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REVIEW

Thyroid Dysfunction as an Unintended Side Effect of Anticancer Drugs

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Background: Several of the currently used anticancer drugs may variably affect thyroid function, with impairment ranging from modified total but not free concentration of thyroid hormones to overt thyroid disease.
Summary: Cytotoxic agents seem to alter thyroid function in a relatively small proportion of adult patients. Anticancer hormone drugs may mainly alter serum levels of thyroid hormone–binding proteins without clinically relevant thyroid dysfunction. Old immunomodulating drugs, such as interferon-α and interleukin-2, are known to induce variably high incidence of autoimmune thyroid dysfunction. Newer immune checkpoint inhibitors, such as anti-CTLA4 monoclonal antibodies, are responsible for a relatively low incidence of thyroiditis and may induce secondary hypothyroidism resulting from hypophysitis. Central hypothyroidism is a well-recognized side effect of bexarotene. Despite their inherent selectivity, tyrosine kinase inhibitors may cause high rates of thyroid dysfunction. Notably, thyroid toxicity seems to be restricted to tyrosine kinase inhibitors targeting key kinase-receptors in angiogenic pathways, but not other kinase-receptors (e.g., epidermal growth factor receptors family or c-KIT). In addition, a number of these agents may also increase the levothyroxine requirement in thyroidectomized patients.
Conclusions: The pathophysiology of thyroid toxicity induced by many anticancer agents is not fully clarified and for others it remains speculative. Thyroid dysfunction induced by anticancer agents is generally manageable and dose reduction or discontinuation of these agents is not required. The prognostic relevance of thyroid autoimmunity, overt and subclinical hypothyroidism induced by anticancer drugs, the value of thyroid hormone replacement in individuals with abnormal thyrotropin following anticancer systemic therapy, and the correct timing of replacement therapy in cancer patients need to be defined more accurately in well-powered prospective clinical trials.

Introduction

In cancer patients, abnormalities in thyroid function and thyroid diseases are variably associated with cancer itself, diagnostic procedures, or anticancer treatments. Abnormalities of thyroid hormone synthesis and metabolism as well as of thyrotropin (TSH) levels, more commonly known as "euthyroid sick syndrome," may occur in patients with advanced cancers (1). Diagnostic procedures using iodinated contrast agents can be associated with acute effects on the thyroid, including hyperthyroidism triggering/exacerbation, as in patients with autonomous thyroid nodules or Graves' disease, or transient hypothyroidism (i.e., in patients with Hashimoto's thyroiditis) (2,3). Radiation therapy (RT) can lead to primary hypothyroidism due to direct damage to the thyroid or, indirectly, through hypopituitarism due to brain irradiation (3,4). External cervical RT received during childhood has been associated with thyroid nodules and papillary thyroid cancer later in life (4).

Systemic anticancer treatments include old and newer cytotoxic and hormone drugs, immune system modulators, and targeted drugs that selectively modulate key molecules in cancer progression or immune response to cancer. Many of these agents may variably affect thyroid function with impairment ranging from modified total but not free concentration of thyroid hormones to overt thyroid disease (5,6). Anticancer hormone drugs may alter thyroxine-binding globulin levels, but marginally affect thyroid function (Table 1). Only aminoglutethimide, used to control adrenal, breast, and prostate cancer, is reported to cause hypothyroidism in up to 31% of patients (7,8).

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This review focuses on thyroid function abnormalities and diseases resulting from exposure to nonhormonal anticancer agents currently used for the treatment of adult malignancies.

Search Strategy

The PubMed and MEDLINE databases were searched for articles published before March 30, 2013. Electronic early-release publications are also included. Only articles published in English were considered. The search terms were "thyroid dysfunction," "hypothyroidism," "thyroid toxicity," "endocrine adverse events," and "autoimmunity," in association with "anticancer drugs," "tyrosine kinase inhibitors," "immune checkpoint inhibitors," "interleukin," and "interferon." Proceedings from the 2000–2012 Conferences of the American Society of Clinical Oncology, the European Society of Medical Oncology, and the Endocrine Society were searched for relevant abstracts.

Thyroid and Cytotoxic Anticancer Agents

In adult survivors of childhood cancers, endocrine toxicity, including thyroid disorders, is a common long-term complication of cytotoxic treatments (9). Conversely, cytotoxic treatments seem to alter thyroid function in a relatively small portion of adult patients (5). However, few studies prospectively evaluated thyroid dysfunction induced by cytotoxic agents in adult populations. Lomustine, vincristine, and cisplatin have shown *in vitro* effects on thyroid cells (10). In small series, 5-fluorouracil and L-asparaginase alter levels of thyroid hormone–binding proteins without clinical consequence (11–16). L-asparaginase may cause transient central hypothyroidism as well (17).

Mitotane, the only active agent against adrenocortical cancer, reduced both activity and viability of mouse pituitary TSH-secreting cells (18). In patients treated with mitotane for adrenocortical cancer, a marked reduction in free thyroxine (free T4) without concomitant reduction in free triiodothyronine (free T3) (possibly by influence on deiodinase activity) and without elevation of TSH was found (19). Free T4 levels dropped in the hypothyroid range in most patients and were inversely correlated with mitotane plasma levels (19).

Very few studies evaluated the effects induced by polychemotherapy on thyroid function in cancer patients. Primary hypothyroidism was diagnosed in 15% of patients with testicular cancer receiving a combination regimen of cisplatin, bleomycin, vinblastine, etoposide, and dactinomycin (20). Increased serum TSH levels were documented in 44% of patients with Hodgkin disease who received mechlorethamine, vinblastine, procarbazine, and prednisolone (MOPP regimen). However, in this small trial, iodine load during lymphangiography may have contributed to the thyroid abnormalities (21).

When delivered concomitantly with head-neck irradiation, cytotoxic chemotherapy increases the risk of RT-induced primary or central hypothyroidism (22–24). In comparison with RT, cytotoxic chemotherapy (CT) alone does not increase the risk of thyroid cancer (5).

Immunoregulatory Drugs

Interferon-α

Interferon-α (IFN-α) is a human recombinant cytokine with direct antiviral and antitumor activity, as well as indirect immune-mediated destruction of cancer cells (25,26). IFN-α is approved for patients affected by melanoma, renal cell carcinoma, AIDS-related Kaposi's sarcoma, some hematologic malignancies, and virus B/C hepatitis (27).

IFN-induced thyroid abnormalities can be classified as autoimmune and nonautoimmune thyroiditis (28,29). Autoimmune IFN-induced thyroiditis (IIT) can manifest as a clinical disease (i.e., Graves' disease or Hashimoto's thyroiditis), or as a subclinical disease, as seen in the presence of thyroid autoantibodies (TAb) without overt thyroid dysfunction (~20% of patients). Nonautoimmune IIT can present as destructive thyroiditis, or nonautoimmune hypothyroidism (28,29). This classification proposed for IIT experienced by patients affected by hepatitis appears suitable for cancer patient as well.

The incidence of thyroid abnormalities in patients receiving IFN therapy for solid tumors is 2.4–31% (30–39), with up to 50% in some trials (40,41). In patients affected by hematological malignancies, the incidence of IFN-related thyroid dysfunction appeared lower (42,43), with the difference remaining unexplained. Autoimmune IIT mainly occurs in the first few weeks of treatment and, following a brief thyrotoxic phase, may lead to hypothyroidism in close temporal relationship with the appearance of TAb, especially Tg-Ab. Hypothyroidism persists in the majority of patients (31,44), although transient hypothyroidism has also been described (45). Pre-existing thyroid peroxidase antibody (TPO-Ab) considerably increases the risk of hypothyroidism (38,46–48). Thyroid abnormalities may recover with the withdrawal of IFN. In two randomized trials of IFN-α on melanoma patients, the association between the appearance of autoantibodies, including TAb, and improved relapse-free interval was not statistically significant. (49).

Rarely, classical Graves' disease and sometimes Graves' ophthalmopathy may develop (50). These conditions may persist despite the withdrawal of the drug (6).

By binding to its receptors, IFN-α triggers several key immune effects, including an increased expression of MHC class I antigens (HLA) on cells, including thyroid epithelial cells (48), enhanced activity of lymphocytes, macrophages, and natural killer cells (NK) (51,52) and decreased T-regs function (53,54). Notably, the IFNα-induced HLA overexpression is associated with activation of cytotoxic T-cells leading to cellular destruction, when lymphocytes are present in the tissue (52). This mechanism was also seen in the thyroid and might explain the worsening of pre-existing subclinical thyroiditis (55). Furthermore, IFN-α can switch the immune response to a Th1 pattern (56,57) with an increased production of interferon-γ and interleukin-2 (IL2), two potent proinflammatory cytokines, and of IL-6 (52,56,57). This immune pattern may trigger an autoimmune response. Finally, thyroid cells may be directly damaged by IFN-α, a suggested mechanism for destructive thyroiditis (29,48,58). Despite accumulating evidence, the precise mechanisms of IIT remain to be elucidated, especially in cancer patients.

Pegylated IFNa

The pegylation of IFNα-2b provides a prolonged plasma half-life of the drug, by decreasing renal clearance (59,60), and improved efficacy in solid tumors and melanoma is reported, compared to unpegylated form (61,62). In the 18991 European

Organisation for Research and Treatment of Cancer trial evaluating pegylated IFNa (Peg-IFN) versus no treatment in high-risk melanoma patients, autoantibodies, including TgAb, were found in 52% of patients in the Peg-IFN group, compared with 18% in the control group (60). Better survival was not associated with the development of autoantibodies when analysis was corrected for guarantee-time bias (Table 1) (63).

Interleukin-2

IL2 is a cytokine involved in several mechanisms of immune response, including activation of NKs and antigen-specific T-cells. IL2 is approved for the treatment of patients affected by metastatic melanoma and renal cell carcinoma, although its use is currently reduced as more effective and better-tolerated agents are available (6).

Thyroid dysfunction and induction of TAb occur in 10–60% of cancer patients treated with IL2 alone or in combination with IFN-α, lymphokine-activated killer cells, or vaccines (64–71). An early phase of presumptive destructive thyrotoxicosis is common, with variable degrees of hyperthyroidism (68,72–74). Hypothyroidism, mostly associated with TAb, occurs 4–17 weeks after treatment has commenced (64,65) and may be reversible following discontinuation of the drug (65,72).

Various autoimmune mechanisms may be involved in IL-induced thyroid toxicity. IL2 is a potent inducer of proinflammatory cytokines such as IL1, tumor necrosis factor alpha, and IFN-γ (75–77). In patients with IL2-induced thyroid diseases, high levels of interferon-γ and tumor necrosis factor alpha have been found. These cytokines may trigger autoimmune thyroiditis by enhancing the presentation of HLA-II and associated autoantigens on thyrocytes. Also, IL2 may have a direct effect on thyrocyte function (78,79). Increase in TAb levels (64,69) and lymphocyte infiltration of the thyroid gland (73,80) were found in patients treated with IL2. Similar to IFN-α, high TAb levels before treatment increase the risk of IL2-induced hypothyroidism (65). Whether occurrence of hypothyroidism during the treatment with IL2 predicts favorable outcomes remains uncertain (Table 1) (64,65,81–85).

Denileukin diftitox

In Denileukin diftitox (DD), the ligand-binding domain of IL2 is fused to diphtheria toxin (86). The drug binds to the IL2 receptors on lymphocytes and macrophages and the toxin inhibits protein synthesis, leading to cell death. It is approved for use in cutaneous T-cell lymphoma and graft-versus-host disease after allogenic stem cell transplant (86,87). In a retrospective study, eight patients showed TPO-Ab and thyrotoxicosis within 1–35 days of treatment; five of them eventually developed permanent hypothyroidism (88). Autoimmunity could not be the mechanism of DD-induced thyroid toxicity, because the IL2-component of the drug does not activate the IL2-lymphocyte receptor. The absence of IL2-receptors on thyrocytes excludes direct thyroid toxicity (88). However, DD might target and lyse intrathyroidal lymphocytes with local release of cytokines leading to thyroiditis/thyrotoxicosis (88).

Thalidomide and lenalidomide

Thalidomide and its derivative lenalidomide are immunomodulatory agents active against multiple myeloma (MM). Lenalidomide is also efficacious in patients with the 5q-myelodysplastic syndrome (89,90). Anticancer activity of these drugs is based on immunomodulatory and antiangiogenic effects and is elicited by NK-mediated cytotoxicity, inhibition of proinflammatory cytokines, and increase in anti-inflammatory cytokines secretion and production of proangiogenic factors (e.g., vascular endothelial growth factor [VEGF], basic-fibroblast growth factor, tumor necrosis factor alpha, interleukin-6) (91). Subclinical hypothyroidism was reported in 20% of patients who received thalidomide for MM with another 7% of overt hypothyroidism, mostly occurring 1–6 months after treatment has begun (92). In a retrospective study, lenalidomide induced thyroid abnormalities in 6% of patients affected by MM and increased the risk of progression of thyroid dysfunction in patients with previous thyroid abnormalities (93). In another study, lenalidomide-induced hypothyroidism was found in 5–10% of patients (94,95). No thyroid abnormalities were reported in a large randomized study on 459 patients with untreated MM, receiving lenalidomide in combination with cytotoxics and prednisone (96).

Mechanisms of thalidomide/lenalidomide-induced hypothyroidism remain uncertain. Interference with thyroid hormone secretion and reduction of iodine uptake into follicular cells have been suggested (97,98). As thalidomide/lenalidomide exert antiangiogenic activity, a compromised thyroid blood flow may trigger thyroid toxicity (92). In some patients, TSH suppression preceded hypothyroidism, suggesting destructive thyroiditis, presumably induced by ischemia (99,100). Alternatively, an immune-mediated destructive thyroiditis may be induced by altered cytokine levels or through direct effects on T-lymphocytes (92).

Immune checkpoint inhibitors

Recent progress in cancer immunotherapy led to the development of immune regulatory monoclonal antibodies (MAb) that inhibit immunologic checkpoints, such as the cytotoxic T-lymphocyte antigen-4 receptor (CTLA-4) and the programmed death-1 receptor pathway (101). The anticancer activity of these drugs is presumably obtained by unleashing tumor immune tolerance (102,103). Ipilimumab and tremelimumab are immunomodulating MAb directed against CTLA-4 (anti-CTLA4-MAb), which have shown variable activity against several malignancies (104). Ipilimumab is approved for clinical use in patients with advanced cutaneous melanoma (105). However, inhibition of CTLA-4 induces a series of immune-related adverse events (106–108), mainly colitis/diarrhea, dermatitis, hepatitis, and endocrinopathies (109). Among endocrine toxicities, hypophysitis has emerged as a distinctive side effect of anti-CTLA4-MAb (106,110). As the damage to TSH-secreting cells and corticotroph is prevalent (111), in patients under ipilimumab the incidence of secondary hypothyroidism is similar to the incidence of hypophysitis (0–17%) (112). Notably, in the majority of cases, endocrine immune-related adverse events are irreversible and lifelong replacement therapy is required.

In two studies, tremelimumab was associated with thyroid dysfunction in 4% of patients (113,114). The incidence of ipilimumab-induced primary thyroid dysfunction appeared lower (0–2%) when ipilimumab was administered at standard dose (3 mg/kg), as a single agent or in combination with CT. In small reports, higher dosage of ipilimumab alone

Table 1. Selected Trials Evaluating the Prognostic or Predictive Role of Cytokine-Induced Thyroid Autoimmunity in Cancer Patients

Authors	*Trial (P/R)*	*Study population*	*Treatment*	*Thyroid antibodies positivity*	*Treatment-induced hypothyroidism*	*Treatment-induced hyperthyroidism*	*Findings/results*
Gogas *et al.* (36)	P	Stage IIB, IIC, or III melanoma (200 patients)	High-dose adjuvant interferon alfa-2b (4 weeks vs. 12 months)	TAb: 43 (22%) patients (16 in the induction-therapy group and 27 in the extended-therapy group ($p=0.12$)	Hypothyroidism: 11 (6%) patients (2 in the induction-therapy group and 9 in the extended-therapy group)	Thyrotoxicosis: 2 (1%) patients	The appearance of autoantibodies including TAb, or clinical manifestations of autoimmunity during adjuvant treatment with IFN-2b is associated with statistically significant improvements in RFS and OS in patients with melanoma, also when corrected for guarantee-time bias.
Satzger *et al.* (37)	R	Stage IB–IIIB melanoma (134 patients)	Low-dose interferon alpha	TAb: 20 (15%) patients	Hypothyroidism: 1 patient during the treatment; 2 patients during the follow-up	Hyperthyroidism: 3 (2%) patients	Kaplan–Meier analyses revealed a significantly better RFS and a trend for a better OS for patients developing autoimmune disease while treated with IFN.
Bouwhuis *et al.* (49,63)	P P	EORTC 18952 study stage IIB–III melanoma (187/855 patients) Nordic IFN study stage IIB–III melanoma (356/1388 patients) EORTC 18991 study stage III melanoma (1256 patients)	Intermediate doses of IFN vs. Observation Pegylated-IFN vs. no treatment	Only TgAb evaluated Observation: 2/23 (9%) patients IFN: 10/102 (10%) patients Observation: 1/70 (1%) patients IFN: 22/160 (14%) patients Observation: 4/113 (4%) Peg-IFN: 19/107 (18%)	NR	NR	When treated as a time-independent variable, appearance of autoantibodies was associated with improved RFI. However, on correction for guarantee-time bias, the association was weaker and not statistically significant.

(*continued*)

Table 1. (Continued)

Authors	*Trial (P/R)*	*Study population*	*Treatment*	*Thyroid antibodies positivity*	*Treatment-induced hypothyroidism*	*Treatment-induced hyperthyroidism*	*Findings/results*
Atkins *et al.* (65)	P	Advanced malignancies (34 patients)	IL2+LAK cells	TAb: 5 (15%) patients	Hypothyroidism: 7 (21%) patients	0	The treatment-induced hypothyroidism may be associated with a favorable tumor response.
Phan *et al.* (83)	R	Metastatic melanoma (374 patients)	IL2	NR	Hypothyroidism: 130 (35%) (LT4 requiring: 9%) patients	Hyperthyroidism: 26 (7%) patients	No significant association was found between thyroid dysfunction and response. The frequency of thyroid dysfunction was significantly associated with IL2 treatment duration.
Weijl *et al.* (64)	P	Advanced malignancies (15 patients)	IL2	TAb: 9 (60%) patients	Hypothyroidism: 7 (47%) patients	0	Development of hypothyroidism correlated significantly with a favorable response to treatment. The likelihood of developing (transient) hypothyroidism was higher in patients who respond to IL2 treatment. The development of vitiligo was among factors strongly related to response.
Franzke *et al.* (81)	P	Metastatic RCC (329 patients)	Subcutaneous IL2 and IFN alfa-2b	TAb: 60 (18%) patients	Subclinical hypothyroidism 14 (4%) patients Overt hypothyroidism 21 (6%) patients	Subclinical hyperthyroidism: 62 (19%) patients Overt hyperthyroidism: 28 (9%) patients	The presence of thyroid autoantibodies was correlated with prolonged survival ($p<0.0001$).

EORTC, The European Organisation for Research and Treatment of Cancer; IFN, interferon; IL2, interleukin-2; LT4, levothyroxine; NR, not reported; OS, overall survival; RCC, renal cell carcinoma; RFS, relapse-free survival; TAb, thyroid antibodies; TgAb, antithyroglobulin antibodies; Peg-IFN, pegylated-interferon; LAK, lymphokine-activated killer; P, prospective; R, retrospective; RFI, relapse-free interval.

(10 mg/kg) or in combination with bevacizumab (7.5–15 mg/kg), an anti-VEGF agent, was associated with a higher rate of thyroiditis (7% and 19% of cases, respectively) (115,116). In patients with metastatic prostate cancer receiving ipilimumab at increasing doses in combination with an anti-prostate specific antigen vaccine, hypothyroidism was diagnosed in 4 (13.3%) patients at the higher dose levels (5–10 mg/kg) (117). Conversely, no cases of endocrinopathy were reported in 36 patients receiving ipilimumab (0.1–3 mg/kg) combined with IL2 (118). The anti-CTLA4-mAb thyroid damage presents as thyroiditis associated with TAb and hypothyroidism, or transient hyperthyroidism. Rare cases of Graves' ophthalmopathy have also been reported, with elevation of TSH-receptor antibodies but normal thyroid function (119,120). However, clinical details are still scarce. Similar to anti-CTLA4-MAb hypophysitis, the onset of anti-CTLA4-MAb thyreopathy occurs after 2–4 infusions. Most cases showed subclinical course or may be transient, consistent with a silent autoimmune thyroiditis. Alternatively, it may evolve into permanent hypothyroidism, requiring thyroid hormone supplementation (106). It is unknown whether the administration of anti-CTLA4-MAbs may worsen previous thyroiditis, as patients with previous autoimmune disease were not included in clinical trials evaluating these agents.

MAb blocking PD-1 or one of its ligands (PD-1L) are at an early phase of clinical development (103,121). Currently, these agents seemed to only slightly affect the endocrine system. Hypothyroidism was reported in 2–3% of patients receiving higher doses of these drugs (122,123). Further studies are needed to better define the pathogenic mechanism of primary and secondary thyroid dysfunction induced by immune checkpoint inhibitors.

Alemtuzumab

Alemtuzumab is a humanized MAb binding the CD52 cell surface antigen on lymphocytes and monocytes. The drug induces complement-mediated lysis of these cells exiting in intense lymphopenia (124). It is approved for high-risk or pretreated B-cell chronic lymphocytic leukemia (125). Alemtuzumab is also used as an immune suppressor in several conditions, including stem cell transplants, graft-versus-host disease after allogeneic stem cell transplant, and multiple sclerosis (MS) (126–128). Thyroid dysfunction has been reported with alemtuzumab in patients who received the drug for autoimmune disease (124,129,130), but not for cancer or rheumatoid arthritis (131,132). In a large study, thyroid dysfunction was found in 48/216 (22%) patients with MS treated with alemtuzumab (126). Autoimmune hypothyroidism was reported in 6.9% and thyroiditis in 4.2%, but Graves' disease in 14.8% of patients. In another study, 30% of MS patients developed Graves' disease, 9–31 months after a course of alemtuzumab (133). Notably, the alemtuzumab-induced autoimmune effects are mostly antibody mediated (type-2 hypersensitivity), including autoimmune neutropenia, thrombocytopenic purpura, and Goodpasture syndrome (134). The reasons underlying the lack of thyroid dysfunction in cancer patients compared to patients with MS are unknown.

Iodine-Based Anticancer Radioimmunotherapy

In cancer radioimmunotherapy, an antibody with specificity for a tumor-associated antigen is used to deliver a lethal dose of radiation to the tumor cells during isotopic decay (135). Tositumomab, an anti-CD20 MAb combined with ^{131}I, is approved for the treatment of non-Hodgkin lymphoma, whereas ^{131}I-metaiodobenzylguanidine is used in pheochromocytoma, neuroblastoma and carcinoid tumors. As the radioactive iodine concentrates in thyroid cells, hypothyroidism may occur in 9–64% of patients (within 6–24 months or later) (136–141). However, this side effect is preventable by the administration of oral iodine (Lugol solution or saturated solution of potassium iodide, SSKI) or potassium perchlorate ($KClO_4$).

Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors (TKI) are small molecules exerting their therapeutic activity by interfering with kinase-receptors that are critical for tumor cell growth, invasion, metastasis, and angiogenesis. Currently, several TKI are approved as anticancer therapeutics and approximately 150 kinase-targeted drugs are under clinical evaluation (142). Despite their selectivity, TKI show variable affinity for different kinase-receptors and none is specific for a single kinase-receptor. Therefore, off-target intracellular activities of normal cells are frequently impaired, leading to a variety of toxicities, often unusual, such as those to the endocrine system. TKI-induced endocrine side effects mainly include thyroid dysfunction, whereas gonadal and adrenal functions, bone, and glucose metabolism are less frequently or occasionally affected (143). TKI may cause *de novo* hypothyroidism or hyperthyroidism, or worsen pre-existing hypothyroidism, thus increasing thyroid hormone requirements in patients on levothyroxine (LT4) replacement. When hyperthyroidism occurs, it may represent the transient thyrotoxicosis phase of a destructive thyroiditis, often followed by hypothyroidism (144). These thyroid dysfunctions may be induced by TKI that inhibit key kinase-receptors in angiogenic pathways, but not by TKI targeting other kinase-receptors, such as epidermal growth factor receptors family (Table 1).

In cancer patients with normal thyroid function, TKI may cause abnormalities in thyroid laboratory tests, primary hypothyroidism (overt hypothyroidism in 32–85%, subclinical hypothyroidism in up to 100%), or decrease in TSH levels/thyrotoxicosis (transient in 0–24%, persistent in 0–5% of cases) (145) (Table 2). The onset of TKI-induced thyroid dysfunction is largely variable, ranging from 4 to 94 weeks after initiation of the treatment (median 4 weeks in prospective studies) (146). Whether prolonged treatment with a TKI, or previous treatments with cytokines (i.e., IFN/IL-2) or another TKI might influence the incidence or the course of thyroid dysfunction remains to be clarified. Among TKI approved for clinical use, sunitinib, a TKI mainly targeting angiogenic kinase-receptors, exposes patients to a higher risk of developing TKI hypothyroidism (14–71% of patients in prospective studies) (146–153). Thyroid dysfunction has also been described with other antiangiogenic TKI, such as sorafenib, motesanib, pazopanib, cediranib, and linifarib, but at lower rates (154–178) (Table 2). Nilotinib and dasatinib are second-generation TKI approved for the treatment of Philadelphia-positive chronic myeloid leukemia, showing structural similarity to imatinib, but greater potency and specificity for inhibition of BCR-ABL (179,180). Thyroid abnormalities during treatment with imatinib, nilotinib, and dasatinib were

retrospectively reported in 25%, 55%, and 70%, respectively (181). In patients under nilotinib, hypothyroidism was diagnosed in 12/55 (22%) patients, (6 subclinical, 6 clinical) and hyperthyroidism in another 18 (33%) patients (10 subclinical, 8 clinical), while 4/55 (7%) patients had evidence of thyroid autoimmunity (181). Similar results were reported with dasatanib (181) (Table 2). Compared with imatinib, nilotinib and dasatanib rarely altered the requirement of LT4 replacement therapy. The causes of the above difference are still unexplained. However, thyroid toxicity induced by newer TKI need to be better evaluated in prospective clinical trials.

Several mechanisms have been suggested to explain the onset of thyroid dysfunction in patients under TKI treatment. As thyrotoxicosis in a few cases preceded the development of hypothyroidism and thyroid atrophy, destructive thyroiditis might have triggered both adverse events (144,147). Other possible mechanisms include direct toxic effects on thyrocytes, leading to an impaired iodine uptake (148) and a reduced synthesis of thyroid hormones related to inhibition of TPO activity (149). However, altered iodine uptake has not been confirmed by *in vitro* studies (182). Similarly, a direct effect against TPO induced by TKI seems an improbable explanation in cases with initial destructive thyrotoxicosis or with thyroid atrophy. Induction of Hashimoto's thyroiditis has also been proposed as another potential mechanism (183). However, TAb infrequently increased during TKI treatment (146).

More likely, the TKI-induced thyroid dysfunction may derive from the inhibition exerted by these agents on kinase-receptors of angiogenic pathways, such as VEGF receptors 1–3 and platelet-derived growth factor receptor (PDGFR). TKI-induced regression of thyroid vascular bed with significant capillary alteration and reduction in density has been demonstrated in experimental animal models (184,185). This could cause the reduction of blood flow in the thyroid, an extremely vascular gland. If the thyroid blood flow decreases rapidly, an ischemic thyroiditis could result, leading to transient thyrotoxicosis (186). If the decreased blood flow develops more slowly, gradual thyroid destruction may occur, resulting in hypothyroidism (186). In humans, reduced thyroid volume and vascularization by Doppler ultrasound rapidly recovered after cessation of sunitinib (186,187). The reduced thyroid volume induced by reduction in blood flow may also explain the impaired iodine uptake seen *in vivo* but not *in vitro* (188). Notably, targeting different molecular components of angiogenesis (receptors vs. ligand) does not trigger the same toxic effect. Unlike antiangiogenic TKI inhibiting vascular endothelial growth factor receptor (VEGFR)/PDGFR, bevacizumab (which targets VEGF-A) occasionally altered thyroid homeostasis (189,190).

The reason why some TKI do not affect thyroid or do this at a lesser extent is unclear. In comparative studies, sunitinib was shown to induce thyroid damage more frequently than other TKI (i.e., sorafenib). This might be because sunitinib inhibits more than a single kinase-receptor regulating normal and tumor angiogenesis (not only VEGFR2, but also PDGFR and VEGFR1) and more potently than other TKI. The thyroid gland shows the highest blood flow rates per unit weight of any tissue in the body (191). Physiologically, thyroid angiogenesis is regulated mainly by VEGF signaling, but under ischemia/hypoxia *PDGF/PDGFR* are upregulated to exert a compensatory function (192,193).

The entire sunitinib-induced inhibition of both angiogenic key molecules (i.e., VEGFR2) and upregulated compensatory receptors (i.e., PDGFR) may result more frequently in thyroid ischemia via capillary regression and constriction (194). This, in turn, might trigger both destructive thyroiditis and thyroid dysfunction (194). This hypothesis might also explain the rarity of thyroid dysfunction induced by bevacizumab, which binds VEGF-A, but not VEGFRs and PDGFR.

The worsening of appropriately treated hypothyroidism in thyroidectomized patients under imatinib, a TKI mainly targeting c-KIT, was the first thyroid hormone abnormality described with TKI (195). Imatinib does not alter euthyroidism in nonthyroidectomized patients (196). An interference with the nondeiodination clearance of LT4 was initially thought to explain the increased LT4 requirement induced by imatinib (195). Several drugs (i.e., phenobarbital, phenytoin, carbamazepine, rifampicin, and nicardipine) increase thyroid hormone clearance and worsen hypothyroidism in patients under LT4, by inducing hepatic microsomal enzymes (12,197–200), and imatinib is a potent competitive inhibitor of mixed function oxygenases (CYP2C9, CYP2D6, CYP3A4/5) (195). Consistently, TSH levels return to normal after discontinuation of imatinib (195).

However, recent studies showed that other TKI may increase the LT4 requirement in thyroidectomized hypothyroid patients by interfering at different steps of thyroid hormone metabolism (171,201–205) (Table 2). In thyroidectomized patients on sorafenib, decreased T3/T4 and T3/rT3 ratios, accompanied by doubling in TSH levels, were found (202). In rats, sunitinib induced a decrease in serum T4 and T3 levels, increased deiodinase-3 (DIO3), and decreased deiodinase-1 activity, together with marked thyroid capillary regression (206). Also, it was suggested that motesanib and vandetanib might increase LT4 metabolism via an increased activity of DIO3 in peripheral tissue (171,204,205) in thyroidectomized patients, while hypothyroidism is infrequently reported in patients with thyroid *in situ* (172). Interestingly, in patients treated with sunitinib, not only did the T3/reverse-T3 ratio decrease and the TSH levels show a twofold increase, but following sunitinib withdrawal, DIO3 activity reversed, whereas thyroid hormone levels remained low (206). Further evidence suggests an impairment in deiodases activity in TKI-induced hypothyroidism. Indeed, in this condition, TSH levels are often inappropriately high for the concomitant serum free T3 and free T4 levels (194,207). This might be related to a far more reduced activity of DIO2 (expressed in the pituitary gland) than of deiodinase-1 (expressed mainly in the liver and kidney), leading to an intracellular depletion of T3 in the thyrotrophs and an inappropriately high TSH level (194). Additionally, in a new mouse model lacking DIO2 activity in pituitary thyrotrophs, normal serum T3 and high serum TSH and T4 levels were found, despite an euthyroid status (208).

Moreover, TKI may interfere with thyroid hormones even at central level, by inhibiting the monocarboxylate transporter-8, a thyroid hormone trans-membrane transporter expressed in the brain (including the hypothalamus and pituitary) and other tissues (i.e., liver, kidney, thyroid). In an *in vitro* model, several TKIs, including sunitinib and imatinib, dose dependently and noncompetitively inhibit T4/T3 uptake, inducing cellular depletion of T3 (209). However, whether this mechanism is relevant in humans requires further investigation.

Table 2. Overview of Results from Clinical Trials Evaluating Thyroid Dysfunction Induced by Tyrosine Kinase Inhibitors

Drug	*Targeted kinases*	*Approval/clinical development*	*Authors*	*Type of study*	*Cancer type*	*No. of patients*[a]
Sunitinib	VEGFRs-1–3, PDGFR-β; C-KIT; FLT-3	Approved for patients with RCC or GIST. Under evaluation for several tumor types, including breast, lung, thyroid, and colorectal cancer.	Desai *et al*. (147)	P	GIST	42
			Mannavola *et al*. (148)	P	GIST	24
			Wong *et al*. (149)	R	Solid tumors	40
			Rini *et al*. (185)	R/P	RCC	66
			Wolter *et al*. (146)	P	RCC/GIST	59
			Shinohara *et al*. (150)	P	RCC	17[c]
			Baldazzi *et al*. (151)	P	RCC	22
			Rutkowski *et al*. (152)	P	GIST	137
			Sabatier *et al*. (153)	P	RCC	111
Sorafenib	VEGFRs, PDGFR-β, c-KIT, RET, B-RAF	Approved for patients with RCC and HCC. Evaluated in lung, pancreatic, prostate, melanoma and DTC.	Tamaskar *et al*. (154)	P	RCC	39
			Clement *et al*. (155)	P	RCC	23
			Miyake *et al*. (156)	P	RCC	69
			Abdulrahman *et al*. (202)	P	MTC	21[d]
			Di Lorenzo *et al*. (157)	P	RCC	52
Sunitinib/ Sorafenib	See above	See above	Riesenbeck *et al*. (158)	P	RCC	52 31
Sunitinib/ Sorafenib	See above	See above	Schmidinger *et al*. (159)	P	RCC	41 37
Sunitinib/ Sorafenib	See above	See above	Kitajima *et al*. (160)	P	RCC	17 25
Sunitinib/ Sorafenib	See above	See above	Clemons *et al*. (161)	R	RCC	34 22
Sunitinib/ Sorafenib	See above	See above	Feldt *et al*. (162)	R (postmarket)	RCC	1295 1214
Sunitinib/ Sorafenib	See above	See above	Zhao *et al*. (163)	R	Early RCC	23 20

No. of patients with altered TFTs after TKI treatment (%)	*No. of patients with positive TAb/evaluated (%)*	*No. of patients with increased TSH after TKI treatment (%)*	*Overt hypo thyroidism after TKI treatment (%)*	*No. of patients with decreased TSH after TKI treatment (%)*	*Time to onset of thyroid dysfunction (median)*	*No. of patients who needed an increased LT4 dosage (%)*	*Prognostic value of TKI-induced hypothyroidism*
26/42 (62)	0/2	22/42 (52)	15/42 (36)	4/42 (10)	50 (12–94) weeks	NR	NR
16/24 (71)	0/23	16/24 (71)	10/24 (46)	0/24	NR	NR	NR
24/40 (60)	NR	21/40 (53)	14/40 (35)	3/40 (8)	5 (1–36) months	4/40 (10)	NR
56/66 (85)	13/44 (30) (TgAb)	46/66 (70)	17/66 (26)[b]	0/66	2 (1–14) cycles	NR	Uncertain
25/59 (42)	2/55 (4)	20/59 (34) transient	16/59 (27)	3/59 (5)	4 (2–46) weeks	NR	NR
9/17 (53)	0/6	1/17 (6)	8/17 (53)	TSH suppressed in 4/8 patients (transiently)	NR	NR	NR
13/22 (59)	0/22	13/22 (59)	2/22 (9)	0/22	3.3 (1–7) cycles	NA	Yes
NR	NR	NR	42/137 (31)	0/137	NR	NR	No
54/102 (53)	NR	51/102 (50)	46/102 (45)	3/102 (3)	5.4 (0.6–22) months	NR	No
16/43 (43)	2/7 (29)	NR	7/39 (18)	1/39 (3) transient	1.8 (0.6–7.3) months	NR	
15/23 (65)	NR	7/23 (30)	NR	NR	NR	NR	NR
46/69 (68)	NR	46/69 (68)	4/69 (6)	11/46 (24) transient	1.7 (0.7–7.5) months	NR	NR
21/21 (100)	NR	21/21 (100)	NA	NA	NA	100	NA
NR	NR	NR	4/52 (8)	0/52	NR	NR	NR
13/52 (25) 8/31 (26)	NR	NR	13/21 (62) 8/21 (38)	NR	16/21 (76%) patients showed TSH increase within the first 4 weeks of treatment	NR	Yes
NR	NR	12/41 (29) 18/37 (49)	NR	NR	25/78 (32%) patients showed TSH increase within the first 4 weeks of treatment	7/14 (50)	Yes
NR	NR	NR	12/17 (71) 9/25 (36)	NR	95 (12–315) days	NR	NR
NR	NR	12/34 (35)	15/34 (44)	0	11 months (range NR)	8/11 (73)	NR
NR	NR	persist 3/34 (9) transient 3/22 (14) transient 3/22 (14) persist	6/22 (27)		20 months (range NR)	2/6 (33)	
NR	NR	178/1295 (14) 77/1214 (6)	178/1295 (14) 77/1214 (6)	35/1295 (3) persist 42/1214 (4) persist	NR	NR	NR
NR	NR	NR	9/23 (39) 3/20 (15)	NR	NR	NR	NR

(*continued*)

Table 2. (Continued)

Drug	Targeted kinases	Approval/clinical development	Authors	Type of study	Cancer type	No. of patients[a]
Axitinib	VEGFRs 1–3	Approved for use in patients with RCC that failed to respond to a previous treatment.	Fujiwara *et al*. (165)	P (phase I)	Solid tumors	18[c]
			Mukohara *et al*. (164)	P	Solid tumors	12
			Tomita *et al*. (166)	P	RCC	64[c]
			Rini *et al*. (167)	P	RCC	62
Axitinib/ Sorafenib	See above	See above	Rini *et al*. (168)	P (phase III)	RCC	359 355
Sunitinib/ Sorafenib/ Axitinib	See above	See above	Daimon *et al*. (169)	R	RCC	15 12 6
Vatalanib	VEGFRs (VEGFR2), PDGFR, KIT	Evaluated in various solid and hemaological cancers	Joensuu (170)	P	GIST	45
Vandetanib	VEGFR-2, EGFR, RET	MTC (advanced or unresectable)	Robinson *et al*. (205)	P	MTC	17[d]
Motesanib	VEGFRs 1–3, PDGFR-β, KIT, and RET	Under clinical evaluation in various cancers	Sherman *et al*. (171)	P	DTC	93[d]
			Schlumberger *et al*. (204)	P	MTC	91[d]
			Blumenschein *et al*. (172)	P	NSCLC Motesanib Bev 15 mg/Kg	181
Pazopanib	VEGFRs, PDGFR, KIT	Approved for use in RCC and soft tissue sarcomas. Active in OC and NSCLC.	Sternberg *et al*. (173)	P	RCC	290
Cediranib	VEGFRs 1–3,	Under clinical evaluation in RCC, NSCLC, CNS cancers	Matulonis *et al*. (174)	P	Ovary	46
			Garland *et al*. (175)	P	PM	47
Linifanib	VEGFR-1,-2, PDGFR-β, CSFR-1, fms-3	Under clinical evaluation in NSCLC; HCC; RCC	Asahina *et al*. (176)	P (phase I)	Solid tumors	18
			Toh *et al*. (177)	P	HCC	44
			Tan *et al*. (178)	P	NSCLC	139
Imatinib	BCR-ABL, c-Kit, PDGFR-β, RET, c-Fms	Approved for use in CML and GISTs	de Groot *et al*. (195)	R	GIST/MTC	11
Imatinib	See above	See above	Kim *et al*. (181)	R	CML	8
Nilotinib	BCR-ABL, c-KIT, PDGFR-β	Approved for use in drug-resistant CML		R	CML	55
Dasatanib	BCR/ABL, Src, c-Kit	Approved as 1st- line therapy in CML and Ph + ALL; under evaluation in several cancers types.		R	CML	10

[a]Evaluable for TFT (baseline + at least one evaluation).
[b]Patients who started LT4 due to overt hypothyroidism.
[c]Only Japanese patients included.
[d]All patients were under LT4 replacement therapy due to thyroidectomy.

Bev, Bevacizumab; CML, chronic myelogenous leukemia; CSFR-1, colony-stimulating factor 1 receptor; DTC, differentiated thyroid cancer; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; MTC, medullary thyroid cancer; NA, not applicable; NSCLC, nonsmall cell lung cancer; PDGFR, platelet derived growth factor receptor; Ph + ALL, Philadelphia chromosome–positive acute lymphoblastic leukemia; PM, pleural mesothelioma; RCC, renal cell carcinoma; TFTs, thyroid function tests; TKI, tyrosine kinase inhibitor; TSH, thyrotropin; VEGFRs, vascular endothelial growth factor receptors. c-KIT, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; FLT3, Fms (feline McDonough sarcoma virus) -like tyrosine kinase 3; RET, rearranged during transfection; B-RAF, v-Raf (rapidly accelerated fibrosarcoma) murine sarcoma viral oncogene homolog B1; OC, ovarian cancer; CNS, central nervous system; BCR-ABL: breakpoint cluster region-Abelson gene.

No. of patients with altered TFTs after TKI treatment (%)	*No. of patients with positive TAb/evaluated (%)*	*No. of patients with increased TSH after TKI treatment (%)*	*Overt hypo thyroidism after TKI treatment (%)*	*No. of patients with decreased TSH after TKI treatment (%)*	*Time to onset of thyroid dysfunction (median)*	*No. of patients who needed an increased LT4 dosage (%)*	*Prognostic value of TKI-induced hypothyroidism*
16/18 (89)	NR	16/18 (89)	NR	0/18	NR	NR	NR
11/12 (92)	NR	11/12 (92)	7/12 (58)	3/12 (25) transient	Within 1 month (range NR)	NR	NR
56/68 (88)	NR	NR	31/64 (48)	NR	NR	NR	NR
NR	NR	NR	11/62 (18)	0/62	NR	NR	NR
NR	NR	NR	69/359 (19) 29/355 (8)	NR	NR NR	NR	Yes
9/15 (60) 6/12 (50) 6/6 (100)	4 (27) 1 (8) 0	NR	7/15 (47) 3/12 (25) 6/6 (100)	0/4 (27) 0 0	16 (range NR) weeks 16 (range NR) weeks 3 (range NR) weeks	NR	NR
1/45 (2)	NR	NR	1/45 (2)	NR	NR	NR	NR
NR	NR	17/17 (100)	NR	0	NA	17/17 (100)	NR
22/93 (24)	NR	11/93 (12)	11/93 (12)	0/93	NR	22/93 (24)	NR
37/93 (41)	NR	13/91 (14)	26/91 (29)	0/91	NR	NR	NR
NR	NR	— 7/121 (11) 1/60 (2)	NR	NR	NR	NR	NR
NR	NR	NR	<10	NR	NR	NR	NR
NR	NR	NR	26/46 (56)	0/46	NR	NR	NR
NR	NR	6747 (13)	NR	0/47	NR	NR	NR
NR	NR	8/18 (44)	NR	0/18	NR	NA	NR
NR	NR	NR	2/44 (5)	NR	NR	NR	NR
NR	NR	10/139 (7)	8/130 (6)	NR	NR	NR	NR
8/11	NR	NR	8/11 (thyroidectomized patients)	0/11	Within 2 weeks	8/11	NR
2/8	NR	1/8 (13)	0	1/8 (13)	Day 7	0/9	NR
30/55	NR	6/55 (11)	6/55 (11)	18/55 (33)	248 (22–944) days		NR
7/10	NR	4/10 (40)	1/10 (10)	2/10 (20)	142 (7–370) days		NR

Finally, it has been shown that inhibition of angiogenesis might impair peripheral metabolism of thyroid hormones. In rats, the expression of the *DIO3* gene increases under hypoxic–ischemic condition via the activation of the hypoxia-inducible factor–dependent pathway (210). If this observation is also confirmed in humans, difference in the hypothyroidism rate seen with sunitinib compared with motesanib and vandetanib may be further explained by the different affinity of each drug for the kinases of angiogenic receptors (194). Indeed, motesanib targets PDGFR with far less affinity than the VEGFR2, and vandetanib targets neither VEGFR1 nor PDGFR, while sunitinib showed the highest affinity for VEGFR2 and PDGFR (194).

Bexarotene

Bexarotene is a selective agonist of the retinoid X receptor, a nuclear hormone receptor with pleiotropic functions on cell growth, apoptosis, and cell differentiation (211,212). Bexarotene is currently approved for treatment of cutaneous T-cell lymphoma (213) and is under investigation for other cancers and autoimmune diseases (214). Bexarotene causes a rapid (4–8 hours) development of central hypothyroidism in 40%–100% of patients (215–217). TSH levels return to normal within a few days of drug discontinuation (213). Bexarotene interferes with the pituitary–thyroid axis at different levels. The normal feedback of thyroid hormone on the pituitary is impaired by bexarotene (216,218), which renders the transcription of the *TSH β-subunit* gene T3-independent (216,218). Additionally, bexarotene directly inhibits the secretion of TSH (219), explaining the rapid fall in TSH levels after administration of the drug. Bexarotene also affects thyroid hormone metabolism. In thyroidectomized thyroid cancer patients under LT4 who receive bexarotene a marked increase in LT4 requirement is needed. In these patients, bexarotene induces a dramatic decrease in thyroid hormones without compensatory elevation of TSH levels (220), presumably by interfering with peripheral thyroid hormone metabolism via non-deiodinase mechanisms. In experimental studies the drug has induced liver cytochrome P450 systems that also metabolize thyroid hormones (221).

Why Is It Important to Assess Thyroid Function in Cancer Patients?

Obviously, the correct and timely identification of thyroid dysfunction induced by anticancer drugs is important in obtaining significant diagnostic and therapeutic advantages. However, in cancer patients the recognition of symptoms due to thyroid dysfunction may be difficult. For example, symptoms such as fatigue and/or constipation may be caused not only by underlying malignancy, anticancer treatment(s), or medications used to control other symptoms (i.e., nausea or pain), but also by drug-induced hypothyroidism. Similarly, symptoms of thyrotoxicosis (i.e., palpitations, weight loss, heat intolerance, tremor, proximal muscle weakness, tachycardia, insomnia, irritability, fever) overlap with other complications (e.g., infection/sepsis). Missing the diagnosis of thyroid dysfunction induced by an anticancer drug may lead to unjustified dose reduction or treatment withdrawal of the drug (6). Moreover, untreated hypothyroidism or thyrotoxicosis may affect the metabolism of other medications, including anticancer drugs themselves, potentially reducing their efficacy (222). Undetected thyroid diseases can trigger life-threatening consequences, such as cardiac toxicity presenting as complication of TKI-induced hypothyroidism or eventually myxedematous coma (223–225). The early diagnosis of hypophysitis allows for the detection of central hypothyroidism and for the prevention of other consequences of hypopituitarism, including a life-threatening condition such as adrenal insufficiency (110).

Notably, it has been suggested that pretreatment hypothyroidism or drug-induced thyroid dysfunction may have a prognostic value in cancer patients. Hypothyroidism has been associated with reduced breast cancer incidence, older age at diagnosis, and less aggressive disease (226). However, correlations between hypothyroidism/thyroid autoimmunity and breast cancer remain conflicting (227). Hypothyroidism following RT is a predictor of better survival in head and neck cancer patients (228). Propylthiouracil-induced hypothyroidism was associated with improved survival in patients with high-grade glioma (229). IFN- and IL2-induced thyroid autoimmunity correlated with better prognosis in various studies (64,65,81,83), but not when guarantee-bias survival analyses were performed (39,49,60). In renal cell carcinoma patients receiving sorafenib/sunitinib, better clinical outcomes were seen when hypothyroidism developed (158,159,168,230). Interestingly, higher risk of hypothyroidism during sunitinib therapy has been significantly associated with *VEGF-A/VEGFR-2* gene single-nucleotide polymorphisms (152), suggesting that TKI-induced thyroid dysfunction may depend on a specific genetic predisposition. However, in this study better survival did not correlate with TKI-induced hypothyroidism. Retrospective analyses suggest that patients who experience immune-related adverse events, including endocrinopathies, may be more likely to benefit from anti-CTLA4-MAb therapy (107,231,232).

Therapeutic Challenges

The above issues emphasize that oncologists should maintain adequate surveillance of thyroid function in cancer patients. When drugs that are potentially associated with thyroid side effects are used, thyroid function should be carefully assessed at baseline and monitored throughout the treatment and follow-up period (6,233). Specific guidelines based on high-level evidence are lacking. However, in clinical practice rational approaches may be a guide in appropriately monitoring and treating thyroid dysfunction induced by anticancer drugs (6,234,235).

Before starting IFN, IL2, DD, thalidomide/lenalidomide, or alemtuzumab, TSH and TPO-Ab should be assessed, followed by TSH measurement every 2–3 months, if TPO-Ab are positive (6). With negative TPO-Ab, a less frequent TSH and TPO-Ab assessment may be indicated. In the case of *de novo* hypothyroidism, the withdrawal of the causative drug is generally not required, based on the efficacy of LT4 replacement. Thyrotoxicosis requires the treatment of symptoms with β-blockers. In the rare cases of drug-induced Graves' disease, methimazole or propylthiouracil may be administered if clinically indicated.

As bexarotene directly affects TSH secretion, thyroid function should be monitored with free T4 rather than TSH levels biweekly for the first 2 months and then every 1–2 months (236,237). Bexarotene-induced hypothyroidism can be prevented by starting high LT4 dosage with the drug. To

obtain the therapeutic goal of free T4 levels in the normal range, an LT4 dosage up to 2–3 times of the usual 1.6 μg/kg/day may be needed due to the drug-induced thyroid hormone degradation (6).

In patients who are candidates to receive ipilimumab, pretreatment thyroid function tests should include both TSH and free T4, as both secondary and primary thyroid dysfunction may occur. Monitoring of pituitary and thyroid function is required on day 1 of every cycle of treatment (238).

Thyroid dysfunction in patients receiving TKI requires specific considerations. In thyroidectomized patients under adequate LT4 replacement who should be treated with imatinib, motesanib, vandetanib, or axitinib, pretreatment TSH evaluation, followed by monthly monitoring of TSH, is recommended. In these patients, a substantial increase up to the doubling of the LT4 dose on initiation of TKI should be considered (6,194). Once TSH levels are stable, monitoring every 2–3 months is advisable. In patients with normal thyroid function, measurement of thyroid function tests before treatment with sunitinib and then measuring TSH on day 1 of every cycle appears appropriate (146,234,235). Elevated TSH levels measured on day 1 of the cycle (at the end of the 2-week rest period) are more likely to indicate clinically relevant thyroid damage requiring further investigation and, if appropriate, initiation of substitutive therapy (234,235,239). Measurement of TSH at day 28 of the cycle (at the end of the 4-week sunitinib treatment period) may increase the chances of early detection of thyroid dysfunction that may be subclinical/transient, thus not requiring treatment (234). Specific prospective trials are needed to better define the best timing of thyroid function assessment in patients under sunitinib and other TKI treatment (235,239). However, as treatment with these agents may be prolonged (more than 1–2 years) and the risk of thyroid toxicity seemed to be higher in the first 2–4 cycles, measurements of TSH may be empirically advised on day 1 of cycles 1–4, and then every 2–3 cycles (6,146).

Patients with overt hypothyroidism (TSH >10 mIU/L) should receive LT4 with the objective of maintaining TSH within the normal range. This may be achieved by an average starting dose of 1.6 μg/kg/day, except in patients with coronary artery disease or arrhythmias, in whom the dosage should be titrated starting with a lower dose (6).

The treatment of subclinical hypothyroidism (TSH 5–10 mIU/L with a normal free T4) is questionable in cancer patients. In healthy population, the correction of subclinical hypothyroidism is discouraged due to a lack of evidence concerning its benefit (240,241). In cancer patients, this may be even more problematic. Some preclinical, epidemiological, and clinical evidence suggests that LT4 replacement therapy may be permissive for tumor growth (242), while T3 obtains this effect only at supraphysiological doses (243). Possible effects of thyroid hormones on cancer cells include the amplification of *EGFR*, phosphorylation of insulin-like growth factor-1 receptor, stimulation of migration, a direct trophic effect on tumor cells, and angiogenesis and cell-specific antiapoptotic activity (242,244). However, effects of thyroid status on cancer cells may be cell type specific (245) and current experimental data need further prospective confirmation.

However, LT4 may be offered to cancer patients presenting with TKI-induced subclinical hypothyroidism and TAb, hypercholesterolemia, thyroid nodules, or symptoms, such as fatigue, that may greatly worsen patients' quality of life. Notably, in one study (185), at least half of patients who started LT4 for sunitinib-associated hypothyroidism had improvement in fatigue (185). Based on preclinical evidence showing that physiological doses of T4, but not T3, contribute to tumor growth, it has been recently reported that selective T3 supplementation in cancer patients may reduce the suggested risk of T4-induced tumor growth (246).

Conclusions

Thyroid dysfunction is emerging as a variably common endocrine toxicity of several anticancer drugs. However, the pathophysiology of thyroid toxicity induced by these agents remains to be fully clarified. Thyroid side effects induced by anticancer agents are generally manageable and dose reduction or discontinuation of the causative drugs is not required. Routine testing for thyroid abnormalities in patients receiving many of the current anticancer agents is recommendable at baseline, during the treatment, and the period of follow-up. Furthermore, thyroid function tests should be included in routine toxicity assessment of new TKIs and possibly of other classes of targeted drugs under clinical evaluation. The prognostic relevance of thyroid autoimmunity, overt and subclinical hypothyroidism induced by anticancer drugs, the value and the safety of thyroid hormone replacement in individuals with abnormal TSH following anticancer systemic therapy, and the correct timing of replacement therapy need to be defined more accurately. Additional prospective clinical trials are necessary to investigate these important aspects. These trials would offer a unique opportunity to clarify the underlying molecular mechanism of thyroid toxicities induced by an increasing number of anticancer agents and to find potentially predictive factors of thyroid toxicity in cancer patients.

Author Disclosure Statement

The authors declare that no competing financial interests exist.

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