Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

Annales d'Endocrinologie 72 (2011) 198–202

Annales d'Endocrinologie
Annals of Endocrinology

Review

Thyroid effects and anticancer treatment

Conséquences thyroïdiennes des traitements anticancéreux

C. Nozières [a,*], C. Damatte-Fauchery [b], F. Borson-Chazot [a]

[a] *Fédération d'endocrinologie du pôle Est, groupement hospitalier Est, 59, boulevard Pinel, 69677 Bron, France*
[b] *53, rue Adolphe-Garilland, 38550 Le Péage-de-Roussillon, France*

Available online 2 June 2011

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.

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.

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

* Corresponding author.
E-mail address: cnozieres@yahoo.fr (C. Nozières).

0003-4266/$ – see front matter © 2011 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ando.2011.04.002

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 plurifocal 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, hemithyroidectomy 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