthy tissues. Thyroid is the gland with the highest blood flow per mass unit, hence reducing this flow would result in the impairment of its function [12].

Another postulated cause of hypothyroidism is the change in the metabolism of thyroxine and triiodothyronine. In the prospective study of renal cell carcinoma and gastrointestinal stromal tumors (GIST) in humans and rats, Kappers et al. found that after 10 weeks of TKI therapy increased thyroid-stimulating hormone (TSH) levels have been associated with a reduced proportion of triiodothyronine to the inverse triiodothyronine (increased concentration of inactive form) [13].

Another potential mechanism of development of hypothyroidism is the inhibition of thyroid iodine uptake during TKI therapy [14].

Recently published research on this subject suggests the involvement of autoimmune processes in the development of hypothyroidism with sunitinib. Pani et al. investigated a group of 27 patients with metastatic neoplasms (renal cell carcinoma, GIST) and found that 25% of them had ATPO antibodies (anti-thyroid peroxidase antibodies). This group was more likely to develop hypothyroidism during sunitinib therapy. These patients presented significantly longer FPS compared to the group without ATPO antibodies [15].
It is described a decrease in thyroid volume during TKI therapy, but this does not prejudge the mechanism of hypothyroidism development [16].

CASE PRESENTATION

A 61-year-old man whose right kidney was removed on March 12, 2015 for renal cell carcinoma (histopathology: Fuhrman grade 3, pT2NxMx), with lung and mediastinal lymph nodes metastases (computed tomography 20.10.2015) and with progression after

11 cycles of sunitinib (partial remission according to RECIST 1.1 was obtained) was admitted to the oncology division to start second-line therapy with cabozantinib within the expanded access program. At the time of admission his general condition was quite good, the patient complained of dry cough, dyspnea on exertion, pain of right hip, weight loss about 4 kg per month. He had not fever. Performance status WHO 1.

His laboratory tests have shown no contraindications for the use of cabozantinib. Concentration of TSH, fT_3 and fT_4 (free T_3 and free T_4) remained within normal limit, the aminotransferase activity was below 3 times the upper limit of normal.

His computed tomography performed before the use of cabozantinib described the normal picture of the central nervous system. There were numerous enlarged hilar and mediastinal lymph nodes (tracheal left lower lymph nodes 39 × 32 mm, below left main bronchus 24 × 19 mm, bronchial right 26 × 19 mm, lateral from left pulmonary artery 32 × 21 mm). There were numerous lung metastases bilaterally (seg. 6 PP – several adjacent foci, the largest: 24 mm and to the back 31 mm, seg. 9 PL – polycyclic focus under pleura 30 mm, seg. 10 PL – pleural nodule 19 mm). The metastatic lesions in other abdominal and pelvic organs have not been described. A large, richly vascularized nodular mass in the proximal stem and partly lower part of the neck of right femur, grown into the marrow cavity, infiltrating muscles medially from the femur, size in transverse plane up to 89 × 54 mm, was also described.

While the first outpatient check-up, after a month of treatment, the patient reported general weakness, drowsiness, tendency to constipation. In the patient's opinion, the color of his voice changed, he became colorless and quiet. In the physical examination his blood pressure was low (110/80 mmHg, HR 60/min, regular), without any significant abnormalities. In laboratory tests, except for stable elevation of transaminases, hypothyroidism was reported – fT_4 6.19 pmol/l (normal limit: 12–22 pmol/l), fT_3 2.62 pmol/l (normal limit: 3.2–6.9 pmol/l), thyrotropic hormone (TSH) 164.7 uIU/ml (normal limit: 0.27–4.2 uIU/ml). A gradually increased dose of L-thyroxine was introduced what caused improvement in the quality of voice, a gradual decline of feelings of weakness, regular bowel movements. In thyroid ultrasonography (9.03.2017) decreased echogenicity of the gland was observed with no other changes. The presence of anti-peroxidase antibodies (ATPO) was not found.

After 3 cycles of cabozantinib therapy, in computed tomography the disease was stable according to RECIST 1.1 with a tendency to decrease of metastatic changes. The patient continues treatment with a dose of 60 mg daily.

Our experience

For 8 months cabozantinib has been available at the Military Medical Institute as well as in a dozen other oncological centers in Poland within the framework of the extended access program. The medication is used in second and subsequent lines of treatment of generalized stadium of clear cell renal cell carcinoma.
In the group of 31 adults (6 women, 25 men) remaining under the care of the Men's Oncology Clinic of Military Medical Institute during the treatment of generalized clear cell renal cell carcinoma with cabozantinib, who remain in a favorable and intermediate risk group according to MSKCC, 61% (19 persons) was diagnosed with hypothyroidism *de novo* (14 persons) or deeping of hyperthyroidism found earlier (5 persons) has been reported.
In the whole group of patients, evaluation of the effectiveness of treatment with imaging technique (computed tomography) after 3 cycles of treatment was performed in 15 patients (48.4%) so far, finding a partial remission of the disease according to RECIST 1.1 in 5 cases. All these patients were *de novo* diagnosed with hypothyroidism or there was a need to escalate the dose of L-thyroxine used before the treatment. In 9 cases, the disease was stable according to RECIST 1.1 (7 patients with hypothyroidism or worsening of the already existing equilibrium of thyroid function, 2 patients with stable pre-existing hypothyroidism). In one case the progression of the disease was confirmed and the patient remained in euthyreosis.

DISCUSSION

This clinical case presents the rapid development of symptomatic hypothyroidism in patients treated with cabozantinib in the second line of treatment for clear cell renal cell carcinoma. In this situation, the implementation of levothyroxine substitution therapy (LT_4) is undisputable due to the presence of clinical symptoms.

Polish recommendations for subclinical and thus asymptomatic hypothyroidism suggest to start treatment in patients diagnosed with or previously treated for thyroid disease at TSH concentration of more than 4–5 mIU/l and in patients without thyroid disease at TSH more than 10 mIU/l. Early treatment should be given to people under 65–70 years of age, with elevated levels of ATPO, coronary heart disease, heart failure or risk factors for these diseases. Other recognized indications for therapy in asymptomatic cases are pregnancy or reproduction plans, dysmenorrhea, infertility, iodine 131 treatment or strumectomy, neck irradiation,

hyperlipidemia. Recently proposed additional indications for treatment, taking into account the adverse effects of subclinical hypothyroidism on cardiovascular system and cardiological risk: diastolic heart failure, diastolic hypertension, diabetes, smoking. Patients over 80 years of age should not be treated for asymptomatic hypothyroidism if TSH is below 10 mIU/l [4]. The recommended interval for performing thyroid function tests is 1–2 months [4, 17, 18]. The recommended interval for performing thyroid function tests is 1–2 months [4, 17, 18]. Replacement therapy for hypothyroidism is usually lifelong [4].

The implementation of levothyroxine substitution improves the quality of life, reducing the symptoms of general weakness, depression, reducing cardiovascular risk, and is beneficial for body metabolism [4]. Although in oncology there are reports of a positive correlation between hypothyroidism and prolonged survival of patients with cancer [19–21]. It is suggested that thyroid hormones stimulate other growth factors, which may be a growth stimulating signal in various types of cancer [22].

CONCLUSIONS

During the cabozantinib therapy, it is necessary to closely monitor thyroid function, as dysfunction of it is a very common complication. The presented case illustrates the rapid development of hypothyroidism (progression of TSH within one month from normal to 164 uIU/ml), therefore the interval of 4 weeks seems to be optimal.

Symptoms of hypothyroidism are not specific, so an oncologist taking care of patients treated with inhibitors of tyrosine kinases, being aware of the high probability of this complication, must be sensitive to it.

Based on the data presented, no positive association of hypothyroidism with PFS prolongation cannot be asked. A larger group of patients and a longer follow-up period should be required.

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