Chapter

Immunotherapy-Related Hypothyroidism: Mechanisms and Management

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Abstract

Immunotherapy has recently emerged as an important tool in the treatment of various malignancies. However, increased use of immune checkpoint inhibitors (ICIs) has brought attention to the associated adverse events, with hypothyroidism being a noteworthy complication. This review explores the mechanisms underlying immunotherapy-induced hypothyroidism and its management. The importance of distinguishing between primary and secondary hypothyroidism in the context of immunotherapy is emphasized, as timely intervention is critical in preventing adrenal crises. Not all patients with immune-related hypothyroidism are treated with levothyroxine. Additionally, only in severe toxicities, ICIs are hold. So, determining the management strategy is important for endocrinologists and oncologists. Therefore, multidisciplinary approach is crucial for immune-related adverse reactions (irAEs). In conclusion, this review provides a comprehensive overview of immunotherapy-induced hypothyroidism, encompassing its mechanisms, diagnostic considerations, and management strategies. By enhancing our understanding of this adverse event, endocrinologists can manage potential complications associated with immunotherapy.

Keywords: malignancy, immunotherapy, immune-related adverse events, hypothyroidism, immunotherapy-induced hypothyroidism, immune checkpoint inhibitors

1. Introduction

Immunotherapy-based regimens are widely used in solid organs and hematological malignancies. By modulating immune mechanisms, immunotherapies increase progression-free survival (PFS) and overall survival (OS) in aggressive cancers. Immune check point inhibitors (ICIs) constitute an important group of immunotherapy-based regimens [1, 2].

Extensively studied immune check point inhibitors (ICIs) include monoclonal antibodies that target programmed death 1 (PD-1), its ligand-programmed death ligand (PD-L1), and cytotoxic T-lymphocyte antigen-4 (CTLA-4). Lymphocyte activation gene protein 3 (LAG-3) is a novel ICI, used mainly in combination with other immunotherapies in the treatment of metastatic malign melanoma [1–3]. ICIs are administered as monotherapy or in combination and aim to restore the inhibitory

Immune-checkpoint inhibitors	Frequent immune-related endocrine adverse events
CTLA-4 inhibitors	
İpilimumab	Hypophysitis, hypothyroidism, and hyperthyroidism
PD-1 inhibitors	
Nivolumab	Hypothyroidism and hyperthyroidism
Pembrolizumab Atezolizumab Cemiplimab	Hypothyroidism, hyperthyroidism, type 1 diabetes mellitus, adrenal insufficiency, and hypophysitis
PD-L1 inhibitors	
Avelumab Durvalumab Dostarlimab	Hypothyroidism
LAG-3 inhibitors	
Relatlimab	

Table 1.
Immune-checkpoint inhibitors.

effects of T-regulatory cells. **Table 1** outlines the most used ICIs and their most frequent immune-related endocrine adverse events.

2. Mechanism of action

To comprehend the pathophysiology of immunotherapy-related hypothyroidism, thorough exploration of immune system physiology is essential.

The journey of a T-cell is complicated but must be fully understood before getting into the mechanisms of immunotherapies. Following selection in thymus, naïve T cells get into blood circulation and search for different foreign or mutated antigens. Getting past through spleen and lymph nodes antigens are presented to T cells by professional antigen-presenting cells. It is noteworthy that some T cells may identify self-antigens as foreign and may result in the activation of immune process which results in autoimmunity.

Immune check point inhibitors play a crucial role in preventing aberrant response. Key pathways in this regulation involve immune checkpoint inhibitors such as CTLA-4 (also known as CD152) and PD-1 (also known as CD279), which exert negative control at distinct stages of the immune system. CTLA-4 regulates the early stages of T-cell activation, immune priming phase especially in lymph nodes. On the other hand, PD-1 inhibits the activated T cells in peripheral tissues. Therefore, combination treatments are preferred strategies to enhance the immune response on malignant cells.

CD28 is a molecule found on T cells and binds to T-cell co-stimulatory factors (CD80/B7–1 and CD86/B7–2) on antigen-presenting cells (APCs). Proliferation and activation of T cells result in interleukin-2 (IL-2) production which occurs after this stimulatory signal.

CTLA-4 is also presented on $CD4^+$ and $CD8^+$ lymphocytes and competes with CD28 to bind to CD80 or CD86. CTLA-4 inhibits this signaling pathway which results in the inhibition of T cells. This competition decreases the immune response, and anergy occurs. **Figure 1** illustrates the pathways explained above and shows the

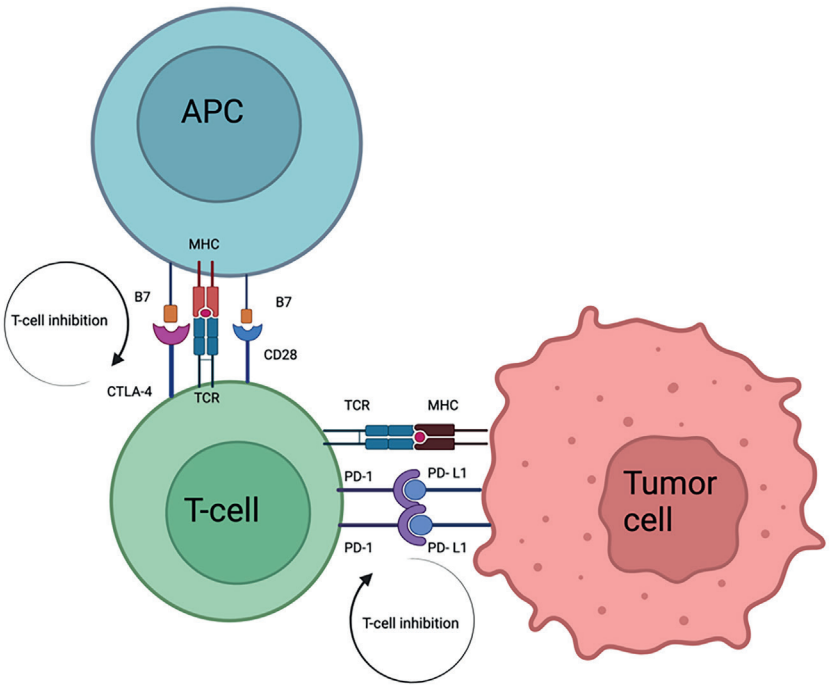


Figure 1.
Immune checkpoint inhibitors mechanism of action (created by BioRender.com). APC: Antigen presenting cells.

dual mechanism that decides whether T cells are going to be activated or inhibited. Although CTLA-4 is located intracellularly on most of the T cells, it is found on the cell surface of T-regulatory (T-reg) cells. This gives the ability to routinely suppress unwanted activation of the immune system [1].

PD-1 molecule is expressed on most of the immune cells such as T cells, B cells, and NK cells. As seen in **Figure 2**, its ligands PD-L1 or PD-L2 are presented on peripheral tissues, like CTLA-4, and B7 signaling inhibits T cells. Different from the CTLA-4 pathway, PD-1 signals only act on activated T cells. This results in self-tolerance in peripheral tissues [2].

LAG-3 is another checkpoint molecule found on T cells and contributes to T-cell exhaustion as in other ICIs discussed before [3].

In the healthy immune system, perforin and granzyme, produced by natural killer and cytotoxic $CD8^+$ T-cells along with interferon gamma secreting $CD4^+$ T cells, promote cell death [4]. Escape mechanisms of tumor cells help them to get through this elimination process. These mechanisms involve the loss of antigenicity and immunogenicity, allowing tumor antigens to evade immune detection. Additionally, overexpression of PDL-1 also induces the immunogenicity of the tumor cells [2, 4, 5].

Targeting these molecules enhances immune response and helps apoptosis and necrosis of tumoral tissues. However, blockage of these signaling pathways by monoclonal antibodies triggers the immune system leading to the elimination of tumor cells causing immune system disbalance. Harnessing immune system with ICIs leads to activation of pro-inflammatory conditions and self-tolerance triggering inflammatory-mediated adverse reactions [6, 7]. Studies show that patients with irAEs have improved survival rates, and this may be used as a predictor of response to the treatment [8].

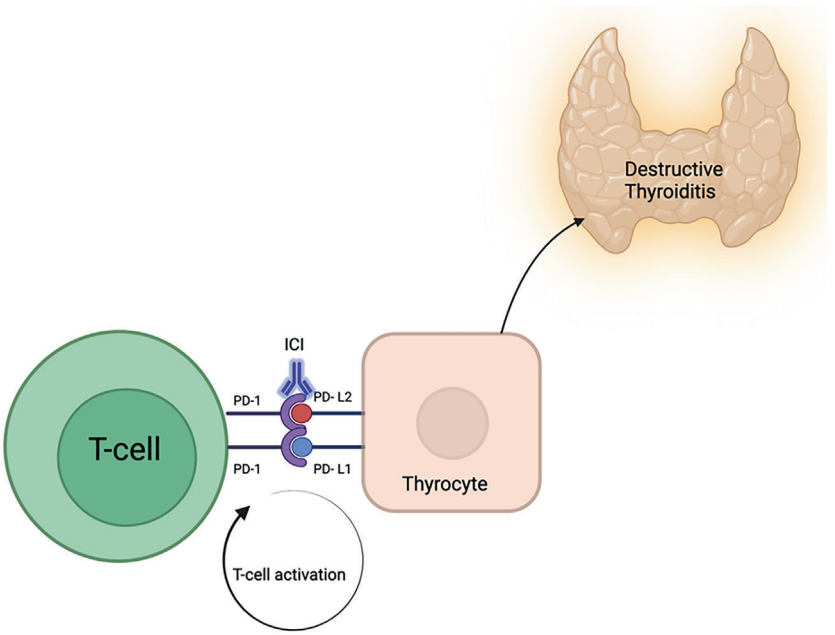


Figure 2.
Immunotherapy related destructive thyroiditis mechanism of action (created by BioRender.com).

The main mechanism of irAEs is peripheral self-tolerance and accumulation of cytotoxic $CD8^+$ T cells in tissues. In a single-center study, thyroid fine needle aspiration was performed in patients with ICI-induced thyroiditis and intra-thyroidal predominance of $CD8^+$ and $CD4^-$ $CD8^-$ T lymphocytes were linked with thyroid dysfunction [8, 9]. In addition to the activation of $CD4^+$ and $CD8^+$ T cells, atypical B-cell proliferation is enhanced with ICIs. B-cell changes occur as soon as the first cycle and are shown to predict and correlate with irAEs [10]. Recently, PD-L1 and PD-L2 molecules have been identified in normal thyroid glands. ICIs, monoclonal antibodies, can potentially bind directly to the thyroid cells, disrupting and infiltrating the thyroid gland with autoreactive T and B lymphocytes, leading to thyroiditis [11, 12].

Increase in immune activity results in a wide range of clinical manifestation. Adverse events (AEs) are potentially immune-mediated disorders due to activation of the immune system response. Most common irAEs are skin abnormalities (e.g., rash and pruritus), gastrointestinal disturbances (e.g., colitis), and endocrinopathies (e.g., thyroid function disturbances and hypophysitis), but all organs can be involved [6]. These AEs may occur de novo or may exacerbate the underlying autoimmune or inflammatory conditions [13].

Although all checkpoint inhibitors have adverse events, when compared, PD-1 inhibitors have less severe ones. This may be due to the restricted peripheral effects of PD-1. As discussed before, CTLA-4 inhibits T-cell activation in early phases, whereas PD-1 inhibits only activated T cells. Ipilimumab, a CTLA-4 inhibitor, accounts for 20% of all severe AEs compared to 10–13% with pembrolizumab, a PD-1 inhibitor [14]. Increased T-cell response with dual immune check point inhibitors may cause an increased adverse reaction. Postow et al. showed that the severe adverse events were seen in 23.9% of the patients receiving ipilimumab treatment alone and 54.3% with nivolumab and ipilimumab combination group [15]. In another study

by Arnaud-Coffin et al., 16,485 patients were analyzed, and severe AEs were seen in 14.0% of patients treated with PD-L1 inhibitors, 34.0% of patients with CTLA-4 inhibitors, 55.0% of patients with immunotherapy combinations, and 46.0% of patients with immunotherapy and chemotherapy combinations [16].

Among all endocrinopathies, the most commonly seen irAEs are hypothyroidism and thyroiditis [17]. Although the irAEs are not predictable and may persist after the cessation of the drugs, Patrizio et al. investigated the ICIs adverse effects and found that thyroid disorders occurred mostly in female patients. In this study, the median occurrence was 9 weeks after the initial treatment [16, 18]. In general, irAEs may occur at any time during and after cessation of the treatment [19]. Still, the predictors of risk factors are an ongoing investigation [20].

3. Primary hypothyroidism

Many endocrinopathies may be seen due to organ destruction by the activation of immune system. The true incidence of immunotherapy-induced endocrinopathies is not known, but it occurs approximately in up to 20.0% of patients; 3.0–8.0% of patients receiving ICI monotherapy and in 15.0% of patients with combination [16, 21]. The most common endocrinopathy is destructive thyroiditis, mostly resulting in hypothyroidism, with an incidence of 5.5–7.8% [22]. Thyrotoxicosis can initially be seen in 4.0–5.0% of patients due to destructive thyroiditis, and in 90.0% of these patients, the destruction and necrosis of thyroid follicles result in hypothyroidism [23]. Immunotherapy-related thyroiditis is painless, and the thyrotoxicosis phase, if occurs, is much shorter (approximately 3 months) compared to other thyroiditis [8]. Thyroid toxicity especially hypothyroidism is much more common in patients on PD-1 inhibitors than CTLA-4 and PD-L1 monotherapies [23–26]. Osorio et al. included 35 clinical trials in a meta-analysis, with a total of 7318 patients, and the incidence of thyroid dysfunction was significantly higher in melanoma patients treated with anti-PD-1 (7.5%) than in those treated with anti-CTLA-4 antibody (3.6%), while no thyroid dysfunction was observed with anti-PD-L1 agents [22].

Regarding the risk factors for hypothyroidism in patients on immunotherapy, data about the association of age and gender are inconsistent. In a small cohort, the male-to-female ratio of hypothyroidism is 6/9, incidences being 4.0 to 10.0% respectively [21]. Lee et al. demonstrated similar incidence of hypothyroidism in 45 patients treated with ICI. Median age was 58 in patients treated with both PD-1 and CTLA-4 inhibitors and 55 in those receiving monotherapy with no statistically significant difference between them [27]. Storm et al. observed irAEs in older patients, but no difference was noted between different age groups [28]. In a multi-ethnic cohort, Caucasian and Hispanic races were found to have increased incidence of hypothyroidism [29]. Recent studies have assessed the heightened risk of obesity with immune-related adverse events (irAEs). In two studies conducted by Pollack et al. an increase in body mass index was found to be associated with thyroid dysfunction [30, 31]. However, the increased risk was specifically linked to thyrotoxicosis rather than hypothyroidism.

Many studies have investigated the time of occurrence of hypothyroidism, and it is observed as early as 3.4 weeks or be delayed until 48.71 weeks [28]. The onset time of biphasic thyroiditis, starting with thyrotoxicosis and then conversion to hypothyroidism, occurs earlier than hypothyroidism alone, with a median of 3.4 weeks. Sabbagh et al. demonstrated an earlier incidence in patients on combination treatments [23].

Primary hypothyroidism usually appears after 10 or 20 weeks of ICI treatment [11, 12]. In the study where 822 patients treated by ICIs were investigated, de novo hypothyroidism occurred as early as 2 weeks [24–26, 32]. The need for change in the levothyroxine replacements dose in patients with pre-existing hypothyroidism occurred later in the course, approximately in the 6th week. Patients with pre-existing hypothyroidism may develop transient hyperthyroidism during ICI treatment [27]. Although most of these patients require an increase in levothyroxine dosage, prophylactic increase is not suggested.

Most patients with hypothyroidism are asymptomatic but may present with nonspecific symptoms like fatigue and weight gain which can be overlapped by the progressing symptoms of the underlying disease [33]. Regularly checking thyroid function tests allow the clinician to detect and treat irAEs in early phases. While there are different recommendations, all involve monitoring thyroid function tests before starting the treatment, before each cycle and continue monitoring after cessation. Existing guidelines recommend checking thyroid function tests every 4–6 weeks during ICI treatment and continuing testing every 6–12 months following the cessation of ICIs [34]. As after the cessation of the treatment, the immune reactivation starts to resolve, but new occurrences of thyroid dysfunction can be observed even after 36 months. Additionally, in patients with thyroid antibodies, the dysfunction may persist [17, 21]. Anti-thyroid peroxidase (anti-TPO) antibody and to a lesser degree anti-thyroglobulin (anti-Tg) positivity were linked with persistent thyroid dysfunction at rates of 11.6 and 8.0%, respectively [28].

Primary hypothyroidism is defined as low free thyroxine (fT4), regardless of thyrotropin (TSH), which may be seen in resolution phases of thyroiditis, or a high TSH, with a low or normal fT4 [23]. In patients with normal fT4 and elevated TSH, cortisol deficiency must be excluded to exclude concurrent adrenal insufficiency and avoid adrenal crisis [22]. Checking autoantibodies, such as anti-TPO and anti-Tg, prior to the treatment is still controversial. Some recommend checking antibodies only in patients with a family or self-history of autoimmunity, while the others suggest checking in all patients prior to immunotherapies [6]. Elevated baseline antibodies may pose a potential risk, but further studies are required to confirm this. In patients with immune-related hypothyroidism, antibody positivity was observed in 80.0%, whereas in patients without thyroid dysfunction, antibody positivity was only 8.0% [35]. Maekura et al. demonstrated that hypothyroidism developed in 44.0% of the patients with antibody positivity at baseline but in only 2.0% of the patients with negative antibody levels [36]. Studies suggest that pre-existing antibodies are risk factors for thyroid dysfunction [24–26, 32]. Not all studies correlate antibodies with ICI-related hypothyroidism and not all patients with antibodies develop hypothyroidism. Anti-TPO positivity was higher than anti-Tg positivity in general.

Thyroid ultrasound can reveal the underlying thyroid disease and help to distinguish diffuse or localized thyroiditis. The use of thyroid scintigraphy and PET scan is useful in hyperthyroidism but have minimal contribution in hypothyroidism [17].

It is also found that the median survival of patients with endocrinologic irAEs is longer [28]. This has been attributed to the increased immune system stimulation, which strengthens the fight against cancer cells by activating the immune response.

Autoimmune thyroid disorders tend to be seen along with other autoimmune diseases [37]. Lee et al. examined this hypothesis in patients with ICI-related hypothyroidism. Among 27 patients receiving combination treatment, 10 patients with

thyroid dysfunction had either hypophysitis or secondary adrenal insufficiency. Additionally, 22.0% of patients on anti-PD-1 monotherapy presented with metachronous endocrine toxicities (hypophysitis, secondary adrenal insufficiency, and diabetes mellitus) [27].

4. Secondary hypothyroidism

Secondary hypothyroidism can manifest as a component of hypophysitis. In hypophysitis, reduced production of one or more hormones in the pituitary gland leads to hypopituitarism. Adrenocorticotropic hormone (ACTH), TSH, follicle-stimulating hormone (FSH), luteinizing hormone (LH), growth hormone (GH), and prolactin are the affected hormones. It is important to distinguish primary hypothyroidism from secondary hypothyroidism because when levothyroxine is initiated before the evaluation of secondary adrenal insufficiency, adrenal crisis may develop. Primary hypothyroidism generally is asymptomatic, but in secondary hypothyroidism due to panhypopituitarism, patients tend to be more symptomatic; fatigue, muscle weakness, headache, anorexia, nausea, weight loss, visual changes, intolerance of temperatures, arthralgias, and electrolyte disturbances may be observed [38].

As seen in primary hypothyroidism, hypophysitis is more common with combination treatments. A study involving 6472 patients reported the incidence of hypophysitis as 6.4% with combination therapies, 3.2% with CTL4 inhibitors, 0.4% with PD-1 inhibitors, and 0.1% PD-L1 inhibitors [39]. While primary hypothyroidism is common in PD-1 inhibitor monotherapies, hypophysitis is more frequently observed in CTLA-4 inhibitor monotherapy [38]. Risk factors are still debatable for secondary hypothyroidism. Cumulative dose, gender, and age data are controversial, and new studies are needed to clarify this [40]. ICI-related hypophysitis tends to be more prevalent in old male patients, whereas hypophysitis is more commonly observed in young female patients [38].

Time of onset is 2–3 months after initiation of ICIs, but the duration may be as long as 19 months. It is observed earlier with CTLA-4 inhibitors and in combination with PD-1 inhibitors, than with PD-1 inhibitors alone, with durations of 12.5 weeks, 9.3 weeks, and 25.8 weeks, respectively [40].

In secondary hypothyroidism, TSH levels are low or normal with low fT4. Morning assessment of ACTH and cortisol levels are necessary to rule out coexisting ACTH insufficiency. Increased heterogenicity and enlarged hypophyseal gland are the radiological findings that support hypophysitis in magnetic resonance imaging.

5. Management

The treatment of irAEs must be multidisciplinary, and patients should be evaluated thoroughly by endocrinologists. The severity of toxicity is crucial for the treatment and determining whether to continue ICIs. The degree of elevation in TSH and patients' symptoms must be carefully evaluated before deciding on the treatment [41]. **Table 2** summarizes the definitions of grading and management of hypothyroidism induced by ICIs. The treatment of hypothyroidism induced by immunotherapies typically involves levothyroxine. Common Terminology Criteria for Adverse Events (CTCAE) points out that Grade 4 toxicity entails life-threatening consequences which requires urgent investigation, and Grade 5 toxicity denotes death resulting from AEs [42].

Grade of Toxicity	Evaluation	Management
Grade 1	Asymptomatic patient TSH > 4,5 mIU/L but <10 mIU/L	• ICIs may be continued • Thyroxine replacement is controversial • Monitoring TSH (+ fT4) every 4–6 weeks
Grade 2	Moderate symptoms TSH > 10 mIU/L	• Endocrine evaluation o Adrenal insufficiency should be excluded • ICIs may be stopped until recovery or continued • Initiation of thyroxine treatment o Monitoring TSH (+ fT4) every 4–6 weeks o Aim TSH in the reference range
Grade 3 - Grade 4	Severe symptoms, cannot perform daily activities	• Endocrine evaluation is necessary • ICIs should be discontinued until recovery • Initiation of thyroxine treatment o Monitoring TSH (+ fT4) every 4–6 weeks o Aim TSH in the reference range • If central hypothyroidism or adrenal insufficiency suspected hydrocortisone should be given • Myxedema coma (bradycardia, hypothermia, and altered mental status) o Life-threatening condition o Follow-up in ICU setting o IV thyroxine treatment should be evaluated

Table 2.
Management of ICIs-induced hypothyroidism.

Grade 1 and 2 toxicities are mild and self-limiting. Patients with subclinical hypothyroidism, where thyroid hormones are normal, but TSH is elevated (<10 mU/L) and evaluated as having Grade 1 toxicity, and thyroid hormone supplementation is not crucial [43]. Toxicities greater than grade 2 should be evaluated by endocrinologists, and levothyroxine treatment should be initiated. Depending on the age and comorbidities of the patient, suggested replacement dose is 1–1.5mcg/kg/day. Preferred starting dose is 75 mcg/day in otherwise healthy patients and in old (>65 years) and frail patients. The starting dosage should be 25–50 mcg/day and titrated slowly [33]. Iyer et al. calculated the median levothyroxine dose in patients treated with ICIs to be 1.2 mcg/kg, which is lower than the usual replacement dose for non-malignant total thyroidectomy cases, which is 1.6 mcg/kg daily [23, 44]. ICIs can be continued in mild settings, whereas in Grade 3 and 4 toxicities, where severe and symptomatic hypothyroidism and myxedema coma ensue, they may be indications for discontinuation [33].

In patients with altered mental status, bradycardia, generalized edema, and hypotension, the life-threatening condition "myxedema coma," should be taken into consideration [22]. Patients should be admitted to intensive care units and monitored closely for requirement of intravenous levothyroxine treatment [41].

Patients must be followed up throughout and after cessation of the treatment. TSH must be monitored every 4–6 weeks and low TSH levels, while taking levothyroxine supplement may suggest recovery or overtreatment. American Society of Clinical Oncology (ASCO) 2018 guidelines suggest continuing monitorization of TSH levels

annually after cessation of ICIs. ASCO recommends titrating the levothyroxine dose every 6–8 weeks by monitoring TSH levels until TSH reaches the normal range. For patients with overt hypothyroidism, free T4 may be monitored every 2 weeks to assess short-term responses. The European Society for Medical Oncology (ESMO) 2017 guidelines differentiate hormonal screening for patients using CTLA-4 inhibitors and PD-1/PD-L1 inhibitors. It is recommended that patients treated with CTLA-4 inhibitors should undergo monitoring after each cycle and every 4 weeks after the fourth cycle. For patients receiving PD-1/PD-L1 inhibitors, screening should occur after every cycle for the first 3 months and subsequently every second cycle. As mentioned earlier, some guidelines do not recommend screening for antibodies before initiating treatment. The French Society of Endocrinology (SFE) 2018 advocates against screening for antibodies before initiating treatment. Their recommendation is to monitor thyroid function every cycle for the first 6 months and then every 2 months for a year. Following the first year, routine monitoring of TSH levels is not recommended. However, in the presence of symptomatic hypothyroidism, they suggest checking thyroid function tests [41].

The importance of anti-thyroid peroxidase antibodies (anti-TPO) and anti-thyroglobulin antibodies (anti-Tg) in the pathogenesis is not fully understood. However, levothyroxine dose requirement during treatment seemed to be increased in patients with pre-treatment antibody positivity [23, 34, 44].

Treatment of ICIs-induced hypophysitis (secondary hypothyroidism) resembles that for any other cause of hypopituitarism. Hydrocortisone replacement is the initial step. TSH levels are not reliable for central hypothyroidism and cannot be used as a guide. Thus, thyroid hormone replacement is based on fT4 levels. The treatment objective is maintaining fT4 being in the mid to upper half of the reference range and with a suggested dose of 1.6 mcg/kg/day [30]. In the study by Kristan et al. the required dose was 0.9 mcg/kg/day [34]. The study emphasized that the patients with secondary hypothyroidism tend to be older, and lower doses of replacement therapy were administered due to comorbidities. In older patients with multiple comorbidities such as coronary heart disease, the starting dose should be 25–50 mcg/day, and the dose should be titrated slowly [40].

In conclusion, primary hypothyroidism can be observed during the treatment with immunocheckpoint inhibitors. This may be due to an immune destruction of the thyroid tissue and is usually seen as a consequence of thyroiditis. Secondary hypothyroidism is another thyroid problem seen due to hypophysitis induced by these agents. For both conditions, there is no consensus on which individuals are at risk of developing thyroid toxicity. Nevertheless, routine monitorization of thyroid function tests during and even after cessation of therapies are recommended. Although discrepancies exist between guidelines, checking thyroid antibody levels before immunotherapy commencement may be of help in predicting the development of immunotherapy-induced hypothyroidism. Management by treatment with levothyroxine according to severity of hypothyroidism and referral to endocrinology are advocated.

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