Thyroid effects and anticancer treatment

Conséquences thyroïdiennes des traitements anticancéreux

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Résumé

Les conséquences thyroïdiennes des thérapeutiques anticancéreuses sont multiples, mieux connues après radiothérapie qu’après chimiothérapie et, récemment, décrites avec les nouvelles thérapeutiques ciblées. La radiothérapie cervicale ou toto corporelle favorise la survenue d’une insuffisance ou d’un cancer de la thyroïde. Les effets secondaires des thérapeutiques ciblant les voies de signalisation cellulaire dérégulées dans la cellule cancéreuse sont encore à l’étude mais leurs conséquences sur la fonction thyroïdienne sont déjà établies. Les troubles hormonaux surviennent, en général, de manière différée, sur plusieurs mois, voire plusieurs années après l’obtention d’une guérison ou d’une rémission, et doivent être dépistés. L’augmentation de l’espérance de vie des patients traités pour cancer et l’avènement des nouvelles thérapeutiques placent donc l’endocrinologue au cœur du suivi. La connaissance des effets secondaires thyroïdiens de chacun des traitements est nécessaire pour optimiser le dépistage et le traitement et améliorer le confort de vie des patients.

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Mots clés : Cancer ; Thyroïde ; Chimiothérapie ; Radiothérapie ; Thérapeutiques ciblées

Abstract

Thyroid consequences of cancer therapy are multiple, better known after radiotherapy than after chemotherapy and recently described with targeted therapies. Cervical or total body irradiation may result in thyroid insufficiency or cancer. The consequences of treatment with new antiangiogenic drugs are under evaluation; however their effect on thyroid function is already well established. Thyroid dysfunction usually occurs late, several months or years after treatment and have to be depicted. There is an improvement in the overall survival of patients suffering from cancer and endocrinologists must be aware of the endocrine effects of treatments to propose an adequate survey and an appropriate treatment to improve well-being of patients.

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Keywords: Cancer; Chemotherapy; Radiotherapy; Antiangiogenic therapy; Thyroid dysfunction

1. Introduction

The emergence of new cancer therapy has profoundly modified the care of patients suffering from cancer and has improved the prognosis in the majority of cancers and in particular tumours in children [1]. Classic treatments such as surgery, chemotherapy and radiotherapy can cause secondary thyroid effects that are more or less well-known. Disorders usually occur later, several months even several years after obtaining a cure or a remission; adequate detection and treatment are necessary to improve the health and quality of life of patients.

Recently, new treatments have been marketed which target the cell pathways which have been deregulated in the cancerous cell [2]. The thyroid side effects of these treatments, called targeted therapies, are still being studied but their consequences on the thyroid function are already well established [3]. In order to initiate appropriate monitoring, it is important to know the type and time of possible endocrine attacks, their sequence, and more generally the factors for predicting when hormonal complications may occur. The purpose of this review is to summarize the characteristics of the thyroid side effects of
conventional cancer treatments and present the specific effects of new-targeted therapies. The main thyroid diseases observed after cancer therapy are hypothyroidism and thyroid carcinoma but other thyroid disorders such as goiter or changes in thyroid hormone metabolism have also been reported. We have deliberately decided not to deal with surgical aspects.

2. Radiotherapy

Radiation therapy could induce thyroid disease in all cases where the thyroid is included in the exposure field: head or neck cancer, cervical lymph node or craniospinal irradiation. Depending on the absorbed dose and age, thyroid irradiation can encourage the occurrence of a thyroid dysfunction or a cancer [4]. The radiosensitivity of thyroid tissue is dose dependent and toxicity can be observed from small doses (9 Gy) with a maximum around 20 Gy, following a bell curve [5]. Beyond that, the gland will be destroyed, the risk of cancer occurring would be less and only complete hypothyroidism would be observed [4,6].

Cervical radiotherapy, when administered in childhood, is the most clearly identified risk factor for thyroid cancer. In the adult, risks are limited, even absent, because the thyroid divides very slowly. Within the cohort of the Childhood Cancer Survivor Study (CCSS), any exposure to ionising rays increases the risk of cancer by 2.6 times [6]. Usually it concerns papillary cancers which are often multifocal and whose occurrence is favoured by RET gene rearrangements such as RET/PTC1, RET/PTC3 [7]. Cancers are diagnosed in 66% of cases 15 to 20 years after treatment of the initial tumour but there is an increasing risk after five years [4]. The prognosis of radiation-induced thyroid cancers would not seem to differ from that of other thyroid cancers of the same stage and histological type [5,6]. Hodgkin’s disease would seem to be an additional risk factor for a thyroid cancer occurring, independently of the dose administered and the age at the first cancer. Current recommendations are annual clinical monitoring; the place of systematic echography is being discussed [8].

The prevalence of morphological anomalies (nodules, goiter) is high, five to six times higher than that of non-irradiated populations [4]. Ultrasonographic anomalies would also seem to be observed in 80% of cases after 12 years of follow-up. Taking these data into account, in particular with patients treated for Hodgkin’s disease, certain authors recommend monitoring the thyroid hormone level twice a year during the first five years following irradiation, and then annually [9].

Hypothyroidism is frequent after neck irradiation; its prevalence is 20 to 30% in the majority of studies. The factors influencing this prevalence highlighted in the studies are the dose, the follow-up duration and the type of initial therapy. Hypothyroidism occurs on average seven years after irradiation and earlier for doses higher than 35 Gy [6]. Hypothyroidism is also frequently observed after total body irradiation, in 52% of cases at 1.9 years in a series of 33 patients [10]. In cases of patients treated for non-Hodgkin lymphoma, hypothyroidism is most frequently described in the group of grafted patients, who have therefore benefited from TBI [11]. In particular, hemothyroidectomy after head and neck cancer increases the risk of hypothyroidism after radiotherapy [12], justifying the monitoring of the TSH every three to six months [13,14]. The risk is then major within five years [4]. An infraclinical hypothyroidism would seem to be more frequent, affecting, at 10 years, up to 63% of patients irradiated [9]. It should be pointed out that the radiosensitivity of thyroid tissue can be dependent on the irradiation programme proposed.

Chin et al. [15] therefore showed, in 48 patients, that hyperfractionation (two sessions a day) reduced the risk of peripheral hypothyroidism. With an equivalent prescribed dose, the risk of developing hypothyroidism was 76% in monofractionated radiotherapy as against 14% in bifractionated therapy ($P<0.02$).

In addition, peripheral hypothyroidisms have been observed in the child after metabolic radiotherapy by Iodine 131 MIBG in the treatment of neuroblastoma [16,17].

3. Chemotherapy

Few studies take account of thyroid anomalies in the event of chemotherapy alone without associated radiotherapy. Trofosfamide and idarubicine in particular have been associated with a significant risk (OR 8.6 [IC 1.3–58.1]) and 17.2 [1.7–173.2]) of modification of the thyroid balance, consistent in infraclinical hypothyroidisms in more than half of cases. These modifications seem not to evolve at four years [18]. Variations of the TBG have also been described, either decreasing after administration of l-Asparaginase [19] and glucocorticoids, or increasing after administration of 5FU. Transitory reductions in T3 were observed after administration of antimetabolites, alkylating agents or cisplatin in association with dexamethasone. Apart from idarubicine, these modifications (infraclinical hypothyroidisms, decreases in T3 and modifications of the TBG) to the thyroid balance observed at the administration of chemotherapy, are thus generally transitory and without any clinical repercussions [18].

4. Mitotane

Mitotane or OP’DD is used as a postoperative treatment for adrenocortical carcinoma. In addition to the most well-known gastrointestinal effects, decreases in T4 without modification to the TSH have been described, thus imitating a central hypothyroidism [20]. An increase in the TBG by mitotane has also been described [21].

5. Targeted therapies

Recent progress in knowledge of the biology of the cancerous cell have led to the development of new molecules, no longer directly cytotoxic but able specifically to block intracellular pathways that are disorganised in the cancerous cell. These treatments do not directly involve the apoptosis but blocking the essential pathways for tumour growth and proliferation weakens the tumour cells and favours the mechanisms of cellular death. Very promising results have been obtained in many tumour types with objective tumoral responses and prolonged...
5.1. Tyrosine kinase inhibitors

Unlike monoclonal antibodies, acting on extracellular targets, tyrosine kinase inhibitors are small molecules with intracellular action, acting on the pathways of growth factors, and, for some, targeting the receptor of an angiogenesis growth factor, the vascular endothelial growth factor (VEGF). These molecules are currently used in the treatment of solid tumours in adults or malignant haemopathies. The oldest, rituximab (Mab Thera\textsuperscript{®}), is indicated in treatment of B-cell lymphomas. By their mechanism which induces the immune response, these molecules are able to induce non-specific immunological reactions, generally cutaneous or gastrointestinal [2]; they can also modify thyroid immunity [22] and thyroid autoantibody levels in Hashimoto’s thyroiditis could decrease after rituximab monotherapy [22,23]. In other cases, monoclonal antibody could increase immunity [24] and autoimmune thyroiditis could be an indicator of cancer treatment efficacy [25,26].

Sunitinib (Sutent\textsuperscript{®}) is above all used at the present time in the treatment of metastatic renal carcinoma. Its targets are among the receptors of the VEGF, the platelet-driven growth factor (PDGF), the proto-oncogene C-KIT and the glial cell line derived growth factor (GDNF). The analysis of 42 subjects with thyroid gland in place treated by sunitinib shows that after an average duration of 50 days, 62% of the patients show a value of abnormal TSH and 36% of them receive treatment by L-T4 for hypothyroidism [28]. According to series [3,28,29], the prevalence of hypothyroidism justifying a substitution varies from 14 to 61% and the proportion of patients with infraclinical hypothyroidism is even greater, between 52 and 85%. The risk of hypothyroidism increases with the length of the treatment and usually persists when the treatment stops (Fig. 1). The mechanisms responsible for deteriorating the thyroid function are still uncertain, but the hypothesis of a destructive thyroiditis is the most probable because of a generally biphasic evolution (thyrotoxicosis phase preceding a hypothyroidism phase) and the absence of spontaneous normalization when the treatment stops [28]. Other mechanisms have been evoked, in particular, inhibition of the radioiodine uptake and/or activity on the thyroperoxidase or deterioration of the vascularisation of the thyroid secondary to the inhibition of VEGF pathway.

Sorafenib (Nexavar\textsuperscript{®}), which, among other effects, inhibits the mutated or wild-type B-Raf protein, can also cause thyroid disturbances. In the series of Tamaskar et al. [29], based on 68 patients, 18% of them showed biological hypothyroidism and 21% an isolated reduction of TSH. However, substitution by thyroid hormones was only necessary in two cases. The physiopathological mechanism of these thyroid disturbances still remains unclear. A recent work suggests that this molecule increases the peripheral metabolism of the thyroid hormones [30].

Motesanib was recently the subject of a phase II study, of 93 patients with differentiated metastatic thyroid cancers [27]; hypothyroidism was observed in 22% of cases and an increase in TSH in 12% of cases. After 100 days of treatment, 59% of the patients show a rise in the TSH, sometimes a tenfold increase compared to basal values. The observations are similar in trials including medullary thyroid cancers. Modification in the plasmatic concentration of thyroid hormone in thyroidectomised subjects supposes a peripheral action of motesanib. It could be a modification in the absorption of L-T4 or the metabolic clearance of thyroid hormones. The thyroid impact of motesanib in euthyroidian subjects is not known.

Imatinib (Glivec\textsuperscript{®}) is mainly used in stromal tumours and certain forms of acute myeloid leukaemia, acute lymphoid leukaemia and myeloproliferative syndromes. It interacts with the receptors of PDGF, C-KIT and RET and with the fusion protein BCR/ABL. In a study [31] based on 10 patients treated for medullary carcinoma and one for a stromal tumour, hypothyroidism was found in all thyroidectomised patients, justifying an increase in the posology of the substitution treatment of levothyroxine up to 200%. On the other hand, in a cohort of 70 patients treated by Imatinib for acute myeloid leukaemia and not thyroidectomised, the plasmatic concentration of TSH was
Table 1
Principal thyroid consequences of anticancer treatments.

<table>
<thead>
<tr>
<th>Treatments used</th>
<th>Thyroid pathologies</th>
<th>Assessment time according to dose and irradiation programme</th>
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<td>Motesanib and imatinib increase the need of L-Thyroxine</td>
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<td>mT or inhibitor</td>
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not modified. These observations suggest a peripheral effect of Imatinib. One of the hypotheses is an acceleration of the metabolic clearance of thyroid hormones under the effect of increased glucuroconjugation [3,31].

Thyroid dysfunction after treatment by second-generation TKI was recently described [32]. In most patients, thyroid dysfunction was transient, and therapy was required in three of the 73 patients of this series.

These different studies suggest that the tyrosine kinase inhibitors have an impact on the thyroid hormonal status according to heterogeneous physiopathological mechanisms. The functional parameters of the thyroid have to be monitored in the first weeks of treatment, whether the patient has a history of thyroid problems or not [33]. The targeted therapy could have other endocrine effects. In particular, work carried out in vitro has shown modifications to the glucidic metabolism under Imatinib. This molecule would appear to preserve the beta function, improve the glucidic parameters and decrease the formation of atherosclerosis in predisposed patients.

5.2. mTor inhibitors

This class of targeted therapies, currently used in endocrine tumours and proposed in the treatment of thyroid cancers inhibits the PI3 K/Akt pathway. Experimentally everolimus increases the radioiodine uptake by the thyroid [34], and would seem to reduce the size of the thyrotropin-secreting adenomas [35] suggesting a possible modification of the thyroid hormone level in patients treated with these molecules.

5.3. Bexarotene (Targretin®)

This selective agonist of the retinoid X receptors is used in treatment of Tepidermotrop al lymphomas. In the rat, bexarotene treatment decreases dose-dependently the plasmatic concentration of TSH, T3 and T4. The mechanism seems to include a reduction in the secretion of pituitary TSH, causing a central hypothyroidism [36]. Injecting bexarotene analogue soon significantly inhibits the TSH peak in response to the TRH and this is prolonged. In man, Sherman et al. [37] observed a significant reduction in TSH and peripheral hormones in 96% of patients treated with bexarotene, in the first 15 days of treatment, reversible when treatment is stopped. The TSH nadir was positively correlated to the bexarotene dose administered. In practice, a preliminary assessment of the thyroid function is necessary during the introduction of bexarotene treatment.

Taking its prevalent hypophysary action into account, monitoring relies on the free T<sub>4</sub> dosage, carried out in the first week of treatment; in the event of a reduction, supplementation by levothyroxine is introduced which can be stopped quickly when the treatment stops. The endocrine consequences of targeted therapy are summarised in Table 1.

6. Conclusion

The thyroid consequences of anticancer therapies are many and various, observed with all types of treatment, whether radiotherapy, chemotherapy or new-targeted therapies. The increase in the life expectancy of patients treated for cancer, and the advent of new therapies therefore place the endocrinologist at the heart of patient monitoring, alongside the oncologists. Knowledge of the side effects of treatments is necessary to optimise detection and follow-up and improve the well-being of patients.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


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