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Consensus

Expert opinion on thyroid complications of new anti-cancer therapies: Tyrosine kinase inhibitors

*Avis d'experts sur les complications thyroïdiennes des nouvelles thérapies anti-cancéreuses :
inhibiteurs de tyrosine kinase*

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Abstract

Thyroid pathology is the most frequent form of endocrinopathy during tyrosine kinase inhibitor (TKI) treatment. Dysthyroidism occurs in 10% to 80% of cases, depending on diagnostic criteria. In patients with intact thyroid gland prior to TKI treatment, incidence of dysthyroidism is 30–40%, with subclinical presentation in half of cases. It mainly involves hypothyroidism, preceded in 20–40% of cases by transient thyrotoxicosis that may go overlooked. The pathophysiological mechanism is “vascular” thyroiditis induced by the anti-angiogenic action of TKIs. Between 20% and 60% of patients receiving levothyroxine ahead of TKI treatment show increased levothyroxine requirements. TKIs should not be discontinued because of onset of thyroid dysfunction. Treatment is symptomatic in case of thyrotoxicosis, and levothyroxine replacement therapy is initiated in case of symptomatic hypothyroidism or TSH > 10 mIU/L. During TKI treatment, TSH should be assayed monthly, or at end of off-period (i.e., day 1 of new cycle after interruption), for the first 6 months, then every 2–3 months or in case of clinical signs of dysthyroidism. In patients already treated for hypothyroidism, TSH should be assayed monthly for 3 months, then every 3 months throughout treatment. At TKI termination, remission of hypothyroidism is possible but unpredictable, and progressive discontinuation of levothyroxine may be considered under monitoring. Teamwork between oncologists and endocrinologists improves screening and treatment of thyroid dysfunction, enabling the patient to be better accompanied during treatment.

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1. Epidemiology and pathophysiology

Thyroid side-effects commonly occur in tyrosine kinase inhibitor (TKI) treatment, and are of 2 types: onset of dysthyroidism in patients with intact thyroid, and increased levothyroxine requirements in patients receiving levothyroxine replacement therapy.

1.1. Risk of dysthyroidism

Analysis of the literature finds dysthyroidism incidences ranging from 10% to 80%, depending on diagnostic criteria, and whether subclinical forms are included and whether pre-treatment assessment was available [1–8]. In most recent studies,

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Table 1
TKIs and risk of dysthyroidism (2013, JCEM, MB Lodish).

Risk of dysthyroidism	TKI
High	Sunitinib, Sorafenib, Imatinib
Moderate	Axitinib, Cabozantinib, Dasatinib, Erlotinib, Nilotinib, Pazopanib, Vandetanib
Not reported	Bosutinib, Crizotinib, Gefitinib, Lapatinib, Ruxolitinib, Vemurafenib

however, incidence of dysthyroidism during TKI treatment, in euthyroid patients with intact gland before treatment, is around 30–40%, half of which are subclinical forms (TSH between 5 and 10 mIU/L) [9,10]. It mainly consists in hypothyroidism, usually primary but preceded in 20–40% of cases by transient thyrotoxicosis, which may be overlooked [11]. As shown in Table 1, there are drug-class effects: thyroid side-effects are most frequent with molecules inhibiting not only VEGFR-2 and -3 but also VEGFR-1 and with those, such as sunitinib, inhibiting PDGFR [8,12] (cf. Table 1). In all reports, thyroid involvement is independent of the type of underlying neoplasia. The impact of TKI treatment duration on dysthyroidism risk is debated, being reported in certain studies, for example on sunitinib [13].

The pathophysiological mechanism is “vascular” thyroiditis induced by the anti-angiogenic effect of TKIs. Molecules acting against VEGFR-1 and PDGFR notably induce thyroid devascularization, leading to lesional thyroiditis then thyroid hypothyrophy [12,14]. This thyroiditis has no autoimmune component.

Decreased vaso-active factor production has been implicated in very early hypothyroidism, accompanied by thyroid atrophy; such hypothyroidism can be reversible [15].

1.2. Increased thyroxine requirements

Increased levothyroxine requirements under TKI are reported in 20–60% of patients with levothyroxine replacement therapy following thyroidectomy for other reasons [16–22]. This is partly due to the digestive side-effects of TKIs, with reduced intestinal absorption of thyroid hormone [23], and may also be due to direct effects of TKIs on thyroid hormone transport and metabolism [24]. Several mechanisms have been suggested:

- dose-dependent inhibition of MCT8 action on T4 and T3 brain transport, accounting for increased thyroxine requirements and for the possible reversibility of hypothyroidism on termination of TKI treatment [25];
- increased type-2 deiodinase activity, with around 20% reduction in T3/T4 and T3/rT3 ratios [24,26];
- hypothalamo-pituitary dysfunction, with reduction in biological TSH activity and in TRH secretion by the paraventricular hypothalamic nucleus due to reduced nitric oxide production [7];
- reduced TSH clearance due to reduced liver glycoprotein endocytosis (which is tyrosine kinase-dependent) [27];

- TKI interaction with retinoic acid receptors may prevent heterodimerization between retinoic acid receptors and T3 receptors [28].

2. Clinical and biological diagnosis

Symptoms are generally non-specific: asthenia, constipation, depression, memory disorder, cold intolerance in the case of hypothyroidism, and palpitations and weight-loss in thyrotoxicosis. They may be mistakenly attributed to underlying malignancy, anti-cancer treatment or support treatments (morphine derivatives, anxiolytics, etc.). Clinical diagnosis of dysthyroidism under TKIs is thus difficult, and relies above all on TSH assay, which ideally should be compared to pre-treatment values.

TSH elevation indicates hypothyroidism, while low or undetectable levels suggest thyrotoxicosis. Before incriminating TKIs, the TSH abnormalities should be read against possible confounding factors: general health and nutritional status, contrast-agent administration during cancer monitoring, co-treatments for neoplasia or other pathology (e.g., amiodarone).

R1: Diagnosis of dysthyroidism during TKI treatment is based on plasma TSH assay, clinical signs being poorly specific.

In the TKI-related thyrotoxicosis phase, complementary examinations usually point to thyroiditis: heterogeneous echogenic aspect on ultrasound, reduced thyroid vascularization on Doppler, absence of antithyroid antibodies and blank scintigraphy, interpretation of the latter being often ambiguous in subjects who have received iodine contrast-agents in oncologic monitoring.

Hypothyroidism may reflect late phase of destructive TKI-induced thyroiditis, associated with antithyroid antibodies or not, with the thyrotoxicosis phase being possibly overlooked, or else due to autoimmune thyroiditis whether aggravated or induced by TKIs. Anti-thyroperoxidase antibody assay and ultrasound aspect may contribute to etiological diagnosis.

3. Severity of dysthyroidism

The CTCAE side-effects grading system used in therapeutic trials in oncology is unsuited to management of thyroid side-effects. Severity should be assessed in terms of TSH/ft4: abnormal TSH with normal ft4 indicates subclinical dysthyroidism; abnormal TSH with abnormal ft4 indicates clear dysthyroidism.

4. Treatment

The thyrotoxicosis phase is generally brief and spontaneously resolving. Treatment is required only in symptomatic forms, and is discussed with the oncologist. It is preferably based on non-cardio-selective beta-blockers. Antithyroid drug treatment has

R2: The most frequent etiological diagnosis for dysthyroidism under TKIs is “vascular” thyroiditis.

- R2a. In thyrotoxicosis, in case of doubt between TKI-related thyroiditis in thyrotoxicosis phase or other hyperthyroidism diagnosis, etiological assessment should comprise: anti-TSH-receptor antibodies and/or thyroid ultrasound coupled to Doppler and/or thyroid scintigraphy, depending on clinical orientation on anterior cervical palpation and on availability of the examinations.
- R2b. In hypothyroidism, in case of doubt between TKI-related thyroiditis in hypothyroidism phase or other hypothyroidism diagnosis, anti-TPO antibody assay (with or without thyroid ultrasound) is recommended.

R3: Thyrotoxicosis severity is assessed by fT4 elevation, and hypothyroidism severity by elevation of TSH (then of fT4 reduction if TSH > 10 mIU/L). Management of thyroid dysfunction under TKIs should be discussed between the endocrinologist and TKI prescriber.

no role to play in this context of thyroiditis. Corticosteroids may be considered in rare severe, prolonged, poorly tolerated forms.

R4: Thyrotoxicosis should be treated in case of clinical symptoms: non-cardio-selective β -blockers are the treatment of choice when not contraindicated. Antithyroid drug treatment is not recommended except in Graves’s disease.

In proven or clinical hypothyroidism (TSH > 10 mIU/L and/or low fT4), levothyroxine replacement therapy should be initiated at 1–1.6 μ g/kg/day, if no ischemic or rhythmic cardiopathy requires progressive up-dosing. Several studies reported no adverse effects of hormone replacement on cancer prognosis, which is even improved in proven hypothyroidism for which replacement therapy is indicated [29]. These findings, however, are not free of possible bias related notably to duration of intensified treatment in responders, who may be more exposed to treatment-related thyroid side-effects.

In subclinical hypothyroidism (TSH 5–10 mIU/L with normal fT4), a second sample should be taken 2–4 weeks later, as hypothyroidism may be transient [30,31]. If biological hypothyroidism is confirmed, levothyroxine treatment may be

considered in symptomatic patients and/or in case of anti-TPO antibody elevation.

R5: Treatment of TKI-induced hypothyroidism is based on levothyroxine, and is indicated in symptomatic patients in case of:

- TSH > 10 mIU/L;
- TSH 5–10 mIU/L on 2 assays, with clinical symptoms, anti-TPO antibodies or ultrasound signs of autoimmune thyroiditis.

Levothyroxine 1–1.6 μ g/kg/day may be initiated, but should be adapted to therapeutic objectives. Up-dosing and therapeutic objectives are the same as in patients not under TKI, and should be adapted to age, comorbidity (including ischemic and rhythmic cardiopathy) and life-expectancy.

Apart from rare thyrotoxic episodes [32], onset of thyroid dysfunction under TKIs is not life-threatening, and treatment should be continued if effective: reducing dosage or duration could reduce efficacy, especially as onset of hypothyroidism may predict better response to TKI [33]. In a recent retrospective study of 568 patients under long-course TKIs, median survival for euthyroid patients was 685 days (95% CI, 523–851 days) versus 1005 days (95% CI, 634–1528) in subclinical hypothyroidism and 1643 days (95% CI, 1215–1991) in proven hypothyroidism; the difference was significant for proven hypothyroidism (HR = 0.56, $P < 0.0001$) after adjustment on age, gender, and cancer type and stage [34]. Thus, in case of onset of hypothyroidism under TKI, dosage should not be reduced and treatment should not be terminated, but rather levothyroxine treatment should be adapted. In severe thyrotoxicosis, treatment may be interrupted temporarily if necessary, but should not be terminated.

R6: In severe thyrotoxicosis, TKI treatment may be interrupted temporarily after discussion with the oncologist, but should never be definitively contraindicated.

5. Monitoring

5.1. Before TKI treatment

Pre-treatment, pre-existing dysthyroidism should be screened for on TSH assay. Thyroid function is often affected by prior treatments, iodine saturation or pre-existing autoimmunity. Pre-treatment TSH assay is also necessary in hypothyroid patients with replacement therapy, due to risk of imbalance under TKIs.

To date, no predictive factors for dysthyroidism have been identified. Thyroid autoimmunity is rare and the predictive value of antithyroid antibodies is unproven [2,4]. Prior thyroid pathology does not contraindicate initiation of TKI treatment.

R7: Before initiating TKIs, TSH should be assayed to screen systematically for thyroid dysfunction requiring specific management. Systematic pre-treatment screening for antithyroid autoimmunity by anti-TPO or anti-TSH-receptor antibodies is not recommended.

R8: Pre-existing treated thyroid pathology or dysfunction does not contraindicate TKI treatment. Thyroid dysfunction secondary to primary TKI treatment does not contraindicate switching to a different TKI.

5.2. During TKI treatment

Time to onset of dysthyroidism varies widely between reports; sometimes later than 1 year, it peaks during the first 6 months. Monitoring is comparable for hypothyroidism under TKI and non-iatrogenic hypothyroidism. In hypothyroid patients under levothyroxine replacement therapy prior to TKI treatment, TSH monitoring is necessary for levothyroxine dose adjustment if needed. Table 1 shows molecules most associated with therapeutic imbalance. Levothyroxine requirements can increase considerably, by up to 50%, making balance difficult to achieve, especially in case of sequential TKI administration.

R9: During TKI treatment, screening for dysthyroidism is based on TSH assay, which should be monthly (or at end of off-period: i.e., day 1 of new cycle in case of treatment interruption) for the first 6 months, then every 2–3 months or in case of clinical signs of dysthyroidism. In patients already treated for hypothyroidism, TKIs may increase levothyroxine requirements, and TSH should be monitored regularly: monthly for 3 months, then every 3 months throughout treatment.

5.3. After TKI treatment

Recovery of euthyroidism or normal thyroid function on termination of TKIs is found at a rate that is not well determined [35,36]. Reduced thyroid volume on ultrasound under TKIs may be predictive of permanent hypothyroidism.

R10: Recovery of normal thyroid function in TKI-related hypothyroidism is possible but unpredictable. Levothyroxine replacement therapy should be continued throughout TKI treatment. At end of TKI treatment, levothyroxine may be progressively discontinued, under monitoring.

Disclosure of interest

The authors declare that they have no competing interest.

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