Rectal and Liver Metachronous Cancers and Sorafenib-Induced Thyroid Dysfunction

Ancuta Augusta Gheorghisan Galateanu1,2, Mara Carsote2,3*, Dan Peretianu4, Cristina Iosif5,6, Dana Terzea2,5 and Catalina Poiana2,3

1Department of Cellular and Molecular Medicine, “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania
2C.I.Parhon” National Institute of Endocrinology, Bucharest, Romania
3Department of Endocrinology, “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania
4SCM Poverine Medical Centre, Bucharest, Romania
5OncoTeam Monza Hospital, Bucharest, Romania
6“Sfanta Maria” Hospital, Bucharest, Romania

Abstract

Background: The tyrosine kinase inhibitor, a new treatment option in hepatic carcinoma, may associate thyroid dysfunction like spontaneously remitting thyrotoxicosis followed by hypothyroidism.

Case report: A 66-year Caucasian female was first diagnosed and operated for a moderately differentiated rectal adenocarcinoma of 5 centimeters. Immunohistochemistry showed positive VEGF receptor 2 (Flk-1, KDR), VEGF receptor 1(Fit-1), and a Ki67 of 30%. 4 years later a hepatic adenocarcinoma (clear cells variant) was diagnosed. After surgery, daily 400 mg of sorafenib was introduced. Three months later mild symptomatic thyrotoxicosis was seen: palpitations, fatigue, and mild bilateral pedal clonus. Thyroid-stimulating hormone (TSH) was suppressed (0.044 µIU/mL, normal levels between 0.4 and 4.5 µIU/mL), and free levothyroxine (fT4) elevated. The TSH receptor antibody, the antithyroglobulin and antithyreoperoxidase antibodies were negative. Thyroid ultrasound pointed hypoechoenic, inhomogeneous aspects. She received beta-blocker and within two months thyrotoxicosis remitted but TSH progressively increased suggesting hypothyroidism with level less 5 µIU/mL so no replacement levothyroxine therapy was added yet.

Discussions: The exact mechanism of the tyrosine kinase inhibitors-related thyroid malfunction is not fully understood. Non-autoimmune destructive thyroiditis of unknown trigger causes thyrotoxicosis and later hypothyroidism as seen in our case. The clinical features vary from one person to another. The hormone replacement is rarely necessary. The baseline cancer seems irrelevant for thyroid toxicity. In our unusual case the patient had a history of two metachronous cancers. The thyroid follow up is essential during each patient therapy yet a specific pattern of follow-up is not precisely designed.

Conclusion: The tyrosine kinase inhibitor-induced thyroid dysfunction includes both thyrotoxicosis and hypothyroidism. We emphasize the idea of periodic endocrine evaluation in oncologic patient treated with this class of drugs.

Keywords: Sorafenib; Tyrosine kinase inhibitor; Thyrotoxicosis; Thyroiditis; Hypothyroidism

Introduction

The drugs involved in destructive thyroiditis exponentially extended during the last decades. The tyrosine kinase inhibitors especially those with small-molecule as sorafenib, sunitinib or axitinib represent an oral treatment options in hepatic or advanced renal cell carcinoma, breast cancer, gastrointestinal stromal tumors, metastatic iodine-refractory thyroid malignancy, or (potential) ovarian cancer [1,2]. This class has less toxicity than traditional systemic cytotoxic drugs although it is potentially correlated to thyroid dysfunction thus a multidisciplinary approach is essential in managing the patient. The initial observations that thyroid malfunction is a relatively rare reaction have been replaced to the concept that actually there is a frequent thyroid disturbance [3-5]. The thyroid involvement includes spontaneously remitting thyrotoxicosis and hypothyroidism [3-5]. The severity of the thyrotoxicosis varies considerably from one patient to another up to thyroid storm especially after sorafenib [3]. One in four cases with sorafenib-induced hypothyroidism had before (within months) a transient thyrotoxicosis associated with a limited number of symptoms or even completely asymptomatic [4,5].

The prevalence of the thyroid diseases in tyrosine kinase inhibitors users varies. For example 36% of a series with 42 gastrointestinal stromal tumors had hypothyroidism within a median of 37 weeks after sunitinib [6]. Up to 85% of a series with patients under sunitinib for renal cells cancer developed hypothyroidism [7]. 8 out of 25 patients with advanced renal cancer developed hypothyroidism and 6 of them had transient thyrotoxicosis [8]. In a series of 33 patients with metastatic renal cells cancer, 6 of 6 (100%) patients treated with axitinib, 9 of 15 (60%) patients treated with sunitinib, and 6 of 12 (50%) patients treated with sorafenib had thyroid dysfunction. [9]. It seems that sunitinib is more frequent correlated with hypothyroidism while sorafenib causes thyroid malfunction in two thirds of the patients, less than a third of them will eventually need thyroid replacement [4]. Pazopanib, another tyrosine kinase inhibitor, has the lowest rate of thyroid toxicity (one tenth of patients) [10].

We report an unusual case with transient mild thyrotoxicosis and later hypothyroidism while using sorafenib in liver cancer, after a previous rectal neoplasia.

*Corresponding author: Mara Carsote, C.I.Parhon National Institute of Endocrinology, Bucharest, Romania, Aviatorilor Ave 34-36, postal cod 011863, Romania, Tel: +40744851934; Fax +40213176007; E-mail: carsote.mil@hotmail.com

Received May 16, 2015; Accepted May 28, 2015; Published May 27, 2015


Copyright: © 2015 Gheorghisan Galateanu AA, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Case Report

A 66-year Caucasian female coming from non-endemic zone has an irrelevant personal and family history of thyroid disease. She was first diagnosed with a rectal tumor of 5 centimeters (cm) that was laparoscopically removed 4 years ago. Pathological report indicated moderately differentiated adenocarcinoma with no lymph nodes invasion (Figure 1a). The immunohistochemistry showed negative reaction for VEGF, EGFR, CerbB2, COX2, zonal positive reaction for VEGF receptor 2 (Flk-1, KDR), VEGF receptor 1 (FLt-1) (Figure 1b), and a Ki67 of 30% (Figure 1c). While she was followed-up a hepatic tumor of 10 cm was revealed by ultrasound (and then confirmed by computed tomography) at the inferior level of right liver lobe. Persistent high levels of hepatic enzymes were registered (up to a level three times higher than normal). A partial liver resection of the fifth hepatic segment was performed (together with colecistectomy). The histological exam showed a second neoplasia (not a hepatic metastasis) represented by a hepatic adenocarcinoma (clear cells variant) (Figure 1d). The immunohistochemistry revealed VIM negative in tumor cells, Ck7 negative in tumor cells and positive in biliary ducts, negative reaction for EMA, CD10, CROMO, Ck19, and diffuse positive reaction for OCH1E5 in tumor cells. Therapy with sorafenib was started. At baseline she had normal thyroid function and 3 months later she developed clinically mild thyrotoxicosis (while she was on a daily dose of 400 miligrams sorafenib). She accused palpitations, fatigue, associating a mild bilateral pedal clonus, some proximal myopathy, and tachycardia (up to 105 beats per minute). The thyroid hormones revealed a very low level of thyroid-stimulating hormone (TSH) of 0.044 µIU/mL (normal levels are between 0.4 and 4.5 µIU/mL), and elevated free thyroxine (fT4) of 26.8 pmol/L (normal levels are between 12 and 22 pmol/L). The TSH progressively increased up to hypothyroidism ranges but the levels remained less than a level of 5 µIU/mL so no levothyroxine therapy was added yet.

Figures:

Figure 1: (a) Moderately differentiated rectal adenocarcinoma, hematoxili- eosin stain 40× (b) moderately differentiated rectal adenocarcinoma. The areas with positive VEGF receptor 1/Flt-1 100× (c) moderately differentiated rectal adenocarcinoma. Areas with positive Ki67 100× (d) Hepatocellular carcinoma clear cell variant hematoxilin-eosin stain 20×.

Figure 2: Thyroid ultrasound with unhomogenous aspect.

Discussions

The exact mechanism of the tyrosine kinase inhibitors-related thyroid toxicity is not fully understood. Apparently the hypothyroidism is secondary to a destructive thyroiditis which causes first a thyrotoxicosis episode [11,12]. The thyroiditis is pointed in our patient by specific thyroiditis-like ultrasound pattern. One of the hyperthyroidism triggers is the iodine exposure but some data report that sunitinib actually blocks thyroid iodine uptake that is why the iodine induced thyrotoxicosis is less possible [11,12]. Two reports from 2011 in patients with hepatocellular carcinoma treated with sorafenib confirmed that thyroiditis is the major part of sorafenib-induced hypothyroidism [12]. Other mechanism is partly explained by main drug targets: raf- ras pathway, VEGF, FMS-like tyrosine kinase 3 (FLT3) [13]. Another potential path involved in sorafenib-related tumor shrinkage is Jak2- Stat3-Mcl1 axis [13]. Extremely high values of serum TSH are registered in some patients treated with tyrosine kinase inhibitors regardless a previously episode of thyrotoxicosis that is recently considered as a pattern of inappropriate elevation of TSH syndrome [14]. But in most of the cases the TSH goes high normal or slightly elevated as we registered. Another hypothyroidism related mechanisms is the fact that tyrosine kinase inhibitors act as an inhibitor of angiogenesis, and vascular endothelial growth factor (VEGF), having a dual effect on the tumor cells and vasculature with thyroid atrophy [15]. The thyroid anomalies are more frequent seen in relationship to sunitinib probably because of the effect not only on VEGF receptor 2 (Flk1, KDR) but also on VEGF receptor 1 (Flt-1), and PDGFR (platelet-derived growth factor receptor) [15]. Other mechanism is abnormal iodine uptake at the level of thyroid and consecutive inhibition of thyroid peroxidase [11,16]. It is generally accepted that no autoimmune mechanism is involved in thyroid dysfunction thus the thyroid related antibodies are negative as in this case where all three thyroid antibodies [17].

The clinical management in oncologic patients includes a multidisciplinary approach: oncology, surgery, pathology, and endocrinology. In patients intend to be treated with tyrosine kinase inhibitors a baseline endocrine (thyroid) evaluation is necessary and then close monitoring every four to eight weeks. A specific pattern of follow-up is not yet precisely designed [15-17]. The thyroid toxicity is registered in a general panel of adverse reactions since the tyrosine
kinase inhibitors as sorafenib (a multikinase inhibitor) or sunitinib (an inhibitor of both VEGFR and PDGFR) have proven their oncologic efficacy and had their approval by Food and Drug Administration since 2005/2006 [18]. The frequent dose interruptions are seen including from the first month of therapy [18]. The discontinuation of the drug in case of severe negative effects does not exclude the possibility of drug re-administration [19]. Severe thyrototoxicosis may represent a life threat situation with rapid medical intervention and hypothyroidism needs long term thyroid hormones replacement at high TSH values while the patient is still under tyrosine kinase inhibitor [18-20]. Different data suggest that thyroid replacement therapy does not influence the surviva [20]. Regarding our case the thyroid hormones excess was clinically evident and the hypothyroidism remained asymptomatic. If the targeted anti-cancer therapy is started in a previously known patient with hypothyroidism the levothyroxine requirement increases [21]. In a cohort study of 1214 patients under sorafenib, and 1295 patients under sunitinib, 6.3% respective 13.7% associated hypothyroidism (incidence rate of 12.1 respective 24.2 per 100 person-years) [22]. The thyroid toxicity does not seem to be influenced by the type of cancer [22]. In our case two major observations are necessary: the diagnosis of thyrototoxicosis was later than seen in most of the studies, and the patient has been diagnosed during her life with two cancers. It is difficult to suggest that metachronous cancer increase the risk of sunitinib related thyroid malfunction.

As the prognosis factors of thyroid dysfunction are still a matter of date, a continuous follow-up of the patients currently treated with tyrosine kinase inhibitors is necessary. A retrospective chart review from 2005 to 2011 pointed that drug induced hypothyroidism is correlated to a longer progression-free survival, and it may be considered as a surrogate in evaluation of disease control under therapy [23]. Similar data are displayed by a prospective study on patients with metastatic renal cancer treated with sorafenib or sunitinib between 2006 and 2009. 31.8% of patients developed hypothyroidism, and this particular group had a longer progression-free survival: 16 ± 0.8 months versus 6 ± 0.8 months, p value=0.032 [20]. 76% of patients with hypothyroidism increased TSH after first months of therapy [20]. A meta-analysis from 2014 (including 12 clinical trials) showed the hypothyroidism relative risk of 3.59 (96% CI=2.4-5.38, p ≤ 0.0001) and the type of tumor did not influence this risk [24].

Recent data pointed that thyroid anomalies may be a class effect, and the general (as well as thyroid) toxicity is not connected to a specific pattern of pharmacokinetics regarding age, sex, ethnicity or weight (that is why the dose are not adjusted based on these factors) [25]. The controversies related to the timing and adequate dose in thyroid hormone replacement are still a matter of debate [26]. Many authors consider that unless clinical sever symptoms the hypothyroidism should not be treated [27] For example apart from low thyroid hormone levels levothyroxine therapy should be initiated in case TSH greater than 10 mIU/l [28]. The thyrototoxicosis management varies from no therapy to corticosteroids and beta-blockers [28]. Thionamides are sometimes empirically administered but there is no real benefit in destructive thyroiditis [28]. In case of hepatic cancer with high serum liver enzymes this biochemistry aspect may also be caused by the thyroid malfunction. Based on all these particular and general data that we presented we conclude the practical endocrine aspects in patients diagnosed with different types of cancer who need to be treated with thyrosine kinase inhibitors. At baseline TSH and freeT4 control is necessary and then periodically repeated (like every 1-2 months). If thyroid dysfunction is found the investigations should also include thyroid ultrasound and antibodies. If thyrototoxicosis is registered the symptomatic therapy as beta-blockers is advised and the thyroid function measured every month up to its normalization. If TSH is increased the levothyroxine replacement therapy is better to be postpone unless TSH is very high while checking TSH level every 4 to 8 weeks. In most of cases the anticancer drug should be continued despite thyroid dysfunction.

**Conclusion**

The tyrosine kinase inhibitor-induced thyroid toxicity is presented as both thyrotoxicosis and hypothyroidism. The periodic thyroid check up is necessary. The clinical aspects vary and the underlying cancer seems to be irrelevant in this adverse reaction.

**References**

18. La Vine DB, Coleman TA, Davis CH, Carbene CE, Davis WB (2010) Frequent


