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Consensus

## Endocrine side-effects of new anticancer therapies: Overall monitoring and conclusions

*Consensus de la Société française d'endocrinologie sur la toxicité endocrinienne des nouveaux traitements anticancéreux : surveillance globale et conclusions*

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### Abstract

The present final consensus statement of the French Society of Endocrinology lays out the assessments that are to be systematically performed before and during anticancer treatment by immunotherapy, tyrosine kinase inhibitors or mTOR inhibitors, even without onset of any endocrinopathy. It also discusses the CTCAE adverse event grading system in oncology and the difficulty of implementing it for endocrine side-effects of these anticancer treatments. Notably, this is why certain treatment steps applied in other side-effects (e.g., high-dose corticosteroids, contraindications to immunotherapy, etc.) need to be discussed before implementation for endocrine side-effects.

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New anticancer therapies are increasingly used, entailing a high incidence of endocrinopathy, of between 5% and 20% depending on the molecule. Teams managing these patients often wonder how these endocrinopathies should best be graded, and this question can impact treatment. In oncology, toxicity grade may lead to initiation of corticosteroid therapy and/or cessation of anticancer treatment, but this attitude is not well-suited to the endocrine complications.

This final section of the present recommendations deals with this question, and with pretreatment assessment and monitoring of patients receiving immunotherapy, tyrosine kinase inhibitors (TKI) or mTOR inhibitors, with a view to standardizing monitoring and management of specifically endocrine side-effects, especially within dedicated multidisciplinary team meetings [1].

### 1. Endocrinopathy grading: is the CTCAE applicable to endocrine side-effects?

Anticancer treatment side-effects are generally graded according to the Common Terminology Criteria for Adverse Events (CTCAE), on a 1-to-5 scale: 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening, 5 = toxicity-related death (National Cancer Institute 2009). However, the distinction between grades 2 and 3, for example, is often difficult to draw in the case of endocrine side-effects, although the corresponding treatments will be very different. In immunotherapy, the implicated molecule is withdrawn in case of grade 2 events and resumed when symptoms and biological disorder resolve; glucocorticoids (0.5–1 mg/kg) should be initiated in case of symptoms persisting more than a week. In grades 3 and 4, high-dose glucocorticoids (1–2 mg/kg) are recommended, with withdrawal of the implicated molecule; in grade 4, resumption of the implicated molecule is theoretically definitively contraindicated [2,3].

The case of endocrine or metabolic side-effects, however, is quite specific. They are rarely grade 3 or 4. Moreover, any initiation of replacement treatment is considered as grade 2, in which case the anticancer molecule should be withdrawn. However, the mechanism underlying endocrinopathy is such that molecule withdrawal is not indicated in hypothyroidism or pituitary deficiency; these endocrinopathies are usually treated by hormone replacement therapy, in which the problem of balance rarely arises. In severe forms (mainly thyrotoxicosis), the anticancer regimen can be temporarily interrupted.

Likewise, there is no real evidence that high-dose corticosteroids alter the natural history of immunotherapy-induced endocrinopathy, and they should therefore not be prescribed in this indication. They may be administered as symptomatic treatment in severe forms, such a clinically very severe hypophysitis with disabling headache or very severe thyrotoxicosis. In the case of TKI, corticosteroids may be considered for severe thyrotoxicosis.

Thus, adverse event grading and the corresponding measures seem not to be applicable for endocrine side-effects. In particular, treatment withdrawal due to endocrine toxicity should

imperatively be discussed between oncologist and endocrinologist, to avoid harm to the patient.

R1: Endocrinopathies induced by the new anticancer treatments are usually easily balanced by replacement therapy in case of deficiency or improved by symptomatic treatment in case of hyperfunction. The CTCAE should therefore be applied only cautiously: onset of endocrinopathy does not in itself contraindicate anticancer treatment. In severe forms (severe thyrotoxicosis, orbitopathy, acute corticotroph deficit, etc.), treatment may be interrupted and resumed in agreement with the oncologist. Anticancer therapy-induced endocrinopathy does not contraindicate using a different anticancer treatment, even of the same class.

R2: Except in clinically severe situations, high-dose glucocorticoids are not recommended in case of anticancer therapy-induced endocrine side-effects. This recommendation does not include high-dose hydrocortisone replacement therapy for suspected adrenal failure or corticotroph deficiency. Corticosteroids may be considered in case of disabling headache associated with hypophysitis or severe thyrotoxicosis under immunotherapy, or of severe thyrotoxicosis under a TKI.

### 2. What initial endocrinologic assessment and follow-up for patients under immunotherapy?

Patients under immunotherapy are at risk of hypophysitis (up to 20% of those under anti-CTLA4), thyroiditis (1–12% of those under anti-CTLA4) and, to a lesser extent, diabetes or primary adrenal failure (Fig. 1). Hormonal assessment ahead of immunotherapy allows normal pretreatment work-up, and is also useful for monitoring hormonal parameters during treatment.

R3: Before initiating immunotherapy, initial assessment should comprise: fasting venous glycemia, natremia, TSH, T4I, 8 am cortisol (without corticosteroid intake), LH, FSH, testosterone in males and FSH in menopausal females (gonadotropic axis activity in non-menopausal females without contraception is determined by cycle regularity).

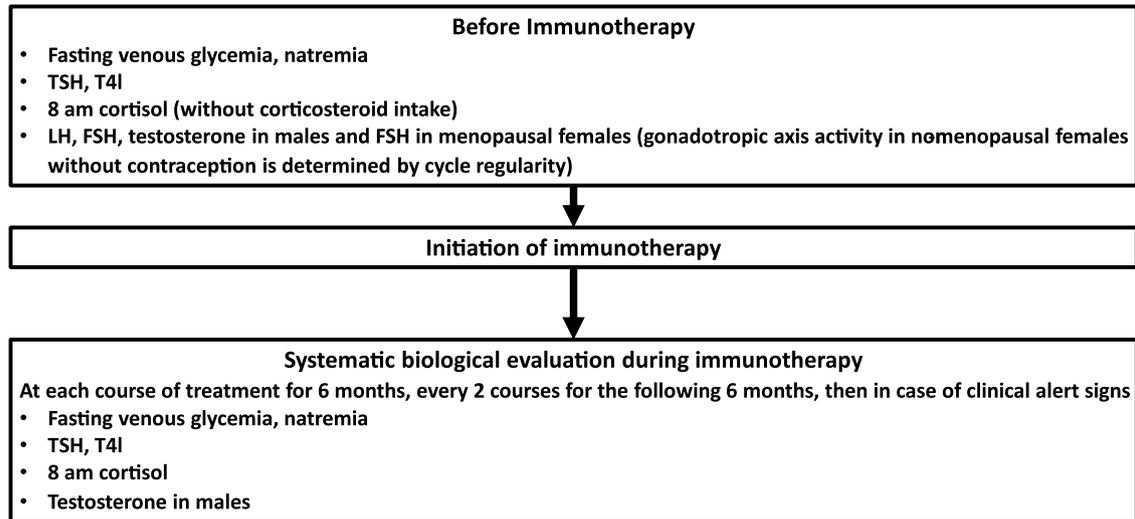


Fig. 1. Biological evaluation and immunotherapy.

Risk of onset of endocrinopathy is greater during the first months of treatment. Monitoring should therefore be closer during this period, then continued systematically although less closely during the following 6 months; afterward, risk of onset is low although not non-existent, some cases having been reported several years later. Complications should therefore always be screened for in case of clinical alert signs. Throughout the immunotherapy course, patient and oncologist should be particularly alert to possible signs of hypophysitis (headache, nausea, pituitary deficit signs), dysthyroidism, adrenal deficiency and explosive-onset diabetes (polyuropolydipsic syndrome, weight-loss), although clinical signs may be relatively non-specific in these cases of advanced cancer.

the course of TKI treatment, onset of endocrinopathy is more frequent during the first months but may occur at any time; regular monitoring is therefore mandatory. Possible TKI side-effects are detailed in the respective previous sections dealing with the thyroid and metabolic toxicity associated with these molecules.

R5: Before initiating a TKI, initial assessment should comprise: TSH, fasting venous glycemia and full lipid assessment.

R4: During immunotherapy treatment, systematic assessment should be made of fasting venous glycemia, natremia, TSH, T4I, 8 am cortisol, and testosterone in males, at each course of treatment for 6 months, every 2 courses for the following 6 months, then in case of clinical alert signs. It is indispensable to educate patient and oncologist regarding clinical signs of endocrinopathy.

R6: During TKI treatment, fasting venous glycemia should be measured 2 weeks after initiation, followed by measurement of TSH and fasting venous glycemia monthly (or at end of off-time: i.e., on day 1 of the new cycle in discontinuous regimens) throughout treatment. Lipid assessment should be checked at 3 months, then every 6 months throughout treatment.

### 3. What initial endocrinologic assessment and follow-up for patients under TKI?

Patients under TKI are at risk of dysthyroidism (around 20% of cases), metabolic disorders such as dyslipidemia (about 50% of cases) and diabetes (15–40% of cases) (Fig. 2). Conversely, some patients show improved glycemia or even hypoglycemia, requiring close surveillance and patient education regarding signs of hyper- and hypo-glycemia. Pretreatment assessment ensures normal initial metabolic work-up before initiation of immunotherapy and screens for diabetes risk factors. It is useful for monitoring hormonal parameters under treatment. During

### 4. What initial endocrinologic assessment and follow-up for patients under mTOR inhibitors?

Patients under mTOR inhibitors are at risk of diabetes (12–50% of cases) and dyslipidemia (7–88% of cases) (Fig. 3). Initial assessment therefore screens for pre-diabetes and pre-existing diabetes or dyslipidemia. Depending on cardiovascular and oncologic prognosis, treatment may be begun ahead of initiation of the mTOR inhibitor. During treatment, risk of onset is higher in the first month but persists throughout, making regular monitoring mandatory.

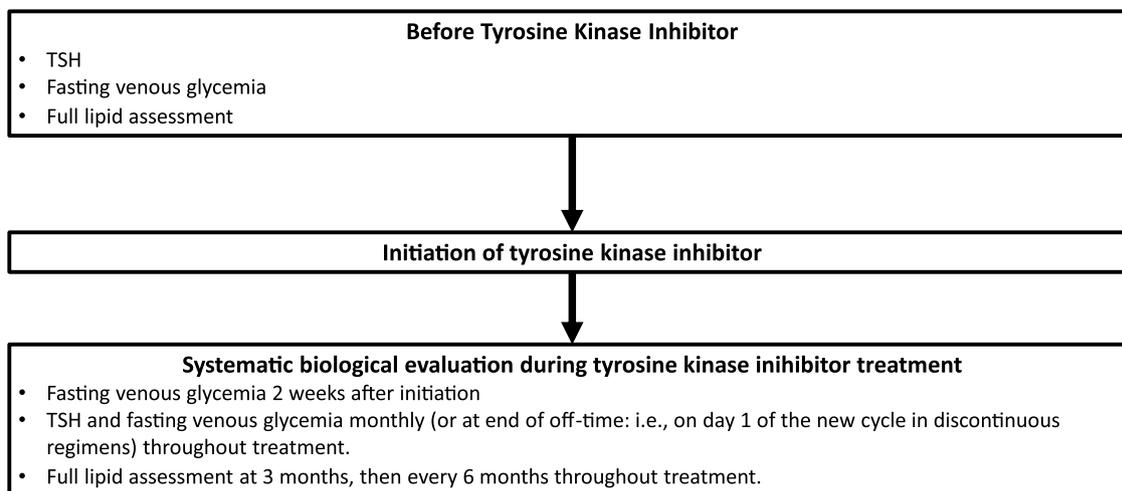


Fig. 2. Biological evaluation and tyrosine kinase inhibitors.

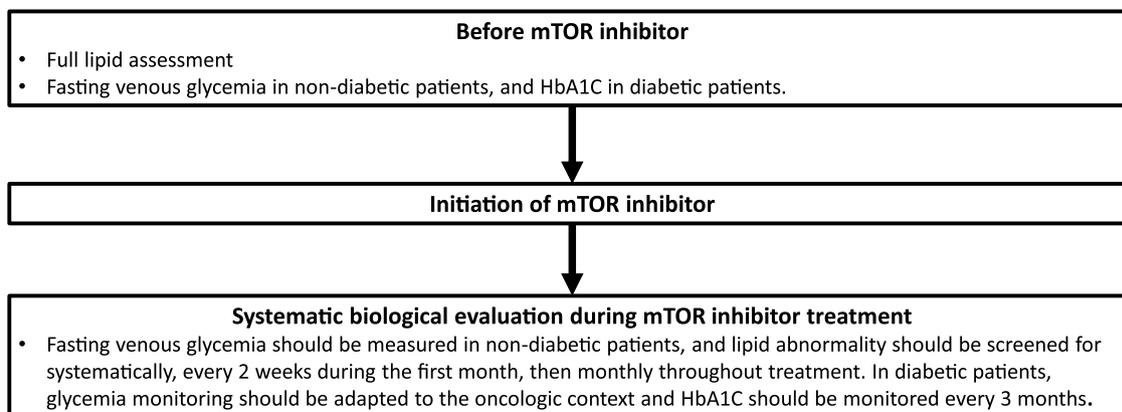


Fig. 3. Biological evaluation and mTOR inhibitors.

**R7:** Before initiating mTORs, lipid abnormality should be screened for systematically; fasting venous glycemia should be measured in non-diabetic patients, and HbA1C in diabetic patients.

**R8:** During mTOR treatment, fasting venous glycemia should be measured in non-diabetic patients, and lipid abnormality should be screened for systematically, every 2 weeks during the first month, then monthly throughout treatment. In diabetic patients, glycemia monitoring should be adapted to the oncologic context and HbA1C should be monitored every 3 months.

described herein are performed systematically. More generally, the 2 essential steps are initiation and adaptation of replacement therapy, any cessation of which should always be discussed between all specialists involved in the patient's care.

**Disclosure of interest**

The authors declare that they have no competing interest.

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In conclusion, onset of endocrinopathy under anticancer treatment necessitates teamwork between endocrinologists and oncologists. The risk requires education of the patient, but also of oncologists, to enable early diagnosis, which is only possible if the initial and monitoring assessments

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