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EDITORIAL

Thyroid dysfunctions induced by molecular cancer therapies: a synopsis for nuclear medicine thyroidologists

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There is increasing evidence and awareness of the impact of targeted cancer therapies, such as tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICPIs) on thyroid function. Tyrosine kinase inhibitors and ICPIs have found applications in different types of cancer as summarized in Table 1. Therefore, a large number of cancer patients are at risk to develop various forms of thyroid dysfunction. In turn, thyroid dysfunctions may negatively impact the course of underlining cancer disease and the quality of life of cancer patients. Nuclear medicine physicians are involved in diagnosis, staging, monitoring (molecular imaging), and therapy (theragnostics) of cancer patients and, especially in Europe, they are also involved in the clinical care of thyroid patients (i.e., nuclear medicine thyroidology). Then, being aware of the multiple and complex interactions between TKIs and ICPIs and thyroid functioning is the key for (1) appropriate diagnosis and management of therapy-induced thyroid dysfunctions and (2) accurate interpretation of thyroid findings on molecular imaging (i.e., [^{18}F]FDG) during targeted therapy.

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Tyrosine kinase inhibitors and thyroid dysfunction

Many studies are suggesting an undeniable effect of TKIs on thyroid function in the form of primary hypothyroidism, commonly preceded by transient thyrotoxic phase, in 20–40% cases [1, 2], while autoimmune hyperthyroidism (i.e., Graves' disease) is rare [3]. The mechanism of TKIs' influence on thyroid dysfunction is not completely understood. Possible explanations, however, are inhibition of the thyroid tyrosine kinases' vascular endothelial growth factor receptors (VEGFRs), inhibition of RET proto-oncogene products, reduction of iodine uptake, and inhibition of peroxidase enzyme activity (Fig. 1). Thyroid dysfunctions occur at very different time points, from a few weeks to several months after TKI initiation. In addition, TKIs may also cause increased levothyroxine demand in thyroidectomized patients. Abdel-Rahman and Fouad performed a meta-analysis of 12 clinical trials to investigate the association of TKI with thyroid dysfunction and found a significantly elevated risk of all-grade hypothyroidism. Additionally, there was no effect of tumor histotype or applied TKI on the relative risk of hypothyroidism [4].

Immune checkpoint inhibitors and thyroid dysfunction

ICPIs are increasingly used in a variety of solid tumors, and multiple reports suggest their frequent influence on the development of thyroid dysfunction [5, 6]. They are used as single or combination therapy and may cause primary thyroid dysfunctions and central hypothyroidism [1] (Fig. 1).

Primary dysfunctions occur in the form of primary hypothyroidism, transient destructive thyrotoxicosis followed by hypothyroidism, or rarely, Graves' disease. Thyroid dysfunction in any form usually manifests within several weeks following therapy initiation. Barroso-Sousa et al. in a meta-analysis of 38 clinical trials including 7551 participants found

Table 1 Tyrosine kinase and immune checkpoint inhibitors and their target receptors and indications

Drugs	Target	Indications
TKI		
Sorafenib	VEGFR	HCC, RCC
Cabozantinib	VEGFR, RET	HCC, RCC
Axitinib	VEGFR	RCC
Regorafenib	VEGFR	Colorectal cancer, HCC, GIST
Pazopanib	VEGFR	RCC, soft tissue sarcomas
Sunitinib	VEGFR2	GIST, pancreatic neuroendocrine neoplasm, RCC
Afatinib	EGFR, HER2, ErB4	NSCLC
Dacomitinib	EGFR	EGFR-mutant NSCLC
Osimertinib	EGFR	NSCLC
Erlotinib	EGFR	NSCLC, pancreatic cancer
Gefitinib	EGFR	NSCLC
Lorlatinib	ALK	ALK-positive NSCLC
Brigatinib	ALK	ALK-positive NSCLC
Alectinib	ALK,RET	ALK-positive NSCLC
Ceritinib	ALK	ALK-positive NSCLC
Crizotinib	ALK, ROS1	ALK or ROS1-positive NSCLC
Upadacitinib	PDGFR	GIST
Avapritinib	PDGFR	GIST
Capmatinib	c-MET	NSCLC
Ripretinib	KIT/PDGFR	GIST
Tucatinib	HER2	HER2-positive breast cancer
Neratinib	HER2	HER2-positive breast cancer
Lapatinib	EGFR, HER2	HER2-positive breast cancer
Selpercatinib	RET	NSCLC
Erdafitinib	FGFR	Urothelial bladder cancer
Entrectinib	TRKA/B/C, ROS1	ROS1-positive NSCLC, solid tumors with NTRK fusion proteins
Fedratinib	JAK2	Myelofibrosis
Ruxolitinib	JAK1/2/3, TYK	Myelofibrosis, polycythemia vera
Larotrectinib	TRKA/B/C	Solid tumors with NTRK fusion proteins
Zanubrutinib	BTK	Mantle cell lymphoma
Acalabrutinib	BTK	Mantle cell lymphoma, CLL, small lymphocytic lymphomas
Ibrutinib	BTK	CLL, mantle cell lymphoma, marginal zone lymphoma
Bosutinib	BCR-Abl	CML
Ponatinib	BCR-Abl	Philadelphia chromosome-positive CML, ALL
Nilotinib	BCR-Abl	Philadelphia chromosome-positive CML
Dasatinib	BCR-Abl	CML
Imatinib	BCR-Abl, KIT, PGFR	Philadelphia chromosome-positive CML or ALL, aggressive systemic mastocytosis, chronic eosinophilic leukemia, dermatofibrosarcoma protuberans, GIST, myelodysplastic/myeloproliferative disease, hypereosinophilic syndrome
Pexidartinib	CSF1R	Tenosynovial giant cell tumors
Binimetinib	MEK1/2	Melanoma
Cobimetinib	MEK1/2	BRAF-positive melanoma
Trametinib	MEK1/2	Melanoma
Midostaurin	Flt3	AML, advanced systemic mastocytosis, mast cell leukemia
ICPI		
Ipilimumab	CTLA-4	Melanoma, RCC, colorectal cancer
Nivolumab	PD-1	

Table 1 (continued)

Drugs	Target	Indications
		Melanoma, RCC, NSCLC, SCLC, Hodgkin's lymphoma, squamous cell cancer of head and neck, urothelial cancer, colorectal cancer, HCC
Pembrolizumab	PD-1	Melanoma, NSCLC, squamous cell cancer of head and neck, Hodgkin's lymphoma, urothelial cancer, solid tumors with biomarker MSI-H or dMMR, gastric or gastroesophageal junction adenocarcinoma, esophageal cancer (squamous and adenocarcinoma), cervical cancer, primary mediastinal large B-cell lymphoma, HCC, MCC, RCC
Cemiplimab	PD-1	Cutaneous squamous cell carcinoma
Avelumab	PD-L1	MCC, urothelial carcinoma, RCC
Durvalumab	PD-L1	Urothelial carcinoma, NSCLC
Atezolizumab	PD-L1	Urothelial carcinoma, NSCLC, SCLC, triple-negative breast cancer

Legend: *TKI*, tyrosine kinase inhibitors; *ICPI*, immune checkpoint inhibitors; *HCC*, hepatocellular carcinoma; *RCC*, renal cell carcinoma; *GIST*, gastrointestinal stromal tumor; *NSCLC*, non-small cell lung carcinoma; *CLL*, chronic lymphocytic leukemia; *CML*, chronic myeloid leukemia; *ALL*, acute lymphocytic leukemia; *AML*, acute myeloid leukemia; *SCLC*, small cell lung carcinoma; *MCC*, Merkel cell carcinoma

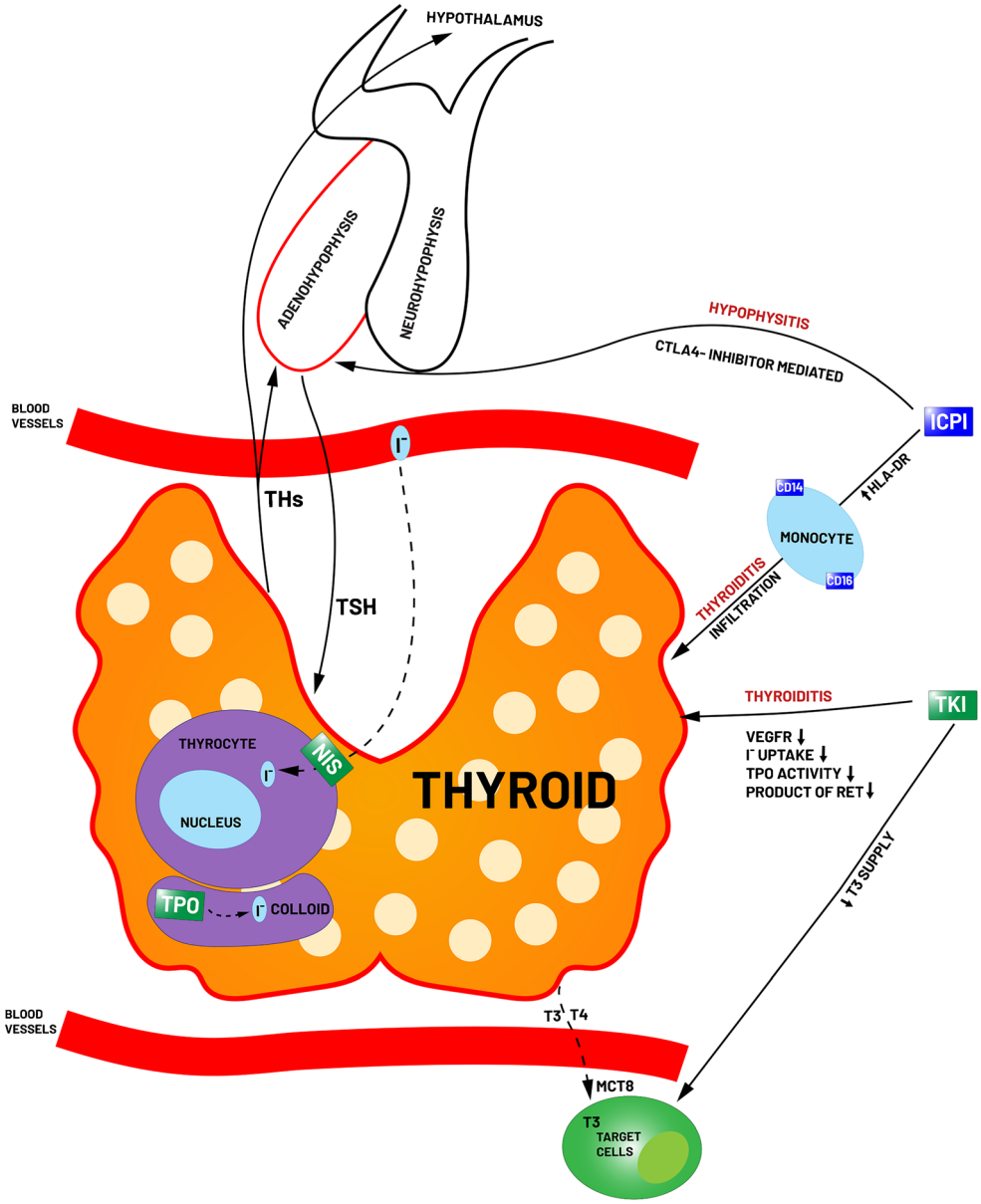

Fig. 1 The mechanism of tyrosine kinase and immune checkpoint inhibitors induced thyroid dysfunction. **Legend**: TKI, tyrosine kinase inhibitors; ICPI, immune checkpoint inhibitors; THs, thyroid hormones; T3, triiodothyronine; T4, thyroxine; TSH, thyrotropin; NIS, sodium/iodide symporter; TPO, thyroid peroxidase; MCT8, monocarboxylate transporter 8; VEGFR, vascular endothelial growth factor receptor; RET, rearranged during transfection; CTLA-4, cytotoxic T lymphocyte-associated protein 4; HLA-DR, human leukocyte antigen DR isotype

that the incidence of thyroid dysfunction was significantly increased in patients receiving a combination of different ICPIs compared with those taking ICPI as monotherapy (i.e., ipilimumab). Patients on combined therapy had a significantly higher chance for hypothyroidism and hyperthyroidism than patients on ipilimumab alone [7].

Diagnosis and management of TKIs/ICPIs-induced thyroid dysfunctions

Tyrosine kinase inhibitors and ICPIs most commonly cause primary hypothyroidism, preceded by the thyrotoxic phase in up to 40% of cases with TKIs and 80% of cases with ICPIs, respectively. Graves' disease rarely occurs during TKIs or ICPIs course but needs to be promptly identified and treated. Notably, ICPIs may also cause central hypothyroidism in almost one-fifth of cases [1]. Clinical presentation of TKIs/ICPIs-induced thyroid dysfunctions varies from subclinical to overt disease as thyroid hormone (TH) levels decrease or increase. However, symptoms of hypothyroidism may be mistakenly understood as cancer-related symptoms. They may negatively affect the patients' quality of life and may lead to a dose reduction of necessary cancer therapy. Hypothyroidism may alter drugs' clearance and cause additional cancer therapy-related side effects. On the other hand, thyrotoxicosis may be mistaken for sepsis or an antineoplastic drug side effect [8].

Measurement of TSH is the mainstay in evaluating thyroid function and the measurement of free thyroxine (fT4) is reflexed when abnormal TSH levels are found. This approach is based on the well-known log-linear relationship between TSH and fT4 making unlikely thyroid dysfunction in the presence of normal TSH levels. In the case of TKI, screening is usually performed at initiation of therapy, once a month for the first 6 months and thereafter every 2 to 3 months [9].

Exceptions occur, however, in rare cases of central or secondary thyroid dysfunction when normal TSH levels occur in the presence of increased or decreased fT4. As previously mentioned, ICPIs (in particular anti-CTLA4) may induce hypophysitis leading to central hypothyroidism (associated or not with thyroiditis) marked by low-normal TSH levels in front of a relevant fT4 reduction and clinical symptoms of hypothyroidism. Accordingly, simultaneous measurement of TSH and fT4 is recommended in patients under ICPIs instead of the TSH-reflex strategy. Screening is performed before initiation of ICPI therapy and repeated before each cycle [1].

If a [^{18}F]FDG PET/CT scan is performed, patients who develop hypophysitis and/or thyroiditis may show a diffuse increase in [^{18}F]FDG uptake in the pituitary gland [10] and/or thyroid gland [11].

Overall, in patients under TKIs/ICPIs, thyrotoxicosis is generally due to drug-induced destructive thyroiditis.

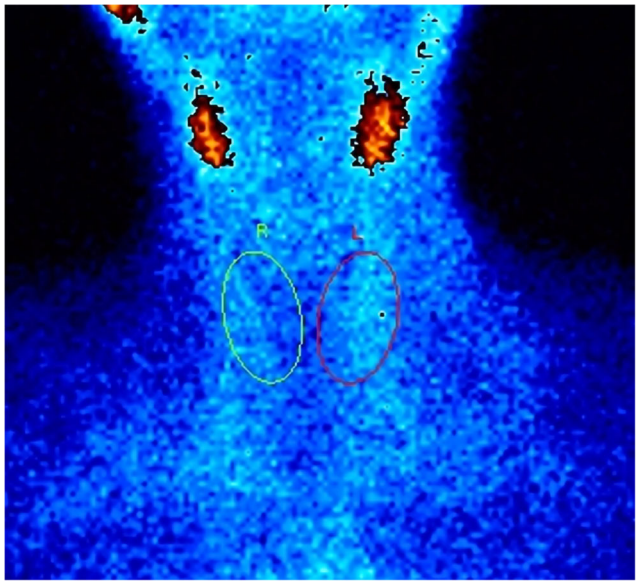

Fig. 2 [^{99m}Tc]Pertechnetate thyroid scintigraphy: absent tracer uptake — destructive thyroiditis induced by Sunitinib (TKI) on a 65-year-old female affected by metastatic renal cell carcinoma (TSH <0.1 mUI/L (0.27–4.2), fT4 27.8 pmol/L (12–22))

Symptoms are mild (i.e., increased pulse rate, anxiety) and transient in most cases but late-onset hypothyroidism will occur in a not negligible part of patients, requiring thyroxine substitution. Thyroid scintigraphy, with or without radioiodine uptake test, can provide a fast and accurate differentiation between destructive thyroiditis and Graves' disease,

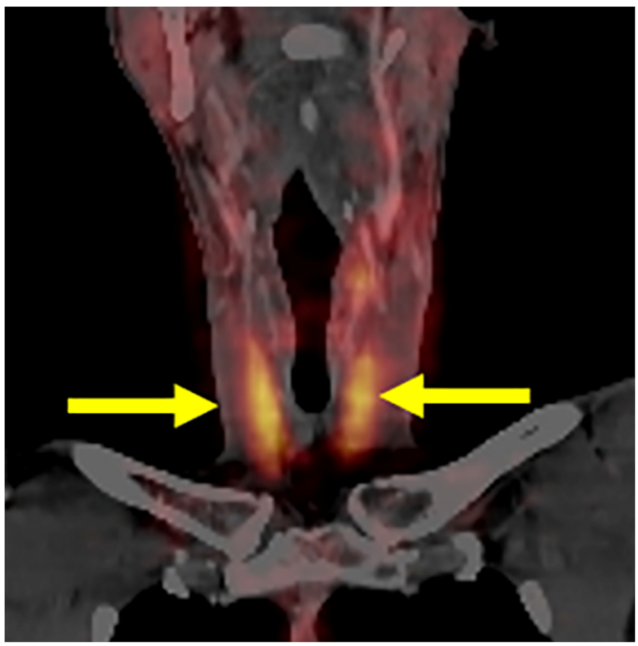

Fig. 3 2-[^{18}F]FDG PET/CT coronal image: diffusely increased tracer uptake in the thyroid, consistent with autoimmune thyroiditis in a 34-year-old male affected by metastatic nasopharynx squamous cell carcinoma treated with Nivolumab (ICPI) (TSH 45 mUI/L (0.27–4.2), fT4 9.2 pmol/L (12–22))

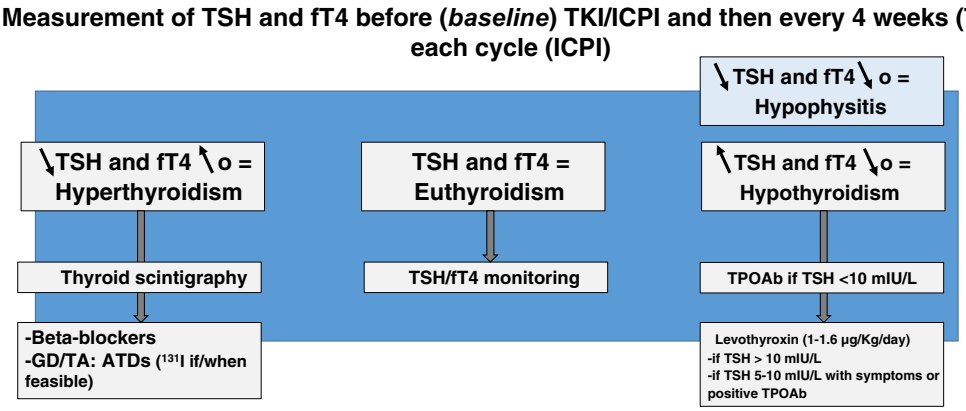

Fig. 4 Flowchart for diagnosis and management of tyrosine kinase and immune checkpoint inhibitors induced thyroid disorders. **Legend:** TSH, thyrotropin; fT4, free thyroxine; GD, Graves' disease; TA, thyroid autonomy; TPOAb, thyroperoxidase autoantibodies; ATDs, anti-thyroid drugs

when clinically required, and properly address specific therapies (Fig. 2). In addition, occasionally detected autonomously functioning thyroid nodules, not related to cancer therapy, will show single or multiple focuses of tracer uptake with variable inhibition of remaining thyroid parenchyma, respectively, and promptly adequate therapy will be applied if needed.

[^{18}F]FDG PET/CT as a predictive biomarker of cancer response

[^{18}F]FDG PET/CT is commonly performed to stage the disease before initiation and monitor the response to TKIs and ICPIs. As above mentioned, thyroiditis and hypophysitis are signalled by increased intra-glandular [^{18}F]FDG uptake that is not related to corresponding function status but requires assessment and monitoring due to the high risk of hypothyroidism and hypopituitarism over time [10, 12]. Notably, the occurrence of drug-induced hypothyroidism usually correlates with a better cancer prognosis [13, 14], while hyperthyroidism or higher reference range thyroid hormone levels are often associated with a less favorable prognosis [15–17]. Thus, we could say that diffusely increased thyroid [^{18}F]FDG uptake may serve as a "surrogate" prognostic marker under TKI/ICPI therapy (Fig. 3). Moreover, it was found that immune-related adverse events are associated with a better cancer outcome and that the development of hypophysitis positively predicts survival in cancer patients under ICPI therapy [18, 19].

Conclusions

Tyrosine kinase inhibitors and ICPIs are associated with early and late thyroid dysfunctions, so it is important to assess thyroid function before and during TKI/ICPI therapies. While TSH-reflex is appropriate in case of TKIs, an additional fT4 measurement is recommended during ICPIs for prompt detection of central hypothyroidism. Thyroid scintigraphy is suggested in selected cases to differentiate destructive thyrotoxicosis from Graves' disease (Fig. 4). On the other hand, [^{18}F]FDG PET/CT is useful to monitor an inflammatory response of the thyroid and pituitary glands, and it may also serve as a prognostic predictor of cancer response, although larger prospective studies are needed to confirm the correlation of diffuse [^{18}F]FDG uptake and cancer prognosis.

Declarations

Ethical approval Not applicable

Informed consent Not applicable

Conflict of interest LG is a member of the Roche Diagnostics advisory board and has received research grants and speaker honoraria from Roche Diagnostics and Sanofi-Genzyme. The other authors declare no conflict of interest.

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