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Thyroid Function Abnormalities in Patients Receiving Anticancer Agents

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1. Introduction

Advances in systemic chemotherapy and radiotherapy have had a profound effect on the prognosis of patients affected by many cancer histotypes. Nonetheless, one of the main challenges for modern oncology is in improving the tolerability of these treatments. The frequency and pathophysiology of the most common side effects induced by cytotoxic agents are well known. They may be immediate or delayed in onset and prevalently involve bone marrow, gastrointestinal system, liver, and cutaneous annexes.

Abnormalities in thyroid function and thyroid disease are variably associated with cancer or cancer therapy [1]. These disorders encompass a broad variety of pathophysiological mechanisms, may be subtle in presentation, sometimes difficult to be identified, and even more difficult to relate to a particular chemotherapeutic regimen due to the lack of specific wide clinical trials [2]. The alteration of thyroid hormone metabolism, more commonly known as “euthyroid sick syndrome”, may occur in patients with advanced cancers. Thyroid dysfunction, such as the altered synthesis or clearance of thyroid hormone-binding proteins are observed in certain malignancies, or may be caused by treatments that modify total but not free concentration of thyroid hormones. However, the clinical influence of this abnormalities is marginal, if any.

Endocrine disorders are among the most commonly reported long-term complications of cancer treatment by adult survivors of childhood cancers [3]. In adults, cytotoxic drugs are infrequently associated to overt endocrine toxicity. However, excluding gonadotoxic consequence [4], only few studies thoroughly evaluated the endocrine dysfunction induced by cytotoxic anticancer therapy in this population [2]. Similarly, hormonal therapies, widely used as effective treatment of patients affected by endocrine responsive breast cancer and

prostate cancer, have shown only marginally influence on thyroid function and thyroid toxicities attributed to these drugs are anecdotic.

In contrast to cytotoxics and hormonal therapies, several novel antineoplastic agents, including targeted therapies and immunotherapies, are unexpectedly associated with thyroid dysfunction and thyroid disease, despite their high selectivity of action [5].

Even diagnostic procedures using iodinated contrast agents can be associated with acute effects on the thyroid, including hyperthyroidism (i.e. in patients with thyroid autonomous nodules or mild Graves disease), or transient hypothyroidism (i.e. in patients with Hashimoto thyroiditis) [6,7]. Radiation therapy can be responsible for hypothyroidism from direct damage on the thyroid or secondary to hypopituitarism from brain irradiation. Irradiation received during childhood has been associated with thyroid nodules and thyroid cancer [8].

In this chapter, available data on thyroid abnormalities induced by anticancer drugs only are discussed.

2. Cytotoxic agents

Cytotoxic chemotherapy seems to alter endocrine functions in a relatively small proportion of patients and is infrequently associated with thyroid abnormalities in the absence of irradiation. Cytotoxics may sensitize the thyroid gland to the effects of concomitant radiation therapy, increasing the risk of radiation-induced primary hypothyroidism [9].

In a small published series, some agents such as 5-fluorouracil, glucocorticoids, estrogens, tamoxifen, podophyllin and L-asparaginase alter levels of thyroid hormone-binding proteins without any clinical consequence [10-15]. L-asparaginase can also be responsible for transient hypothalamic or pituitary hypothyroidism [16]. Other agents such as lomustine, vincristine, and cisplatin have *in vitro* effects on thyroid cells, but clinically relevant consequences have not been reported [17]. Mitotane is the only active agent against advanced adrenocortical cancer (ACC) and is under evaluation in patients who underwent radical resection of this rare disease. Mitotane showed a complex interference on the endocrine system that may require multiple hormone replacement therapy. In a prospective trial [18] on 17 patients who underwent radical resection for ACC, a marked reduction in free-T4 (FT4) levels was found, without any significant changes in serum thyroid stimulating hormone (TSH) and free-T3 (FT3) concentration. FT4 reduction was inversely correlated with mitotane concentrations and dropped in the hypothyroid range in most evaluable patients. These findings mimic central hypothyroidism and are consistent with data from clinical experiments which showed that mitotane directly reduces both secretory activity and cell viability on pituitary TSH-secreting mouse cells [19]. Alternatively, it has been suggested that mitotane may affect deiodase activity, thus changing the FT4 to FT3 ratio. However, despite limited information on free thyroid hormone concentrations during mitotane treatment has been reported, for some patients thyroxine replacement may be necessary [20].

An increased incidence of primary hypothyroidism has been documented in patients treated with multiple drug regimens, with or without radiotherapy [2]. In patients with testicular cancer who received combinations of cisplatin, bleomycin, vinblastine, etoposide, and dactinomycin, 4 out of 27 individuals (15%) developed primary hypothyroidism. In particular, the cumulative doses of cisplatin and vincristine seem to exacerbate these symptoms [21]. In another trial evaluating the combination of mechlorethamine, vinblastine, procarbazine and prednisolone (MOPP regimen) as treatment of Hodgkin's disease, 44% of patients developed elevated serum TSH concentrations, even though a causative role of iodine load during lymphangiography cannot be excluded [22]. Children with brain tumors (not involving the hypothalamic-pituitary axis) who receive vincristine, carmustine or lomustine, and procarbazine in combination and brain irradiation have a 35% incidence of hypothyroidism, compared with a 10% incidence in the group with brain irradiation alone [23]. Young age and use of chemotherapy have been associated with a higher incidence of hypothyroidism in patients receiving radiotherapy for medulloblastoma [24]. Again, the highest incidence occurred when the thyroid gland was included in the radiation field. Finally, there is no evidence that cytotoxic agents by itself may represent a risk factor for developing thyroid tumors, compared to radiotherapy [2].

3. Immunoregulatory agents

3.1. Cytokines

3.1.1. *Interferon- α*

Interferon- α is a human recombinant cytokine that increases the expression of major histocompatibility complex (MHC) class I and tumor-specific antigens on the tumor cell surface, stimulating immune-mediated destruction of these cells, as well as possibly exerting direct antitumor effects [25]. Interferon- α demonstrated variable efficacy in patients affected by melanoma, renal cell carcinoma (RCC), AIDS-related Kaposi's sarcoma, follicular lymphoma, hairy cell leukemia, and chronic myelogenous leukemia [25]. Reduction in viral load is another relevant activity of interferons. In combination with ribavirin, interferon- α prolongs survival in patients with hepatitis C [26,27]. Flu-like syndrome, malaise, neuropsychiatric disorders, hematologic and liver toxicity are the most common dose-limiting side-effects.

Thyroid diseases secondary to treatment with Interferon- α are common and may become clinically evident as destructive thyroiditis, autoimmune hypothyroidism or Graves-like hyperthyroidism. Patients receiving the drug for hepatitis appear more prone to present thyroid dysfunction than patients with malignant disease [28]. However, the infection from the hepatitis C virus itself has been demonstrated to increase the risk of thyroid damage [28]. The pegylated form of interferon- α is more effective than interferon- α in triggering antiviral response, but showed a similar rate of thyroid dysfunction [29].

Destructive or autoimmune thyroiditis is the most common thyroid abnormality following treatment with interferon- α . This condition may lead to hypothyroidism after a brief

thyrotoxic phase and usually occurs in the first few weeks of interferon treatment and is in close temporal relationship with the appearance of thyroid autoantibodies, especially anti-thyroglobulin (anti-TG) antibodies. Another form of autoimmune thyroid toxicity associated to interferon- α is characterized by the development of thyroid antibodies without hypothyroidism. In the setting of interferon therapy, the risk of hypothyroidism is 2.4%–10% [30–35], with a risk of thyroid autoimmunity onset (including development of thyroid autoantibodies) approaching 20% [36,37]. Hypothyroidism is persistent in the majority of patients [33,38], even though although transient hypothyroidism has also been described [39]. The presence of anti-thyroperoxidase (anti-TPO) antibodies before treatment considerably increases the risk of hypothyroidism [40–42]. Thyroid abnormalities can occur as early as 4 weeks and as late as 23 months after initiating treatment, with a median of 4 months [30,34].

Interferon- α has also been associated with classical Graves disease and sometimes Graves' ophthalmopathy also develops, however the latter is less common [30]. This condition does not generally remit on withdrawal of the drug [35].

Several evidence supports the hypothesis that thyroid toxicity may likely be related to an autoimmune response to interferon- α . Overexpression of MHC class I antigens are associated with activation of cytotoxic T-cells resulting in cellular destruction [43]. It has been reported that interferon- α increases MHC class I expression on thyroid tissue from Graves patients, provided that lymphocytes are present in the thyroid tissue [44]. Hence, interferon- α might worsen local immune response in subjects who have preexisting subclinical thyroiditis with intrathyroidal lymphocytes [44]. In addition, interferon- α can shift the immune response to a Th1-mediated immune response, with increased production of the proinflammatory cytokines interferon- γ and interleukin-2, which may in turn amplify an autoimmune response. Interferon- α has been demonstrated to elicit a direct damage on thyroid cells, which may be responsible for the onset of destructive thyroiditis [28,35,42,45]. However, despite accumulating evidence, the precise mechanisms underlying thyroid toxicity associated to interferon, especially in cancer patients, remain to be elucidated.

Levothyroxine (LT4) therapy is indicated as treatment of interferon-induced hypothyroidism and withdrawal of interferon is not generally needed. When destructive thyroiditis is present, treatment with corticosteroids is needed and β -blockers are often useful to control the signs and symptoms of thyrotoxicosis. When interferon causes hyperthyroidism, antithyroid agents such as methimazole or propylthiouracil may be administered, if clinically indicated. In patients with relapsing flares of thyroiditis during prolonged courses of interferon- α , ablation with ^{131}I during remission may be offered to prevent further episodes of the condition [46].

Despite specific recommendations for patients treated with interferon- α for oncological diseases are lacking, it appears rational to apply the recommendations available for patients with hepatitis C [47]. In particular, the same serological screening is suggested, including pretreatment TSH and anti-TPO antibodies evaluation, followed by TSH serum

measurement every 2 months and then every six months in the case of negative anti-thyroid peroxidase (anti-TPO) antibodies [1].

3.1.2. *Interleukin-2*

Interleukin-2 is a cytokine involved in several mechanisms of immune response, including activation of natural killer cells and antigen-specific T-cells. These properties are used to stimulate tumor cell killing, also in combination with interferon or lymphokine-activated killer cells. Interleukin-2 is approved for the treatment of metastatic melanoma and RCC, although its use has been recently reduced in concomitance with the availability of more effective and better tolerated agents.

Several autoimmune side-effects have been associated to interleukin-2 therapy, including thyroid disease with an incidence of 10%–50% [48-54]. Hypothyroidism usually occurs 4–17 weeks after initiation of treatment [48,49]. It may be reversible following discontinuation of the drug [49,55]. Most patients who developed hypothyroidism showed positive anti-TG or anti-TPO antibodies. In addition to hypothyroidism, thyroiditis and thyrotoxicosis have also been reported at a lesser frequency [55,56]. An early phase of presumably destructive thyrotoxicosis is common, with variable degrees of hyperthyroidism [57].

Evidence suggests that thyroid disease associated to interleukin-2 may be induced by stimulating autoreactive lymphocytes, leading to autoimmune thyroiditis. Patients under treatment with interleukin-2 showed high levels of interferon- γ and tumor necrosis factor- α , which may trigger autoimmunity by enhancing the presentation of human leukocyte antigen class II and associated autoantigens by thyrocytes. Also, interleukin-2 may have direct effects on thyrocyte functioning [58,59]. Increase in serum thyroid autoantibodies levels [48,53] and lymphocyte infiltration of the thyroid gland [57] were found in patients treated with interleukin-2, suggesting a cell-mediated autoimmune mechanism. Similarly to interferon, preexisting positivity of thyroid autoantibodies seems to predict an increased risk of developing hypothyroidism during interleukin-2 treatment [49].

Occurrence of hypothyroidism was associated with a favorable response to treatment [48,60], but other studies did not confirm these results [61]. It has been suggested that thyroid dysfunction may develop more often in the responders because they receive longer courses of the treatment [46,62]. Patients with interleukin-2-induced hypothyroidism may be treated with LT₄, while thyrotoxicosis only requires symptom control with β -blockers and corticosteroids. Measuring TSH before treatment and then every 2–3 months during treatment with interleukin-2 is advisable [1].

3.2. **Thalidomide and lenalidomide**

Thalidomide and lenalidomide are immunomodulatory drugs with antineoplastic activity [63,64]. These agents enhance T-cell stimulation and proliferation, induce endogenous cytokine release, and increase number and function of natural killer cells, thus enhancing

immune-mediated destruction of tumor cells. They also inhibit proliferation and induce apoptosis of tumor cells and exert antiangiogenic activity [63,64].

Thalidomide and lenalidomide are approved for the treatment of multiple myeloma. Lenalidomide has also been approved for 5q myelodysplastic syndrome. Both agents are under evaluation for the treatment of several solid tumors, including thyroid cancer [65-67] and for a range of autoimmune diseases [68].

Hypothyroidism has been associated to treatment with these drugs with varying grades and frequency [68-71]. In a recent study on patients affected by multiple myeloma and treated with thalidomide [69], subclinical hypothyroidism was reported in 20% of participants, and 7% showed overt hypothyroidism, mostly occurring 1–6 months after initiating treatment [69].

Lenalidomide is more potent and showed a more favorable toxicity profile compared to thalidomide [72,73]. Hypothyroidism due to lenalidomide has been reported in 5%–10% of patients [74,75]. Thyroid abnormalities were found in 10 out of 170 patients who received lenalidomide for various hematological cancers. After a median of 5 months of therapy the patients reported both hypothyroidism and thyrotoxicosis. However, many of them had been exposed to prior radiation or thalidomide [76].

Many mechanisms have been suggested for the hypothyroidism induced by these drugs [69], including inhibition of thyroid hormone secretion [77] or a reduction of iodine uptake into follicular cells [78]. Most probably, since thalidomide and lenalidomide exert an antiangiogenic activity, compromise the blood flow to the thyroid may explain thyroid toxicity [69]. In some patients, TSH suppression has been documented before the development of hypothyroidism, suggesting ischemic thyroiditis [69]. Alternatively, a thyrotoxicosis triggered by an immune-mediated destructive thyroiditis may be hypothesized. This condition may be induced by deregulation of cytokine levels or through direct effects on T-lymphocytes [69]. A direct toxic effect on thyroid cells is also possible, but this has not been evaluated. TSH measurement before treatment and then every 2–3 months during treatment is recommended [1,79].

3.3. Anti-CTLA4 monoclonal antibodies

Ipilimumab and tremelimumab are monoclonal antibodies directed against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) (anti-CTLA-4 mAbs), a receptor expressed on T-cells that exerts a suppressive effect on the immune response after T-cell/antigen-presenting cell interaction [80]. Blocking the receptor, an increased T-cell activation and antitumor effects are obtained. Ipilimumab is approved for the treatment of unresectable or metastatic melanoma.

These agents have been associated with several immune-related adverse events (IRAEs), most frequently enterocolitis, hepatitis, cutaneous reactions [81-83]. The spectrum of autoimmune endocrine adverse events experienced by patients treated with anti-CTLA-4 mAbs includes hypopituitarism, primary thyroid disease, and sporadically primary adrenal

insufficiency [84]. The prevalence of autoimmune hypophysitis varies among different studies (0%–17%) [85], being 3-5% in larger studies. Similarly to classical autoimmune hypophysitis, secondary hypothyroidism has been reported in patients who develop hypophysitis induced by anti-CTLA-4 monoclonal antibodies.

Direct damage to the thyroid induced by these agents presents two clinical common forms: hyperthyroidism in Graves' disease and thyroid destruction with hypothyroidism in Hashimoto's thyroiditis. Since these conditions are classically included in autoimmune thyroid diseases phenotype and previous studies suggested that *CTLA-4* is a candidate gene conferring susceptibility to thyroid autoimmunity [86], an autoimmune pathogenesis has also been suggested for thyropathies induced by anti-CTLA4-mAbs (anti-CTLA4-IT). The incidence of these conditions varies from 0 to 4% among the different trials. In two studies [87,88], tremelimumab (15 mg/Kg body weight) was associated with thyreopathy (hyper/hypothyroidism, autoimmune-thyroiditis, or Graves' disease) in 4% of cases. In studies on ipilimumab, the reported incidence of anti-CTLA4-IT was apparently lower, namely 0-2%, being mild hypothyroidism the most frequent thyroid side-effect. Recently, Hodi et al. in a large phase III trial, reported for the first time an improvement in overall survival obtained by ipilimumab in pretreated patients affected by metastatic melanoma [89]. The treatment was associated with thyroid disorders or abnormal thyroid function tests in approximately 2% of patients. In a randomized phase II study on a cohort of 115 patients affected by metastatic melanoma, evaluating the potential protective effect of budesonide on IRAEs induced by ipilimumab, hypothyroidism was diagnosed in 5.3% of patients who received ipilimumab with placebo (3 out of 57 patients; with severe hypothyroidism in one of them, 1.8%), compared with no cases in the group of patients treated with budesonide as well. These data suggest a potential protective effect of budesonide in terms of reduced incidence of ipilimumab-related thyroiditis, but this hypothesis needs to be confirmed in specifically designed clinical trials [90].

In a phase I study [91] evaluating the combination of ipilimumab (10 mg/Kg every 3 weeks for 4 cycles, than every 3 months) with bevacizumab (7.5 mg/kg - Cohort 1; 15 mg/kg - cohort 2 every 3 weeks) in a group of 21 patients affected by unresectable stage III or stage IV melanoma, thyroiditis was diagnosed in 4 (19%) patients. No cases of endocrine-IRAEs were reported in a trial on 36 patients who received both ipilimumab (0.1-3 mg/kg; 24 patients received the higher dose) and interleukin-2 (720,000 IU/kg every 8 hours) which is not infrequently associated with autoimmune thyroiditis [92].

The onset of anti-CTLA4-IT appears rather earlier than other IRAEs, occurring after 2-4 infusions. In most cases the anti-CTLA4-ITs have a subclinical course or may be transient. Alternatively, this condition may be characterized either by hypothyroidism with increased serum TSH concentrations, normal free-T4, and presence of anti-TPO antibodies, less frequently anti-TG antibodies or evolve in permanent hypothyroidism, requiring thyroid hormone supplementation [93].

Sporadic cases of Graves' ophthalmopathy associated with ipilimumab therapy in euthyroid patients have been reported [82,94]. In these cases the effective treatment was to administer a high dose of glucocorticoids in the acute phase, rapidly tapered down and continue with

hydrocortisone, if required. None of the patients affected by anti-CTLA4-IT showed concomitant hypophysitis or other IRAEs.

Patients who need to receive anti-CTLA-4 mAbs should be carefully informed on the importance of observing and early reporting signs or symptoms potentially related to IRAEs, and that these symptoms may occur weeks to months after starting treatment. In these patients, TSH, free-T₄, serum electrolytes, serum glucose, and blood cell counts should be assessed before initiating treatment and before each cycle.

3.4. Tyrosine kinase inhibitors

Tyrosine kinase inhibitors (TKIs) have emerged as a new class of molecular targeted anti-cancer agents with proven efficacy in several types of carcinoma and in some hematologic cancers. At the moment, about 150 kinase-targeted drugs are in clinical development and many more are in various stages of preclinical development [95].

The registered kinase inhibitors are small molecules, that, with sporadic exceptions, exert their pharmacological action at the ATP-site of a wide variety of tyrosine kinases critical for tumor cell survival and proliferation and angiogenesis. TKIs compete with ATP for binding to the catalytic domain that act by preventing ATP binding to these targets with different selectivity, potency and pharmacokinetic properties. However, despite their inherent selectivity, the available TKIs showed a variable grade of affinity for the different tyrosine kinases, but none specific for a single kinase. In addition, interference is frequently extended to off-target intracellular processes of normal cells. As a direct consequence, TKIs may cause a number of infrequent or even new toxicities. TKI-induced endocrine side effects mainly include thyroid dysfunction and disease, but also may be responsible for gonadal and adrenal dysfunction, bone and glucose altered metabolism, impairment in linear growth and fetal development [96].

Two types of thyroid dysfunctions have been observed with TKIs [97]. The first is worsening of hypothyroidism in patients under satisfactory treatment with thyroid hormone replacement. This effect was initially noted in patients under treatment with imatinib, but also other TKIs were found responsible for increase in LT₄ supplementation in hypothyroid patients [98-102]. The second type of thyroid disturbance is primary hypothyroidism in patients with previously normal thyroid function. Almost all TKIs are responsible, at a variable extent, of primary hypothyroidism, with the exception of gefitinib and erlotinib.

The mechanisms of TKI-induced thyroid dysfunction are unclear. An increase in the requirement of replacement therapy with LT₄ during certain TKIs has been suggested to be dependent on possible interference of the drug at nondeiodination clearance of LT₄ [98]. Several drugs (e.g. phenobarbital, phenytoin, carbamazepine, rifampicin, and nifedipine) can increase thyroid hormone clearance through the induction of hepatic microsomal enzymes, including mixed function oxygenases and uridine diphosphate-glucuronosyltransferases [103]. These drugs can cause hypothyroidism in patients who

undergo LT4 [11,104-106]. For example, imatinib is a potent competitive inhibitor of several mixed function oxygenases (CYP2C9, CYP2D6, and CYP3A4/5), and the induction of uridine diphosphate–glucuronosyl transferases has been hypothesized to be a possible mechanism of interference of imatinib on levothyroxine metabolism [98]. Alternatively, an interference of sunitinib with thyroid hormone action at the pituitary level has been suggested [122].

TKI-induced hypothyroidism (*de novo* primary hypothyroidism) may have several explanations. In some cases thyrotoxicosis may precede the development of hypothyroidism, suggesting a thyroiditis-induced thyrotoxicosis [107,108,123]. Other possible mechanisms include direct toxic effects on thyrocytes, namely the reduced synthesis of thyroid hormones related to inhibition of thyroid peroxidase activity [109], impaired iodine uptake [110], the drug induced regression of the gland vascular bed with significant capillary alteration and reduction in density [111]. However, a role for iodine uptake in TKI-hypothyroidism was not confirmed by *in vitro* studies [112] and anti-peroxidase effect seems unable to provide an explanation for cases with initial destructive thyrotoxicosis, or with thyroid atrophy.

Induction of Hashimoto thyroiditis has also been proposed [113], although Hashimoto thyroiditis is unlikely to be the main mechanism because of the low prevalence of anti-TPO antibodies.

The most likely explanation is that the thyroid dysfunction may be related to the effects of these agents on tyrosine kinase receptors involved in vascular function, such as vascular endothelial growth factor (VEGF) receptor (VEGFR). This could cause a reduction in thyroid blood flow to this extremely vascular gland. If the blood flow decreases rapidly, an ischemic thyroiditis could result, leading to a transient period of thyrotoxicosis. If the decreased blood flow develops more slowly, gradual thyroid destruction may occur with resulting hypothyroidism [114]. Supporting evidence for this theory include findings that thyroid cells express VEGF and VEGFR mRNA, and preclinical studies in mouse models have shown glandular capillary regression with TKI exposure [115]. In humans, case reports demonstrated reduced thyroid volume and reduced vascularity by Doppler ultrasound [116,117], with rapid increase in the size of the thyroid with cessation of sunitinib. This reduced thyroid volume secondary to reduced blood flow, may also explain the impaired radioactive iodine uptake *in vivo*, but not *in vitro* [118]. However, the role of VEGF in thyroid signaling is uncertain. Unlike treatment with antiangiogenic TKIs, bevacizumab is not associated with altered thyroid homeostasis [119]. In addition, *in vitro* experiments showed that VEGF reduces TSH induced iodine uptake by thyroid cells, and inhibition of VEGF restores iodine uptake [120]. Other factors, such as platelet derived growth factor α and c-KIT, contribute to maintaining thyroid homeostasis, but so far no data on their role in this toxicity have been published.

3.4.1. Imatinib

Imatinib inhibits the kinase activity of the tyrosine kinases of breakpoint cluster region proto-oncogene ABL1 (BCR-ABL fusion protein), c-Kit and platelet derived growth factor

receptor (PDGFR) α/β . It is currently approved for the treatment of chronic myeloid leukemia, gastrointestinal stromal tumors (GIST) and dermatofibrosarcoma protuberans. The influence of daily 400–800 mg imatinib on LT4 was reported in a cohort of 11 patients (10 with medullary thyroid carcinoma and 1 with GIST) [98]. Among the patients with medullary thyroid carcinoma, eight underwent thyroidectomy and received LT4 and three had thyroid carcinoma *in situ*. Thyroid function was evaluated before, during and 2 weeks after therapy with imatinib or LT4. Symptoms of hypothyroidism occurred in all patients who had undergone thyroidectomy, but not in those with intact thyroid. Patients who had undergone thyroidectomy had markedly elevated TSH levels, and required an increase of LT4 during imatinib dosing. The effect was reversible after discontinuation of treatment, suggesting that imatinib might be the causative agent.

In another study on 68 patients with intact thyroid gland who received imatinib for chronic myeloid leukemia, no case of drug-induced alterations in thyroid laboratory parameters was observed. These data sustain the hypothesis that imatinib-induced thyroid dysfunction is limited to athyreotic patients and are not the consequence of a direct action of the drug on thyroid gland [121], but more probably of an interference of the drug in the nondeiodination clearance of LT4 through the induction of hepatic microsomal enzymes [98].

3.4.2. Sunitinib

Sunitinib is an oral, multitarget inhibitor of VEGF receptor 1 (VEGFR1), VEGFR2, Fms-like tyrosine kinase 3 (Flt3), colony stimulating factor 1 receptor (CSF1R), RET, c-Kit, and PDGFR. This agent has been found to influence the thyroid function of patients with GIST or RCC.

In total, 2 out of 56 patients with RCC and a history of well controlled hypothyroidism, and 7 out of 21 patients with imatinib-resistant GIST, had a worsening hypothyroidism during sunitinib treatment [109,111,122], reported the case of a woman with GIST who was resistant to imatinib and received LT4 after thyroidectomy and ^{131}I -ablation for follicular thyroid carcinoma. The patient's dose of LT4 needed to be increased after sunitinib treatment. In this report, the marked increase in TSH levels has been attributed to a potential interference of sunitinib with thyroid hormone action at the pituitary level [122].

Desai *et al.* [123] prospectively evaluated the thyroid function tests (TFTs) in a phase I/II study of sunitinib therapy in 42 patients with imatinib-resistant GIST. Most patients received 50 mg sunitinib daily every 4–6 weeks, each consisting of 2–4 weeks of sunitinib followed by 2 weeks of wash-out. Initially, TFT were performed only if clinically indicated. Thereafter, serum TSH was evaluated before each sunitinib cycle. In total, 42 patients with normal baseline TFT who received at least 3 sunitinib treatment cycles for a median of 37 weeks were evaluated. Abnormal serum TSH concentrations were documented in 26 patients (62%). Sunitinib caused persistent primary hypothyroidism in 15 patients (36%), after an average of 50 weeks of therapy (range 12–94 weeks). Seven additional patients (17%) experienced transient, mild serum TSH elevation (5.0–7.0 mU/L). In 4 patients TSH was suppressed, but they discontinued treatment before the TFTs could be repeated. Out of

15 patients with hypothyroidism, 6 (40%) had at least one TSH value below 0.5 mU/L before developing the condition, which suggests a thyroiditis-induced thyrotoxicosis. The risk of hypothyroidism increased with the duration of sunitinib therapy. Subclinical or overt hypothyroidism was observed in 4 out of 22 patients [18%] who received sunitinib for 9 months, and in 5 of 17 patients (29%) who received sunitinib for longer than 12 months. In patients treated for longer than 96 weeks, 90% developed increased levels of TSH. The mean time to onset of hypothyroidism was 50 weeks. Among the patients with TSH concentrations greater than 10 mU/L, none had spontaneous biochemical resolution. During the titration of LT4, serum TSH values remained elevated for a median of 17 weeks (range 4–117 weeks). The TSH concentrations returned to normal in all patients who received conventional doses of LT4. Interestingly, in 2 patients with hypothyroidism and normal baseline TFTs, ultrasonography revealed atrophic thyroid tissue, which suggests destructive thyroiditis. This clinical trial was the first to report the prevalence of sunitinib related hypothyroidism [123].

Rini *et al.* [111] described thyroid abnormalities in a retrospective study of 66 patients with metastatic RCC treated with sunitinib. In all, 30 patients were pretreated with cytokine-based therapy (6 of them were treated with bevacizumab), and 30 patients were treatment-naive. All patients received the standard sunitinib dose of 50 mg daily for 4 weeks, followed by 2 weeks off therapy. TFT assessment, including free thyroxine index, was initiated in 29 patients (and subsequently in another 37 patients) as a routine laboratory assessment at baseline and on day 28 of every even numbered cycle. Out of the 66 patients, 56 (85%) had one or more TFT abnormality. These abnormalities were consistent with hypothyroidism in all patients and primarily included the elevation of TSH, decreased levels of T3 and, less commonly, decreases in T4 and/or of the free thyroxine index. TFT abnormalities were detected early (the median time of detection was at cycle 2). Among patients with abnormal TFTs, signs and symptoms related to hypothyroidism were found in 47 patients (84%). These symptoms included fatigue, cold intolerance, anorexia, periorbital edema, fluid retention, and alterations in skin or hair. LT4 therapy was given at the discretion of the physician, on the basis of the degree of biochemical abnormality and/or clinical symptoms. A resolution of biochemical abnormalities occurred in all 17 patients treated with LT4, and an improvement of symptoms was recorded in 9 patients. Anti-TG antibodies were measured in 44 patients and were abnormal in 13 (30%). No association was observed between the presence of anti-TG antibodies and the incidence or severity of TFT abnormalities [111].

Feldman *et al.* [124] reported that hypothyroidism was found in 14 (18%) out of the 80 patients enrolled in a prospective clinical trial that investigated the efficacy of sunitinib in metastatic RCC. Serum TSH levels were obtained only from symptomatic patients and ranged from 6.0 to 146.4 mU/L (normal range 0.35–5.5 mU/L). Hypothyroidism was detected after a median time of 10 months of therapy (range 1–26 months), being fatigue the predominant symptom. The Authors highlighted that the lower incidence of hypothyroidism reported might depend on the fact that TFT assessment was performed on symptomatic patients only [124].

Wong *et al.* [109] explored the potential effects of sunitinib on thyroid function in a cohort of 40 patients affected by different tumor histotypes, the majority of whom were affected by imatinib-resistant GIST. In this study a new onset or worsening condition of hypothyroidism occurred in 21 out of 40 patients (53%) patients who underwent TFTs. Patients developed elevated TSH levels after a median of 5 months of treatment (range, 1–36 months). The median TSH level was 21.4 mU/L (range, 4.6–174 mU/L). The influence of sunitinib on peroxidase activity was assessed by testing its effects on guaiacol oxidation and protein iodination caused by lactoperoxidase. The potency of sunitinib antiperoxidase activity was about 25% of that noted with propylthiouracil. The Authors proposed that the antithyroid effect of sunitinib is mediated by the inhibition of peroxidase activity, which is involved in the synthesis of the thyroid hormone [109].

Wolter *et al.* [125] prospectively evaluated the incidence of hypothyroidism in patients with GIST or metastatic RCC treated with sunitinib at the standard dose [125]. TFTs included assessment of serum TSH, T3, free thyroxine index and thyroid antibodies (anti-TG, anti-TPO antibodies, and TSH receptor antibodies) and was measured on days 1 and 28 of each treatment cycle. The analysis revealed that 16 patients (27%) developed sub- or clinical hypothyroidism requiring thyroid hormone replacement and 20 patients (34%) showed at least one thyroid test abnormality. The median time to develop thyroid dysfunction was 4 weeks and patients who did not develop hypothyroidism within the first cycles did not develop hypothyroidism later during therapy.

In another prospective phase I-II study, Mannavola *et al.* [110] evaluated TFT (serum TSH, free T3 and T4, thyroglobulin, anti-TG and anti-TPO antibodies) in 24 patients with GIST who were treated with sunitinib (4 weeks of 50 mg daily and 2 weeks of withdrawal). Urinary iodine was measured in 18 patients and urinary fluorine was assessed in 10 patients. Thyroid ultrasonography and echocolor-Doppler were performed, both at enrollment and after a variable number of treatment cycles. To study thyroid function, ¹²³I thyroidal uptake and scintigraphy were performed in 6 unselected patients at the end of the treatment and withdrawal periods. Hypothyroidism was documented in 46% of patients, and a transient elevation of TSH levels in 25% of cases. The overall prevalence of elevated TSH levels after sunitinib was 71%. At onset, hypothyroidism was subclinical in all but one patient with Hashimoto thyroiditis, the only one with detectable antithyroid autoantibodies. TSH levels were found to fluctuate according to whether treatment was given or withdrawn, and progressively increased during treatment. In most cases, progressive worsening of hypothyroidism was shown, but in a few cases a sudden development of severe hypothyroidism was observed. The normal echographic and echocolor-Doppler patterns, obtained both at baseline and during treatment, indicate that hypothyroidism is unlikely to be the consequence of a direct toxic effect on thyroid cells or secondary to an autoimmune process. Inhibition of iodine uptake seems to be a more likely explanation for hypothyroidism. Indeed, radioiodine uptake impairment has been demonstrated by a reduced uptake at the end of treatment periods, with a partial or total recovery during the withdrawal phase. Of particular interest was the observation of a blunted early ¹²³I uptake curve, which suggests an alteration in the uptake phase rather than in the organification

process. The Authors noted that after sunitinib withdrawal, TSH levels returned to the normal range in a maximum of 60 days.

Interestingly, the association between TKI-induced thyroid dysfunction and clinical efficacy has been demonstrated in two larger studies. Schmidinger *et al.* [126] in a prospective analysis of 87 patients with metastatic RCC who were to receive treatment with sunitinib or sorafenib, thyroid function was monitored every 4 weeks during the first 2 months of treatment and every 2 to 4 weeks thereafter. Subclinical hypothyroidism was present in five patients at baseline and was diagnosed in 30 patients (36.1%) within the first 2 months of therapy. Patients with subclinical hypothyroidism had a statistically significant objective remission rate of 28.3% *versus* 3.3% in euthyroid patients ($p < 0.001$) and median duration of survival (not reached *versus* 13.9 months in euthyroid patients; $p = 0.016$). In addition, in a multivariate analysis, the development of subclinical hypothyroidism within 2 months of treatment was found to be an independent predictor of survival ($p = 0.014$). In another study on patients with metastatic RCC who received sunitinib or sorafenib, Riesenbeck *et al.* [127] found that 21 (38.1%) out of the 66 evaluable patients developed hypothyroidism. Hypothyroidism was associated with a longer PFS (16.0 ± 0.8 months *versus* 6.0 ± 0.8 months, $p = 0.032$). In agreement with the study by Schmidinger *et al.* [126], hypothyroidism was found to be an independent predictor of survival ($p = 0.01$) in a multivariate analysis.

3.4.3. Sorafenib

Sorafenib is an oral multikinase inhibitor that inhibits the kinase activity of RAF/MEK/ERK, VEGFR2 and VEGFR3, Flt3, fibroblast growth factor receptor 1, RET, cMET, PDGFR β , Kit and other receptors involved in tumor progression and angiogenesis. It is approved for the treatment of advanced RCC and unresectable hepatocellular carcinoma. In addition, it is under clinical evaluation in a number of tumor types, including lung, pancreatic, prostate, melanoma and differentiated thyroid cancer. Tamaskar *et al.* [114] retrospectively investigated the incidence of TFT abnormalities in 39 patients with metastatic RCC treated with 400 mg sorafenib twice daily. Most patients had received at least one prior treatment. Out of the 39 patients, 16 (41%) had one or more serum TFT values outside the laboratory normal reference range during treatment with sorafenib. The median timing of the abnormal test was 1.8 months (range 0.6–7.3 months). Biochemical hypothyroidism occurred in 7 out of 39 patients (18%) during treatment, which was first observed 2–4 months after sorafenib initiation. Six of these patients had mild TSH level elevations (5.5–10.0 mU/L). Another patient showed a rapid onset of hypothyroidism with TSH level rising from 5.74 to 160.64 mU/L, and T3 level decreasing from 72 to 49 ng/dl over 1.5 months. One patient had normal TSH concentration (2.42 mU/L) but low T3 and T4 at 4 months after starting sorafenib treatment, these abnormalities worsened over the next 4 months with further reductions of T3 and T4 levels, and abnormal TSH (9.930 mU/L). Both these patients received LT4. In two of the seven hypothyroid patients anti-TG antibody titers increased; two patients had persistent serum TSH elevation and in one case a normalization of the TSH values was observed.

Clement *et al.* [128] prospectively monitored thyroid function in 38 patients with metastatic RCC who were treated with sorafenib 400 mg twice daily. Thyroid function was assessed at baseline and on day 1 of each treatment cycle. Out of 23 patients with normal baseline thyroid function, seven patients (30%) developed at least one elevated serum TSH and 1 patient (5%) developed low TSH levels. For these abnormalities no therapy was required. In addition, out of 15 patients with either thyroid dysfunction at baseline or previous treatment potentially interfering with thyroid function, two patients with baseline subclinical hypothyroidism (defined as an increase in serum TSH above normal and ≤ 10 mU/L, with normal T3 and T4 values) developed clinical hypothyroidism (TSH ≥ 10 mU/L or T3 and T4 values below the normal range) requiring thyroid hormone replacement therapy.

In another prospective observational study [129] on 69 Japanese patients affected by metastatic RCC refractory to cytokine therapy and subsequently treated with sorafenib for at least 12 weeks, thyroid function was assessed before and every 4 weeks after the initiation of sorafenib treatment. Forty-six (67.7%) patients developed hypothyroidism. Interestingly, 11 (23.9%) of these patients first showed a suppressed TSH value accompanying the increase in free T3 and/or free T4, before developing hypothyroidism. This pattern clearly suggests that sorafenib may have induced thyroiditis. LT4 was needed by 4 patients (5.8%) who presented severe clinical symptoms caused by hypothyroidism. Among several factors examined, only age was significantly associated with the risk of developing hypothyroidism.

Sorafenib-associated thyroid dysfunction was not reported in two registration trials in patients affected by advanced hepatocellular carcinoma (HCC). More recently, in a series of 38 consecutive patients with HCC treated with sorafenib, 5 (13%) of them developed subclinical hypothyroidism (TSH levels, 7,41 μ IU/mL; range, 6,38-8,94 μ IU/mL (unpublished data) [130]. Other case reports of patients affected by HCC showed progressive destructive thyroiditis after taking sorafenib. These data highlight the possibility that also hypothyroidism induced by sorafenib may be the result of an initial thyrotoxicosis [131].

Abdulrahman *et al.* [132] in a small prospective study on 21 patients with progressive nonmedullary thyroid carcinoma treated with sorafenib, measured serum total T4, free T4, total T3, free T3, reverse T3, and TSH concentrations at baseline and after 26 weeks of treatment with sorafenib. Results from this study suggested that sorafenib enhances T4 and T3 metabolism, which may be probably caused by an increased type 3 deiodination.

3.4.4. Motesanib

Motesanib diphosphate is a highly selective, oral inhibitor of VEGFR-1, -2, and -3; PDGFRs and c-KIT. The association between motesanib and thyroid function was recognized in a phase II study of 93 patients with progressive radioiodine-resistant differentiated thyroid cancer who daily received motesanib diphosphate [102]. All the patients had previously undergone thyroidectomies and were on thyroid hormone replacement therapy. Increased serum TSH concentrations, hypothyroidism or both were observed in 20 patients (22%). The Authors suggested that alterations in the absorption or metabolism of LT4 may explain changes in thyroid hormone levels while on motesanib.

In a phase II study [101] on 91 patients affected by locally advanced or metastatic medullary thyroid cancer (MTC), motesanib was taken orally at the standard dose for up to 48 weeks or until unacceptable toxicity or disease progression. Thirty-seven patients (41%) had elevated serum TSH levels compared with baseline and/or hypothyroidism.

In another phase II study assessing the tolerability and activity of motesanib in 138 patients with imatinib-resistant GIST, only 3 patients (2%) developed hypothyroidism, but only in one case related to treatment [133].

3.4.5. Vandetanib

Vandetanib is an oral inhibitor of VEGFR-2 and -3, RET kinases, and at higher concentrations, the epidermal growth factor receptor kinases. This drug has been approved in the United States for unresectable locally advanced or metastatic MTC and is under evaluation in phase III trials on patients affected by several cancer types [134].

In a phase II study of vandetanib, 19 patients with advanced hereditary MTC received vandetanib 100 mg daily [135]. All patients had undergone prior total thyroidectomy and were receiving LT₄ therapy. In all 17 patients who had available baseline TFTs, an increase in serum TSH levels was observed. TSH elevation reached a maximum by day 84 after the start of vandetanib treatment with a median 7.3-fold increases over baseline. No patients were reported to have symptomatic hypothyroidism, but LT₄ was increased in two patients.

Interestingly, in a study on 39 patients with progressive medullary or differentiated thyroid cancer included in two randomized placebo-controlled trials using vandetanib 300 mg/day [136] LT₄ had to be increased by 50 µg/d to maintain serum TSH within the normal range, probably by increased type 3 deiodinase activity as described using sorafenib [132].

3.4.6. Axitinib

Axitinib is an oral TKI that acts selectively inhibiting all VEGFR kinases [137]. The drug is approved by the FDA for the treatment of advanced RCC after the failure of one prior systemic therapy. In a Japanese study on 18 patients affected by various solid tumors receiving axitinib at different dosage, 16 (89%) patients experienced elevation in serum TSH above the upper limit of normal range [138].

In a phase II study on 60 patients with thyroid cancers resistant or not appropriate for ¹³¹I, who received axitinib (starting dose, 5 mg orally twice daily), no thyroid tests abnormalities were registered, except for the initial decreases in thyroglobulin seen in most patients, regardless of their clinical response to therapy. In another phase II study on 62 patients with metastatic RCC refractory to prior therapies, including sorafenib, G1-2 hypothyroidism was registered in 29% of patients [139]. In preclinical studies with axitinib inhibition of VEGFR-2 and VEGFR-3 induced by axitinib lead to thyroid capillary regression [115,140]. Again, destructive thyroiditis mediated by the destruction of thyroid capillary appears a plausible mechanism of action explaining axitinib-associated hypothyroidism.

3.4.7. Nilotinib

Nilotinib is a second-generation TKI with greater potency and specificity for BCR-ABL inhibition compared with imatinib [141,142]. It is approved for the treatment of Philadelphia-positive chronic myeloid leukemia (Ph-positive CML). Kim et al. [143] retrospectively assessed the effect of nilotinib on TFT in 55 patients with Ph-positive CML. In 12 patients (22%), TFTs were consistent with hypothyroidism (6 subclinical, 6 clinical) and in 18 (33%) patients with hyperthyroidism (10 subclinical, 8 clinical) at some point during their therapy. Six (11%) of these patients were on thyroid medication prior to starting the nilotinib and in most patients an increase in LT4 dose was not required. In 4 patients evidence of thyroiditis was found (3 had positive anti-thyroid antibodies) with an episode of hyperthyroidism preceding the development of hypothyroidism.

Recently, a case of overt hypothyroidism following initiation of treatment with nilotinib has been described in a 76-year-old euthyroid male with CML [144]. Serum TSH was 30.23 $\mu\text{U/mL}$ with low free T4 and free T3, and negative anti-thyroid antibodies. The ultrasound examination showed a normal size gland, markedly decreased inhomogeneous echo signals and slightly reduced vascularity, all compatible with thyroiditis. In this case symptoms dramatically regressed following the initiation of LT4 and nilotinib was not withdrawn.

3.4.8. Dasatinib

Dasatinib is another second-generation TKI with activity against BCR-ABL and Src family kinases that is approved for the treatment of imatinib-resistant Ph-positive CML and Ph-positive acute lymphoblastic leukemia [145]. In a retrospective survey on patients with Ph-positive CML who received dasatinib, 5 (50%) patients had TFT abnormalities consistent with hypothyroidism (4 subclinical, 1 clinical) and 2 patients (20%) had thyroid values consistent with subclinical hyperthyroidism. No patient required LT4, except one patient who developed hypothyroidism and was also taking amiodarone, a medication known to cause thyroid dysfunction. Two patients were on LT4 prior to starting dasatinib and modification of LT4 was not required [143].

3.4.9. Pazopanib

Pazopanib is an oral angiogenesis inhibitor targeting VEGFR-1, PDGFR, and c-Kit. Pazopanib is under clinical development for the treatment of multiple tumor types and has been recently approved for the treatment of advanced RCC. Preliminary data on the incidence and severity of thyroid dysfunction in patients who received pazopanib as treatment for RCC in 3 prospective trials have been recently reported [146]. TFTs were systematically assessed in 578 patients with serum TSH values collected at baseline and every 12 weeks and serum free T3 and T4 at baseline and if TSH was abnormal during the treatment. Elevated TSH ($>5 \mu\text{UI/mL}$) before initiating pazopanib was found in 37 (6%) patients. TSH value $>5 \mu\text{UI/mL}$ during the treatment was found in 167 (29%) patients. Overt hypothyroidism was diagnosed in 34 (6%) patients. Hyperthyroidism was seen in 8 (1%)

patients. Only 20 (3%) patients with a TSH elevation received LT4. Hypothyroidism was registered as a Grade 1/2 adverse event in 26 (4%) patients. Thyroid dysfunction was never reported as a severe adverse event in any patient.

3.4.10. Cediranib

Hypothyroidism was also reported with cediranib, another blocker of VEGFR 1-3 and c-Kit kinases in 45% of patients affected by advanced non-small-cell lung cancer enrolled in a randomized, double-blind trial of carboplatin and paclitaxel taking either oral cediranib or placebo daily [147]. Similarly, in a randomized phase II study on 46 patients affected by recurrent epithelial ovarian or fallopian tube cancer and treated with cediranib as single agent, Grade 2 hypothyroidism occurred in 56% of patients [148]. Details regarding the rate of patients requiring LT4 or effects of this treatment on hypothyroidism-related symptoms was not reported.

3.5. Bexarotene

Bexarotene is a selective agonist of the retinoid X receptor (RXR), a nuclear hormone receptor. It is approved for the treatment of cutaneous T cell lymphoma and has been found to induce secondary hypothyroidism [102]. Bexarotene appears to interfere with the normal feedback of thyroid hormone on the pituitary gland [102,149]. T3 binding to its receptor in the pituitary leads to heterodimerization of the receptor with RXR, which suppresses transcription of the β -subunit of TSH, which is required for thyroid stimulation. Bexarotene also has TSH-independent effects on thyroid hormone metabolism. Thyroidectomized thyroid cancer patients receiving thyroid hormone replacement who started bexarotene had a dramatic decrease in total T3 and T4, and free T4 levels with TSH levels that failed to rise appropriately [150]. This may be probably due to an effect on peripheral thyroid hormone metabolism via non-deiodinase mechanisms.

4. Why is it important to assess thyroid function in cancer patients?

Abnormalities of thyroid function induced by anticancer drugs are variably common, accordingly to the agent used. Identifying thyroid dysfunction and disease in cancer patients may have important consequences for diagnostic, therapeutic and prognostic purpose.

Diagnostic challenges are tendered by symptoms of thyroid dysfunction. For example, fatigue and constipation are present in the majority of patients with hypothyroidism, but they may be caused also by underlying malignancy, antineoplastic treatment(s) received, or medications used for control of other symptoms (i.e. nausea or pain) [1]. Similarly, many symptoms of thyrotoxicosis are similar to those attributable to other complications, such as sepsis. Inability to diagnose the presence of thyroid dysfunction or disease as treatment-related toxic effects may lead to misguided treatment strategies, unjustified dose reduction or even to treatment withdrawal [1]. In addition, unrecognized hypothyroidism or

thyrotoxicosis may affect the metabolism of other medications [151]. Finally, it should be considered that thyroid dysfunction, although rarely, can lead to life-threatening consequences in cancer patients, as warned by case reports of patients who experienced myxedematous coma [152] or impaired cardiac function [153,154] as a complication of TKI-induced hypothyroidism (i.e. sunitinib).

Therefore, clinicians should maintain an adequate level of surveillance for thyroid abnormalities when patients receive certain anticancer treatments, such as TKI or certain immunomodulatory drugs, present with symptoms consistent with hypothyroidism (i.e. constipation, bradycardia, hypothermia, unexpected weight gain, dry skin or dry hair and brittle nails) or thyrotoxicosis (i.e. palpitations, weight loss, heat intolerance, frequent bowel movements, tremor, proximal muscle weakness, tachycardia, lid retraction or lid lag, insomnia, irritability, fever). Of note, hypophysitis has recently emerged as an unusual, peculiar side effect of ipilimumab/tremelimumab. Symptoms like headache, visual impairment, nausea, vomiting, loss of appetite, fatigue, weakness, asthenia, fever, lethargy, hypotension, hypoglycemia and hyponatremia in patients recently treated with ipilimumab should lead physicians to suspect hypophysitis. The early diagnosis of this side-effect allows to prevent primarily a life-threatening complication such as adrenal insufficiency, but also central hypothyroidism and other endocrine consequences of hypopituitarism [84]. Monitoring thyroid function even in asymptomatic patients has emerged as a prognostic tool as well. A lower cancer risk and a more indolent disease has been noted in patients with primary hypothyroidism and breast cancer [155]. The association between the appearance of treatment-induced hypothyroidism has been related to an increased likelihood of response to therapy and even of better outcomes. The development of hypothyroidism following radiotherapy for head and neck cancer was associated with better survival [156]. Propylthiouracil-induced hypothyroidism was associated with improved survival in patients with glioma [157]. Thyroid autoimmunity may predict an improved tumor response to interleukin 2 therapy for melanoma [62] and RCC [48,49,60]. When patients with RCC are treated with sorafenib or sunitinib, a higher rate of remission and better overall survival are seen in those who developed hypothyroidism compared to those who did not [126,158]. Studies of anti-CTLA4 monoclonal antibodies suggest that the presence of immune-related adverse events, including hypophysitis and thyroiditis, is associated with better clinical outcomes [159].

In patients who are going to start drugs potentially associated with thyroid side-effects, an accurate screening for thyroid function should be carried out at baseline and monitored throughout the period of treatment and follow-up. Despite specific guidelines generated by high level evidence are lacking, rational approaches have been proposed [1,160].

Successful treatment of thyroid dysfunction such as hypo- and hyperthyroidism, is likely to improve patient quality of life and may prevent erroneous withdrawal from effective anticancer therapies. Patients with TSH greater than 10 mIU/L or with low free T4 levels, should receive thyroid hormone replacement with LT4 at an average dose of 1.6 µg/kg per day. In the case of coronary artery disease, a lower initial dose (e.g. 50 µg/d) should be used

for the first few weeks [1]. Monitoring thyroid hormone replacement is usually carried out by serum TSH measurements, aimed at maintaining TSH within the normal range. On the contrary, in patients who develop central hypothyroidism (i.e. secondary to bexarotene and anti-CTLA4 monoclonal antibodies), TSH concentrations cannot be used, and free T4 levels should be monitored, with a goal of about 1–1.5 ng/dL [1].

The treatment of subclinical hypothyroidism (TSH 5–10 mIU/L with a normal free T4) is questionable in cancer patients. In general, treatment of this condition is discouraged in a healthy population because there is insufficient evidence of benefit [161,162]. However, it may be offered to patients with subclinical hypothyroidism and antiTPO/anti-TG antibodies, hypercholesterolemia, thyroid nodules, or symptoms (i.e. fatigue) that may greatly worsen quality of life of patients [5]. In one study [111], at least half of patients who started LT4 for sunitinib-associated hypothyroidism had improvement of their symptoms of fatigue [111]. Conversely, Garfield et al. [163] warned that some preclinical, epidemiological and clinical evidence suggests that LT4 is permissive for tumor growth. Possible actions 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, cell specific anti apoptotic activity and angiogenesis [164].

Practical suggestions for the treatment of individual cancer patients showing TKI-induced subclinical hypothyroidism are available [5]. However, the best approach seems to start low-dose LT4 in individual patients as a therapeutic trial [1]. This prudent method may be extended to patients who develop this condition as a side effect of other anticancer agents. However, specific prospective studies evaluating the influence of thyroid replacement therapy in cancer patients, not only in term of quality of life, but also in term of survival, are urgently needed [165]. Thyrotoxicosis induced by anticancer drugs may result from an Hashi-toxicosis or Graves' disease. Thyrotoxicosis from thyroiditis is generally self-limiting and specific treatment is not required. Corticosteroid and β -blockers, usually propranolol, can be efficacious in symptom control. However, patients with this side effect should be monitored for subsequent hypothyroidism. Patients presenting with Graves disease, are usually treated with antithyroid drugs (i.e. methimazole), followed by ¹³¹I ablation if indicated. However, due to its complexity, anticancer drug-induced thyrotoxicosis is advisable to be managed under close consultation with an endocrinologist [1].

5. Conclusions

Thyroid dysfunctions are emerging as a variably common endocrine toxicity of several highly selective anticancer drugs. Routine testing for thyroid abnormalities in patients receiving these agents are recommended at baseline, during the treatment and follow up. Furthermore, thyroid function tests should be included in routine toxicity assessment of TKIs and possibly in other classes of targeted drugs under clinical evaluation. Hypothyroidism *per se* is not an indication for dose reduction or discontinuation of these agents. The clinical relevance of overt and subclinical hypothyroidism, the value of thyroid hormone replacement in individuals with abnormal serum TSH levels following anticancer

systemic therapy, and the correct timing of thyroid replacement therapy need to be more accurately defined. Additional prospective clinical trials are necessary to investigate these important aspects. In parallel, these trials could offer the unique opportunity to clarify the molecular mechanisms underlying thyroid toxicities induced by an increasing number of anticancer agents.

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