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Amaya Sainz de los Terreros[a,*], Álvaro Cecilio[b]

[a]*Servicio de Endocrinología, Hospital García Orcoyen, Estella, Navarra, Spain*
[b]*Servicio de Medicina Interna, Hospital García Orcoyen, Estella, Navarra, Spain*

*Corresponding author.
E-mail address: amaya_ st@hotmail.com
(A. Sainz de los Terreros).

Management of hypothyroidism secondary to tyrosine kinase inhibitors: description of treatment in three distinct clinical settings

Manejo del hipotiroidismo secundario a inhibidores de la tirosina quinasa: descripción del tratamiento en tres escenarios clínicos distintos

The pharmacological development of tyrosine kinase inhibitors (TKIs) is relatively recent, and TKIs are currently used as first or second line therapy for some solid and hematological tumors[1]. Several studies have shown TKIs to be able to induce thyroid changes in 30% to 80% of treated patients depending on the series[2-5].

The mechanisms proposed for the development of hypothyroidism during treatment with TKIs include thyroid atrophy induced by the drug either directly (cytotoxic versus autoimmune thyroiditis) or by inhibiting thyroid vascularization, the progressive depletion of thyroid reserves, and inhibition of iodine uptake.

Recommendations are available for the management of hypothyroidism induced by TKIs[6], but none of them are based on scientific research, but rather on observations made in standard clinical practice and on retrospective studies. Three different clinical scenarios of TKI-induced hypothyroidism assessed in our outpatient clinics are reported.

Case 1

A 62-year-old female patient diagnosed with metastatic gastrointestinal stromal tumor (GIST). She was initially treated with imatinib (with no thyroid function impairment),but, due to therapeutic failure, this was switched to sunitinib 50 mg PO daily for 4 weeks with a 2 week rest (4-2 regimen). Laboratory tests during the third week of the fourth cycle showed subclinical hypothyroidism (TSH 7.90 µIU/mL FT_4 1.2 ng/dL, FT_3 32 pg/mL) with negative antithyroid antibodies (ATAbs). The patient was therefore referred to the endocrinology outpatient clinic for work-up. Since laboratory tests had been performed during the third week of the cycle, the tests were scheduled for the start and end of the following cycle. The results from laboratory tests performed on day 1 of the cycle after the 2 week rest period were normal (TSH 4.00 µIU/mL, FT_4 1.4 ng/dL, FT_3 3.9 pg/mL, negative ATAbs), and the results of tests performed on the last day of the cycle were consistent with asymptomatic subclinical hypothyroidism requiring no treatment (TSH 6.80 µIU/mL, FT_4 1.4 ng/dL, FT_3 3.6 pg/mL, negative ATAbs). The same occurred in the two subsequent cycles, and clinical observation with no replacement therapy was therefore decided upon.

Case 2

A 44-year-old female patient diagnosed with stage IV ectopic pleural thymoma. She was initially treated with sunitinib 50 mg PO daily (compassionate use) using a 4-2 regimen, which was reduced at the end of the third cycle due to a hypertensive crisis (her blood pressure was normal prior to treatment). No thyroid function tests were available before the end of the third cycle. At her first visit to the endocrinology outpatient clinic, laboratory test results performed at the end of the third cycle were consistent with subclinical hypothyroidism (TSH 12.80 µIU/mL, FT_4 1.0 ng/dL, FT_3 2.6 pg/mL) and ATAbs were negative. The patient was being treated with sunitinib 25 mg PO on alternate days (without rest) and enalapril 20 mg PO. She reported moderate to severe fatigue, in addition to non-quantified weight gain and cold intolerance. Treatment was started with levothyroxine (LT4) 125 mcg PO daily because she was on uninterrupted treatment and thyroid function could not therefore be assessed either at the start or end of the cycle. In the 12th week of treatment with LT4, the patient was found to have normal thyroid function (TSH 4.50 µIU/mL, FT_4 1.4 ng/dL, FT_3 3.0 pg/mL, negative ATAbs) and to show a significant improvement in fatigue symptoms. Replacement therapy was therefore continued.

Case 3

A 52-year-old female patient with a history of high blood pressure being treated with valsartan 320 mg/hydrochlorothiazide 12.5 mg PO daily. She had been diagnosed with advanced renal cell carcinoma (RCC) and was failing to respond to interferon alfa (IFN-α). Sorafenib 200 mg PO every 12 hours was being administered as a second line treatment. Prior to treatment with interferon alfa, the patient was euthyroid and had no ATAbs. When treatment with IFN-α was completed, the patient showed subclinical hypothyroidism (TSH 6.50 µIU/mL, FT_4 1.1 ng/dL, FT_3 2.4 pg/mL) and positive ATAbs (anti-TPO 210 IU/mL and anti-Tg 448 IU/mL). After 8 weeks of treatment with sorafenib, the patient showed clinical and biochemical primary hypothyroidism (TSH 13.60 µIU/mL, FT_4 0.5 ng/dL, FT_3 1.6 pg/mL) associated with higher antibody levels (anti-TPO 670 IU/mL and anti-Tg 860 IU/mL), and an endocrinological assessment was therefore requested. Treatment was started at our outpatient clinic with LT4 100 mcg PO daily (except in the 2 week rest period to prevent hyperthyroidism during this phase), and the dose was titrated up to 175 mcg PO daily on week 18 of treatment (except in the 2 week rest period). At that time, the patient was euthyroid (TSH 4 µIU/mL, FT_4 0.8 ng/dL, FT_3 2.0 pg/mL), asymptomatic, and with persistently positive ATAbs (anti-TPO 320 IU/mL and anti-Tg 510 IU/mL). Therefore,the same treatment was continued.

These three case reports describe different scenarios that may be found in standard clinical practice.

The first report describes the typical clinical presentation of a patient treated with sunitinib, usually based on the 4-2 regimen. While no clinical studies testing the different recommendations in the literature[7,8] are available, it is generally advised to assess thyroid function on the first day of each cycle, although we also assess thyroid function at the end of each cycle.

The results of laboratory tests requested by the patient's oncologist were not valid because they were obtained at almost the end of the cycle, and thyroid function tests were therefore repeated at the start and end of three consecutive cycles. The patient was euthyroid at the start of each cycle and showed asymptomatic subclinical hypothyroidism requiring no treatment at the end of each cycle. Clinical observation with thyroid function monitoring was therefore decided upon.

The impact of cyclic subclinical hypothyroidism on cardiovascular risk and bone metabolism is unknown, and so could be a research area of special interest. Wolter et al[7], in a review of management of TKI-induced hypothyroidism, proposed that TSH should be measured on day 1 (first day) and day 28 (last day) of the first 4 sunitinib cycles and, if normal TSH levels were maintained, TSH measurements should be repeated every 3 cycles.

A controversy in the management of TKI-induced hypothyroidism relates to the decision as to when replacement therapy with LT4 should be given and as to what the target thyroid hormone levels should be, because *in vitro* studies have related this therapy to an increase in tumor growth[9], although studies are also available reporting conflicting results in this regard[10].

In our second case report, the patient apparently had no thyroid dysfunction (no prior laboratory tests were available) until the end of the third cycle, when the dose was reduced by a half and administered on alternate days and with no rest period after the occurrence of a hypertensive crisis. The prescription information for sunitinib suggests the possibility of dose modifications based on individual safety and tolerability levels. Since initial patient assessment showed clear clinical and biochemical primary hypothyroidism and sunitinib was being administered continuously (every 48 hours) without the usual 2 weeks' rest, replacement therapy was started, resulting in clinical and biochemical improvement after 12 weeks of treatment with LT4.

The American Thyroid Association suggests that replacement therapy with LT4 should follow the same guidelines as those used for patients with primary and subclinical hypothyroidism. However, it is not completely clear whether recommendations by the ATA and other scientific societies are valid for cancer patients being treated with TKIs. In this regard, the conduct of clinical trials with low LT4 doses has been recommended[8].

The third case report refers to a patient given sorafenib as second line treatment after the failure of IFN-α therapy. Indication of sorafenib as second line treatment for advanced RCC after IFN-α has failed has opened up a debate about the pathogenesis of hypothyroidism in these patients because cytokines (including interferon-α and IL-2) may cause primary hypothyroidism. Interferon-α and interleukin-2 may impair thyroid function in patients being treated for melanoma and RCC, causing thyroiditis. Increased ATAb levels or hypothyroidism with no antibodies in patients treated with interferon-α have been associated with a better prognosis in patients with RCC or metastatic melanoma[6].

Our patient showed euthyroidism with positivization of ATAbs at the end of her treatment with interferon-α (and at the start of sorafenib treatment). After the eighth week of sorafenib treatment, she showed frank primary hypothyroidism (autoimmune versus cytotoxic thyroiditis) and was therefore administered replacement therapy, which achieved euthyroidism with persistence of high ATAb levels.

Clinical assessment of thyroid dysfunction secondary to TKI therapy will be increasingly common as indications of TKIs for first or second line treatment of oncological conditions increase.

The clinical relevance of hypothyroidism, the LT4 dosage to be used in patients with thyroid dysfunction after TKI therapy, and the appropriate time to start treatment are all issues requiring further clarification and should be prospectively addressed in adequately designed clinical trials. Close cooperation between oncologists and endocrinologists will help clarify these issues, improving the treatments used and the quality of life for cancer patients.

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Gilberto Pérez López[a,*], Marta Carrasco De La Fuente[b], Miriam Menacho Román[c], Olga González Albarrán[a], Marta Cano Megías[a]

[a]*Servicio de Endocrinología y Nutrición, Hospital Universitario Ramón y Cajal, Madrid, Spain*
[b]*Servicio de Endocrinología y Nutrición, Hospital La Moraleja, Madrid, Spain*
[c]*Servicio de Bioquímica Clínica, Hospital Universitario Ramón y Cajal, Madrid, Spain*

*Corresponding author.
E-mail address: beto_med@hotmail.com (G. Pérez López).

Primary adrenalin sufficiency due to bilateral adrenal lymphoma

Insuficiencia suprarrenal primaria por linfoma adrenal bilateral

To the Editor:

A patient with adrenal insufficiency secondary to a bilateral primary adrenal lymphoma (PAL) is reported. A brief review of the literature on the most relevant clinical and pathological characteristics of this condition is also provided.

An 80-year-old female patient with a history of high blood pressure complained of constitutional symptoms, nausea, and vomiting during the previous four months. Supplementary tests performed revealed persistently elevated serum LDH levels (2,000 IU/L) and normal electrolyte levels. A CT scan of chest and abdomen (Fig. 1) showed masses in both adrenal glands. A study of the adrenal axis showed ACTH levels ranging from between 300 and 500 pg/mL (normal range,10-50 pg/mL) and basal cortisol levels ranging from between 10 and 14 μg/dL (normal range, 3-18 μg/dL). Following glucocorticoid replacement therapy, laparotomy was performed, at which a biopsy could only be performed because both lesions were surgically non-resectable. A pathological study reported a large diffuse B-cell non-Hodgkin lymphoma, CD20 positive and Ki-67 positive in approximately 90% and P53 positive in approximately 80%. No bone marrow infiltration was found. Chemotherapy was started and well tolerated, and, at the time of writing, response to it is pending evaluation.

Primary lymphoma of the adrenal gland accounts for approximately 1% of extranodal lymphomas, and there are less than 100 tumors of this type reported in the literature[1]. It is more common in males than in females (2/1), and mean age at tumor occurrence is approximately 68 years[2]. Bilateral adrenal involvement is found in 65% of cases[3]. Ninety percent of PALs are large B-cell non-Hodgkin lymphomas[4].

The most common initial symptoms include abdominal pain, lumbar pain, fever, and weight loss. In patients with bilateral involvement, some degree of adrenal insufficiency may be found in up to 60% of cases, but insufficiency is usually subclinical in most of them.

Despite its low incidence, PAL should be included in differential diagnosis of an adrenal gland together with other malignant tumors such as carcinoma of the breast and lung, gastrointestinal tract tumors, and malignant melanoma, in which the incidence of adrenal metastases, often bilateral, is high. Differential diagnosis should also include other con-

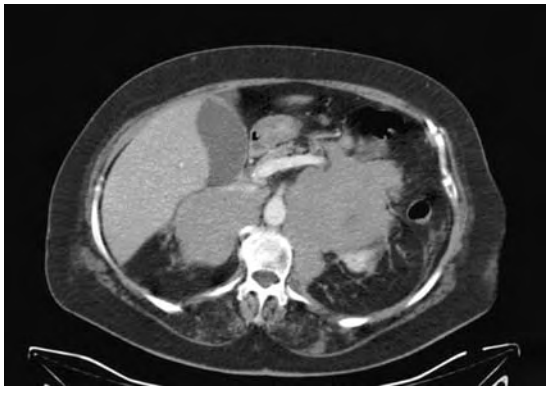

Figure 1 CT of the chest and abdomen.