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Review

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The influence of monoclonal antibodies for cancer treatment on the endocrine system

Wpływ przeciwciał monoklonalnych stosowanych w leczeniu nowotworów na układ endokrynny

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Summary

Cancer is one of the main causes of mortality worldwide. Thanks to scientific research, new methods of cancer treatment, including molecularly targeted therapy, are being developed. Monoclonal antibodies are used to treat many diseases, including some types of cancer, and affect various systems of the human body. The presented article aims to present the adverse effects of molecularly targeted cancer therapy on the endocrine system based on the current literature data. Immune checkpoint inhibitors, such as anti-CTLA-4 and anti-PD-1 or its ligand PD-L1, can cause a variety of autoimmune adverse effects, among others, thyroid dysfunction, hypophysitis, and diabetes mellitus. The authors also paid attention to monitoring selected diagnostic parameters to prevent endocrine adverse effects during a therapy with monoclonal antibodies. The development of adverse effects may sometimes progress atypically and rapidly, and may be a life-threatening condition. Clinicians should choose individual schemes of treatment for particular patients. The patient's condition should also be monitored before, during and after the therapy. The decision about the continuation of treatment with monoclonal antibodies should be based especially on a risk connected with the cessation of treatment. Clinical trials should be continued to improve knowledge about the side effects of monoclonal antibodies.

Keywords: **adverse effects, CTLA-4, cancer immunotherapy, endocrine system, immune checkpoint inhibitors, molecular targeted therapy, monoclonal antibody, PD-1, PD-L1**

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INTRODUCTION

Cancer results from the outgrowth of a clonal population of cells from the tissue [65]. There were an estimated 3.91 million new cancer cases (excluding non-melanoma skin cancer) and 1.93 million deaths from cancer in Europe in 2018. The most common cancer sites were cancers of the female breast (523,000 cases), followed by colorectal (500,000), lung (470,000), and prostate cancer (450,000) [24]. One quarter of all annual cancer deaths are attributable to cancers of the lung and bronchus, making them the most common cause of cancer death for both men and women [75].

The burden of cancer has increased worldwide. Alarmingly, the World Health Organization (WHO) predicts that the number of new cancer cases is expected to rise by approximately 70% over the next 20 years [80]. Common types of cancers overlap considerably all over the world. Developing countries tend to have a higher incidence and death rates for viral infection-related cancers. The examples are hepatitis-related liver cancer and human papillomavirus (HPV)-related cervical cancer [44, 69]. Known cancer risk factors include social determinants, lifestyle factors, occupational exposures, infectious agents, hormones, radiation, and genetic as well as epigenetic alterations [73]. It is estimated that one third to one half of cancers could be prevented by healthier lifestyle choices. Among the modifiable risk factors, attention is paid to reducing tobacco smoking, moderate alcohol consumption, maintaining normal body weight (within the Body Mass Index (BMI) range of 18.5 to 24.9), a healthy diet and leading an active lifestyle [44, 69]. Screening is a powerful strategy to control some cancers, such as cervical cancer. Challenges remain in studying the effectiveness of screening for other cancers [73].

In recent years, conventional treatments including surgery, chemotherapy and radiotherapy, have been the main approaches in tumor therapy. Cancer immunotherapy is a new type of cancer treatment. It helps to fight cancer by harnessing the power of the patients' own immune system. Cancer immunotherapy may be more targeted than conventional cancer treatments. Numerous cancer immunotherapy strategies are under investigation. A few have been approved for cancer treatment. These include molecular therapy, cellular therapy, and vaccination therapy [49].

DRUGS USED IN MOLECULAR CANCER THERAPY

Molecular targeted therapy refers to the use of drugs or other substances that target specific molecules (molecular targets). It blocks the growth and spread of cancer cells. The concept for targeted therapy was derived from the idea of "the magic bullet", which was first expatiated by Paul Rich in the late 1800s. It was initially used to depict the ability of a chemical that targeted microorganisms specifically, but the method has since been expanded to cancer treatment. These drugs interfere with specific molecules to block cancer growth, progression, and metastasis. Many molecular targeted therapies approved by the Food and Drug Administration (FDA), have demonstrated remarkable clinical success in the treatment of a myriad of cancer types, including breast, leukemia, colorectal, lung, and ovarian cancer [48]. Targets selected for molecular therapy include growth factors, signaling molecules, cell-cycle proteins, modulators of apoptosis and molecules that promote angiogenesis [11]. Target engagement can be achieved through several modalities. These regulate or interact with cell surface receptors (monoclonal antibodies), intracellular cascade pathways and signaling (small molecule tyrosine kinase inhibitors) or micro-environment effects related to tumor vasculature or hypoxia. Interesting results describing the use of antibody-drug conjugates to increase cytotoxic drug delivery have also been obtained [72]. Improved delivery of targeted agents to cancer cells using nanoparticles, such as porphysomes, presents a tremendous opportunity to precision-bomb cancer cells and reduce bystander or collateral toxicity [64].

MONOCLONAL ANTIBODIES IN CANCER THERAPY

Monoclonal antibodies (mAbs) are typically developed for targets that are located outside the cells, as they are relatively too large to enter the cells [40]. MAbs specifically target extracellular proteins and inhibit tumor growth by interrupting the interactions between the receptors and ligands. The antibodies can mediate their actions either through an indirect or direct mechanism, after binding to cancer cells [78]. MAbs are able to act via different mechanisms to exert their action through any of the following means: antibody dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), complement-dependent cytotoxicity (CDC), blockage of signal transduction, induction of apoptosis, or delivery of cytotoxic payloads [70]. The role of CDC is binding of mAb to recruit the classic complement-activating protein C1q which induces the activation of the complement cascade, leading to the formation of the membrane attack complex (MAC), and causes cell lysis. The function of ADCC is binding of mAb, so that it recruits an effector cell, such as a natural killer (NK) cell, a macrophage or monocytes through their Fc receptors, and lyses the cancer cells. In turn, the role of ADCP is binding of mAb to recruit a macrophage, which leads to phagocytosis of the cancer cell. Direct tumor cell killing includes the induction of apoptosis after the binding of mAb to the cancer cells. The binding of mAb to the cancer cell receptor or ligands leads to the disruption of the signaling pathway, inhibiting cell proliferation or activating cell death. What is more, mAb acts as a carrier to deliver toxic payload, such as radioisotopes, toxins, drugs or cytokines, in order to kill tumor cells [48].

MAbs are usually well tolerated in comparison to cytotoxic chemotherapy or chemoradiotherapy; they do have potential adverse effects that are connected to

Table 1. Adverse reactions caused by monoclonal antibodies in the endocrine system

Monoclonal antibody	Therapeutic indications	Very common and common adverse reactions (≥ 1/100)	Uncommon adverse reactions (≥ 1/1,000 to < 1/100)	Rare and very rare adverse reactions (< 1/1000)	References
Atezolizumab	• Locally advanced or metastatic UC as monotherapy • Locally advanced or metastatic NSCLC after prior chemotherapy • Unresectable locally advanced or metastatic TNBC (in combination with nab-paclitaxel)	hypothyroidism (very common in combination therapy, common as monotherapy)	hyperthyroidism, diabetes mellitus, adrenal insufficiency	hypophysitis	[71]
Avelumab	• Metastatic MCC • RCC (in combination with axitinib)	hypothyroidism	adrenal insufficiency, hyperthyroidism, thyroiditis, autoimmune thyroiditis, adrenocortical insufficiency acute, autoimmune hypothyroidism, hypopituitarism, type 1 diabetes mellitus	-	[4]
Durvalumab	• Locally advanced, unresectable NSCLC	hypothyroidism, hyperthyroidism	adrenal insufficiency, type 1 diabetes mellitus	hypophysitis / hypopituitarism, diabetes insipidus	[37]
Ipilimumab	• Advanced melanoma (as monotherapy/in combination with ipilimumab) • Adjuvant treatment of melanoma • NSCLC as monotherapy • RCC • relapsed or refractory cHL after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin • SCCHN • Urothelial Carcinoma	hypothyroidism, hyperthyroidism	adrenal insufficiency, hypopituitarism, hypophysitis, thyroiditis, diabetes mellitus	diabetic ketoacidosis	[57]
Pemprolizumab *Monotherapy*	• Advanced melanoma • Adjuvant treatment of adults with Stage III melanoma • NSCLC • cHL • Urothelial carcinoma • SCCHN	hypothyroidism, hyperthyroidism	adrenal insufficiency, hypophysitis, thyroiditis	-	[45]
Pemprolizumab *Combination with chemotherapy*	• NSCLC	hypothyroidism, hyperthyroidism	hypophysitis, thyroiditis, adrenal insufficiency	-	[45]
Pemprolizumab *Combination with axitinib*	• Advanced RCC	hypothyroidism, hyperthyroidism, hypophysitis, thyroiditis, adrenal insufficiency	-	-	[45]

Abbreviations: CU: urothelial carcinoma, NSCLC: non-small-cell lung carcinoma, TNBC: triple-negative breast cancer, MCC: Merkel cell carcinoma, RCC: renal cell carcinoma, cHL: classical Hodgkin lymphoma, SCCHN: Squamous Cell Cancer of the Head and Neck

their mechanism of action. Their side effects usually do not overlap with those of cytotoxic chemotherapy [32]. The most frequent side effects of mAbs are allergic reactions, such as infusion reactions (anaphylactic or less frequently anaphylactoid), hives and/or pruritus, influenza-like symptoms, as well as fatigue, chills, mild fever, headaches, muscular pain, gastrointestinal upset with nausea, vomiting and/or diarrhea, low blood pressure and skin rashes [28].

Antibodies binding to cell surface antigens

Antibodies bind specifically to their target antigens, which can be produced directly on the surface of cancer cells. The clusters of differentiation (CD) antigens are usually a target for haematological cancers. For example, the anti-CD52 monoclonal antibody (Alemtuzumab) is a single agent in the treatment of patients with B cell chronic lymphocytic leukemia (B-CLL), the anti-CD38 monoclonal antibody (Daratumumab) is approved for the treatment of multiple myeloma (MM). Rituximab, Y-ibritumomabtiuxetan, Ofatumumab, Obinutuzumab and I-Tositumomab belong to anti-CD20 antibodies, which are associated with infusion reactions. Solid tumors can be targeted through various antigens. They are divided into different categories based on their function. Therapy with the use of EGFR inhibitors is an example of this and includes the following antibodies: Cetuximab, Necitumumab and Panitumumab. They are used in the treatment of colorectal carcinoma, head and neck squamous cell carcinoma (HNSCC) and non-small-cell lung carcinoma (NSCLC). Most patients treated with anti-EGFR mAbs come down with dermatological toxicities in a dose-related manner. Cardiac toxicity is the most common and the most important adverse event connected to trastuzumab therapy. Trastuzumab, the HER2 targeted antibody, has been proven effective in breast and gastric cancer therapy. Pertuzumab is one more inhibitor of HER2 signaling [58]. Another example for of an antibody binding to a cell receptor is Ramucirumab, which is related to VEGF receptor (VEGF-R2) and also affects vasculature in the tumor microenvironment. It is approved for the management of advanced gastric and gastroesophageal adenocarcinomas, metastatic non-small cell lung cancer (NSCLC) and metastatic colorectal cancer [32].

Antibodies against cytokines and tumor support structures

There are also antibodies that target significant events in the tumor microenvironment such as VEGF inhibitors (Bevacizumab, Ramucirumab). Malignant tumor cells divide and grow rapidly. They need their own blood supply to support their growth. Bevacizumab blocks binding of vascular endothelial growth factor A VEGF-A to its receptor and inhibit angiogenesis. It is approved for the treatment of colorectal, ovarian, fallopian tube, peritoneal and renal cell cancer, glioblastoma multiforme and non-small-cell lung cancer in combination with cytotoxic chemotherapy [32]. Anti-cytokine antibodies are used mostly in treating chronic inflammatory diseases and autoimmune diseases, so they are not described in this article.

Antibody-drug conjugates

It is worth paying attention to antibody-drug conjugates (ADCs), which are also used in the treatment of cancer, namely brentuximab vedotin, ado-trastuzumab emtansine, inotuzuma-bozogamicin, gemtuzumabozogamicin, and polatuzumabvedotin-piiq [15]. ADC are considered revolutionary in terms of a potent therapy for cancer treatment, as they are highly selective and allow specific delivery of cytotoxic agents to the intended cancer cell target. ADCs comprise of target-specific mAbs covalently linked to small-molecule anticancer drugs, internalized to the targeted cancer cells through receptor-mediated endocytosis, and release potent cytotoxins that lead to apoptotic cancer cell death [61].

Immune checkpoint inhibitors

Immune checkpoint inhibitors, such asanti-cytotoxic T lymphocyte antigen-4 (CTLA-4) and anti-programmed cell death-1 (PD-1) or its ligand (PD-L1), can cause a variety of autoimmune side effects [28]. These immune-related adverse events (irAEs) can become severe and life threatening. The primary irAEs associated with these mAbs, among others, are dermal, digestive (gastrointestinal and hepatic) and endocrine (hypophysitis, inflammation of the thyroid gland and adrenal insufficiency) irAEs [35].

Tumor cells avoid the immune system and progress through various mechanisms, including the activation of the immune checkpoint pathways that reduce antitumor immune reactions [17]. Immunotherapy is a type of oncologic treatment whose purpose is to enhance the host immune system against cancer. Manipulation of the immune checkpoints or pathways has appeared to be a significant and effective kind of immunotherapy [52]. Among the immune checkpoint inhibitors, PD-1/PD-L1 and CTLA-4 inhibitors have demonstrated promising therapeutic results, and some of them have been approved for particular cancer treatments, while others are under clinical tests [17]. Unfortunately, these treatments could be the reason for often subtle, possible deadly, immune-related adverse events [35]. The general incidence of hypophysitis with these medications is close to 9%. Primary thyroid dysfunction appears in up to 15% of patients. Adrenalitis is reported in about 1%. The mean onset of endocrine adverse events is 9 weeks after their initiation (range 5–36 weeks) [41]. The irreversibility ratio of immune-related endocrine toxicities is usually 50%. Hypophysitis in particular is the most common anti-CTLA-4-antibodies-related irAE, whereas thyroid abnormalities (as well as hypothyroidism, thyrotoxicosis, painless thyroiditis, or even "thyroid storm") occur particularly during treatment with anti-PD-1-antibodies [25]. CTLA-4 is a co-inhibitory receptor whose role is to control T lymphocyte activation at the time when

adaptive immune response begins and progresses. CTLA-4 binds to B7 ligands (CD80, CD86), which are expressed on antigen-presenting cells, with a higher affinity, compared to the co-stimulatory molecule CD28 [10, 41]. Engagement of CTLA-4 with B7 ligands causes T cell downregulation [31]. MAbs like ipilimumab binding CTLA-4 block CTLA-4 interactions with B7 ligands. It may enhance the effector T cell (Teff) function and lead to the inhibition of the regulatory T cell (Treg) activity [10]. In this way, the immune system is able to attack tumor cells [25]. Regulatory T cells express CTLA-4 constitutively, and it has recently been reported that CTLA-4 antibodies may act independently of the interactions between CTLA-4 and B7 ligands in vitro. ADCC and ADCP activity of this mAbs selectively depleted Treg cells and expanded specifically for tumor-antigen CD8+T cells [29]. Ipilimumab was one of the earliest immune checkpoint inhibitors approved for cancer treatment [41]. FDA approved ipilimumab for the treatment of advanced melanoma in March 2011 and as an adjuvant therapy for melanoma in the third stage in October 2015 [32].

PD-1 is a membrane inhibitory receptor which, like CTLA-4, is expressed on activated T cells [1, 41]. However, PD-1 is more widespread on the surface of immune cells. Similarly to B cells, NK cells and macrophages express PD-1 [32, 41]. The significant role of PD1 is to limit the activity of T lymphocytes in peripheral tissues during an inflammatory response to an infection, as well as to limit autoimmunity [59]. The ligands for PD-1 are PDL-1 and PDL-2, while they interact with CD80 and RGMb (repulsive guidance molecule B), respectively [32]. Binding PD-L1 or PD-L2 with PD1-expressing T cells causes the downregulation of TCR-mediated signaling, the culminating point being functional nonresponsive T cells [31]. This engagement reduces also the production of pro-inflammatory Th1 cytokines, like IFN-□ and IL-2 [41]. According to the reports, most melanoma, ovarian and lung cancer samples express PDL-1 in high levels, and many other human cancers also up regulate the PDL1 expression [59]. Blocking PD-1 pathways can partly enhance the T cell function, overturn T cell suppression and induce responses against cancer. Antibodies inhibiting PD-1, like nivolumab, pembrolizumab, cemiplimab [3] and PD-L1, as e.g. atezolizumab, avelumab and durvalumab [21, 32, 34, 68] have been approved for treatment of various cancers.

IMMUNE CHECKPOINT INHIBITORS (ICPIS): RELATED HYPOPHYSITIS

Hypophysitis is a very rare acute or chronic inflammation of the pituitary gland [50]. It may occur as an adverse effect during therapy with ICPis. Ipilimumab is an antibody that has been more strongly related to this immune-related adverse event [26, 46].

Histopathological findings in patients with Ipilimumab-induced hypophysitis revealed the pathogenesis of this disorder. The evidence of pituitary antibodies in the serum of these patients and in animal models of anti-CTLA-4-induced hypohysitis suggested that the pathogenesis involved type II and IV hypersensitivity, as well as the humoral immune response [8, 38]. However, de Filette and coworkers confirmed that hypophysitis is more common during therapy with ipilimumab (5.6%) compared to nivolumab (0.5%) and pembrolizumab (1.1%) [18].

The CTLA-4 antibody binds to the pituitary CTLA-4 antigen. It induces complement activation and infiltration with macrophages and other inflammatory cells, leading to phagocytosis and enhanced antigen presentation. Afterwards, autoreactive T-lymphocytes infiltrate the anterior pituitary, which leads to pituitary cytotoxicity and inflammation. What is more, patients with induced hypohysitis develop pituitary antibodies that recognize thyroid-stimulating hormone- (TSH-), follicle-stimulating hormone- (FSH-) and adrenocorticotropic hormone- (ACTH-) secreting cells. Therefore, central hypothyroidism, central adrenal insufficiency, and hypogonadotropic hypogonadism are the most common pituitary abnormalities in anti-CTLA-4-related hypophysitis [8, 9, 38]. Almost 90% of patients who evolve hypophysitis have ACTH deficiency, and cases of mortal acute adrenal insufficiency have been described [33]. An early onset of ipilimumab-related hypophysitis has been reported. It typically presents itself ~2 to 3 months after the ipilimumab initiation, but it can also appear several months after the initiation of treatment with antibodies [67, 81].

Patients suffer from non-specific symptoms, like headache, nausea, fatigue and myalgia. Visual disorders occur rarely and central diabetes insipidus is highly uncommon [16, 83]. Other symptoms may also occur, e.g. memory loss, confusion, hallucinations, insomnia, decreased appetite, cold intolerance or chills [74]. In imaging, a normal-appearing pituitary gland does not rule out hypophysitis. Clinical and biochemical evaluation should define the therapeutic management [14].

Thyroid axis

Central hypothyroidism is one of the most frequent anterior pituitary hormone deficiencies in ICPi-related hypophysitis. Biochemically, central hypothyroidism is characterized by low or normal TSH concentrations and a disproportionately low concentration of free thyroxine (FT4). Optionally, the TSH concentration is mildly elevated, probably due to decreased bioactivity. The most common symptoms of hypothyroidism in adults are fatigue, lethargy, cold intolerance, weight gain, constipation, change in voice, and dry skin, but there is a wide spectrum of symptoms depending on age, sex, and time between the onset and diagnosis [7, 60].

Adrenal axis

Central adrenal insufficiency is common in ICPi-related hypophysitis. The symptoms of adrenal crisis include hypotension, electrolyte imbalances (especially hyponatremia) and dehydration. Adrenal insufficiency caused by antibodies should be differentiated from other causes. Several

types of malignancy show that adrenal gland metastasis can result in primary adrenal insufficiency [23, 47]. What is more, metastases to the pituitary gland can result in secondary adrenal insufficiency [63]. Increased hypothalamic secretion of corticotropin-releasing hormone (CRH) stimulates antidiuretic hormone (ADH) secretion. Increased ADH retains water through decreased sodium concentration in plasma. This is the cause of hyponatremia in central adrenal insufficiency [43, 56].

Gonadal axis

Hypogonadotropic hypogonadism is also common. Low FSH and/or LH values are present. In men, testosterone levels are low, and in premenopausal women, estradiol levels are below normal. In postmenopausal women, inappropriately low FSH and LH suggest hypogonadotropic hypogonadism [5]. The symptoms include, among others, labile moods, decreased libido and hot flashes [74].

Growth hormone (GH) axis

GH deficiency in ICPi-related hypophysitis is uncertain. We have to take into account the fact that the treatment of GH deficiency with GH replacement is contraindicated in the case of active malignancy. What is more, a confirmation of GH deficiency typically requires provocative testing [54].

Prolactin

Hyperprolactinemia is very rare in ICPi-related hypophysitis. Prolactin levels may be below normal [22, 53].

ADH

Diabetes insipidus (DI) is extremely rare. DI can be due to an ADH deficiency. The symptoms are polyuria and the production of diluted urine, which, in turn, can cause hypernatremia, if fluid loss is greater than fluid gain [19, 83].

It is necessary to monitor the general condition of the patients and conduct hormonal tests during the treatment with immune checkpoint inhibitors. The treatment involves supportive management and hormone replacement with levothyroxine, corticosteroids and estrogen/testosterone, depending on the pituitary hormone deficiency [14].

ICPI-RELATED PRIMARY HYPOPARATHYROIDISM

ICPi-related hypoparathyroidism is a rare disorder. To date, there have been only two case reports on severe hypocalcemia with confirmed hypoparathyroidism. The first melanoma patient, treated with nivolumab/ipilimumab, developed the symptoms of acute hypocalcemia 6 weeks after the first dose of ICIs. The second case of hypocalcemia was observed in a patient with a small cell lung cancer receiving nivolumab treatment [62, 79]. Hypocalcemia has been found to be considerably associated with the PD-1 inhibitor pembrolizumab treatment in a recent meta-analysis by Manohar et al., notably as a rare (11 out of 604 patients) adverse effect [51]. The pathomechanism is still unknown. Typically, the calcium sensing receptor (CaSR) of the parathyroid glands stimulates the release of PTH upon sensing of low blood calcium. CaSR autoantibodies and CaSR-activating autoantibodies have been described in a patient treated with nivolumab. Another pathomechanism includes cross-presentation of tumor-antigens. It leads to the expansion of T cell clones that then infiltrate healthy tissue and cause inflammation [42, 62].

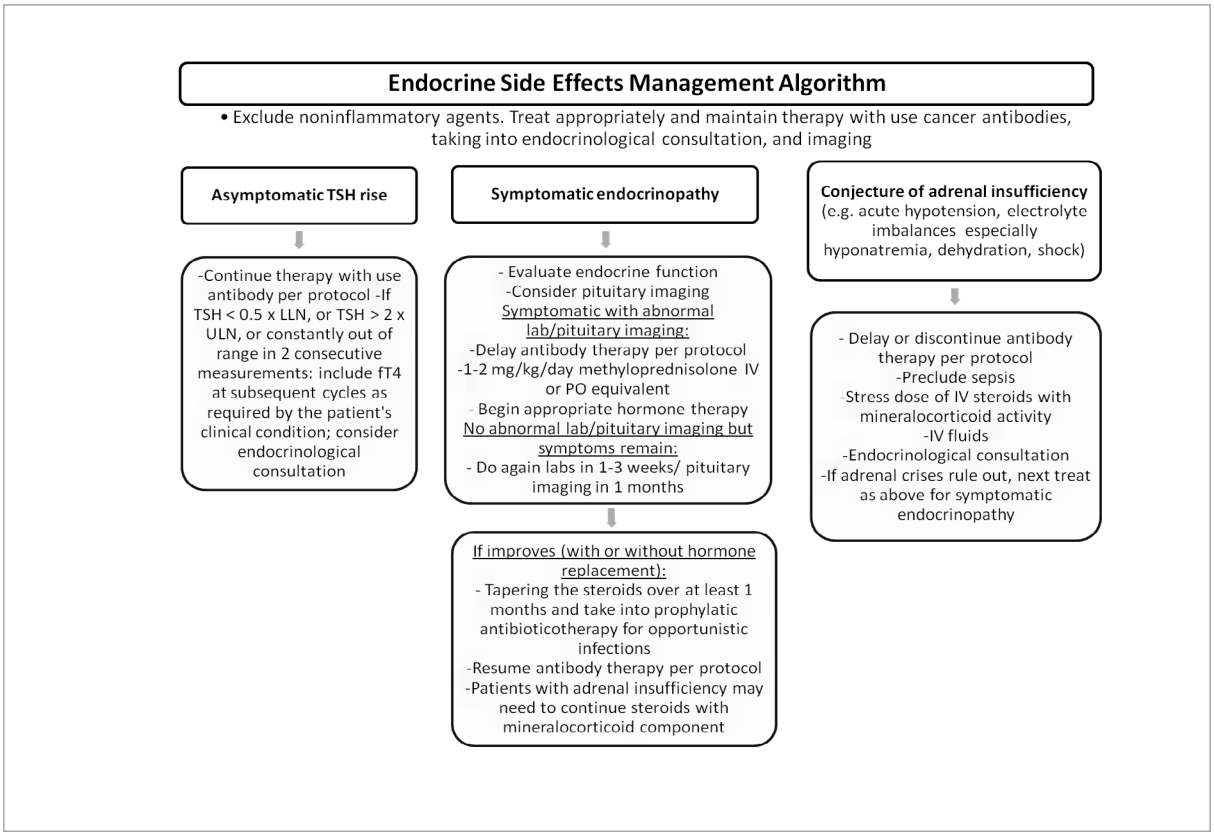
ICPI-RELATED THYROID DYSFUNCTION

Thyroid dysfunction belongs to one of the most frequently endocrine-related irAEs connected with ICPi therapy. ICI-thyropathy manifests itself as hyperthyroidism, hypothyroidism, and/or thyroiditis. Graves' disease (GD) appears to be very rare, but it has been reported [14]. Compared to anti-CTLA-4, these conditions are a more characteristic result of anti PD-1 therapy (up to 40%), while, according to available reports, they appear in 1–7% of patients with anti-CTL4 therapy. Immune checkpoint inhibitors are also associated with a significant risk of thyroid autoimmunity. This risk is higher for the anti-PD-1 treatment and increases during therapy with combination of checkpoint inhibitors [12]. Thyroid-related adverse effects are more common in women and include the whole spectrum of thyroid dysfunctions [66].

The mechanisms underlying thyroid dysfunction after treatment with immune checkpoint inhibitors remain to be clarified, similarly to other adverse effects that are not associated with the thyroid [12]. CTLA-4 is a major susceptibility gene for autoimmune thyroid disorders (AITDs), including GD and Hashimoto thyroiditis (HT). Whether polymorphisms in these genes have an influence on susceptibility to ICPi-related thyroid dysfunction remains unclear. Elevated levels of TPO Ab and TgAb have been identified in many patients with ICPi-related thyroid dysfunction. It is unclear whether these autoantibodies are the reason of ICPi-related thyroid dysfunction, and whether their elevated levels at baseline increase the risk of the occurrence of ICPi-related thyroid dysfunction [14]. Interaction between environmental and genetic factors influences the development of ATIDs. In one of the meta-analyses the authors evaluated polymorphism in the CTLA-4 gene. This study suggested that CT60 polymorphism (rs3087243) in CTLA-4 gene might confer susceptibility to the AITDs (GD/HT) [55]. Monoclonal antibodies are not the only drugs that cause thyroid disorders. Also, antivirals, including IFN-α and ribavirin, can induce AITDs [20].

Thyroiditis and primary hypothyroidism

Immune-Related Thyroiditis (IrT) appears as early onset of thyrotoxicosis, which is mostly asymptomatic, followed by a rapid conversion to hypothyroidism that requires long-term levothyroxine substitution [39]. This thyrotoxicosis resulting from an excessive release of the stored thyroid hormone is a consequence of destructive thyroiditis [46].



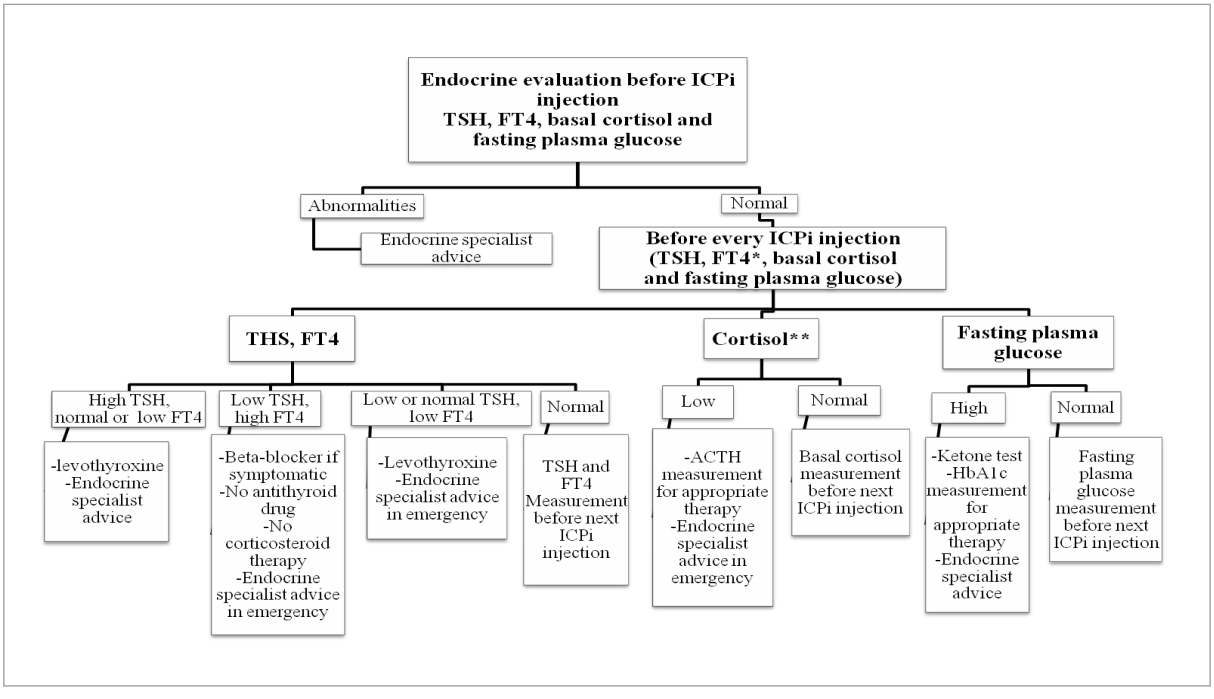


Fig. 1. Endocrine parameters that should be monitored in patients during monoclonal antibody treatment. A – endocrine side effects management algorithm [77], B – proposition of endocrine inspection during ICPi treatment [36]

*TSH and FT4 measurement could be done each week during the first 2 months of ICPi treatment

**If there is no corticosteroid treatment

Abbreviations: ICPi: Immune checkpoint inhibitor, TSH: Thyroid-stimulating hormone, FT4: Free thyroxine, ACTH: Adrenocorticotropic hormone, HbA1c: Hemoglobin A1c, LLN: below limit of normal, ULN: upper limit of normal, IV: intravenous, PO: per os.

The symptoms of thyrotoxicosis, when they appear, include palpitations, diaphoresis, fever, diarrhea, trembling, weight loss, or general fatigue [2]. Some patients may recover to the euthyroid state without levothyroxine. It seems that ICI-mediated thyroiditis is more frequently associated with anti-PD1 drugs used in monotherapy or in combination with anti-CTLA-4 agents. The evolution of thyroiditis seems to be more rapid when anti-CTLA-4 and anti-PD1 therapy is combined. Thyroiditis is very rarely reported as a single irAE. In the majority of studies examining ICI-mediated thyroiditis, a distinction is made between hypothyroidism, hyperthyroidism, and thyroiditis cases, when in fact these are a possible part of the same disease process [39].

Hypothyroidism can occur without a thyrotoxic phase presented as subclinical (elevated TSH with normal FT4) or overt hypothyroidism (elevated TSH with low FT4) [46]. The manifestation of hypothyroidism induced by ICIs generally consists of general fatigue, inappetence, constipation, bradycardia, or weight gain [2].

Hyperthyroidism independent of thyroiditis

It usually results from a GD like pattern and can develop either as subclinical (low TSH with normal FT4) or overt hyperthyroidism (low TSH with elevated FT4) [46]. Hyperthyroidism is usually the result of destructive thyroiditis, but cases of Graves' disease during ipilimumab and tremelimumab treatment have been reported [18]. To differentiate the two forms of thyrotoxicosis, with GD and without (painless thyroiditis) hyperthyroidism, TSH receptor antibodies (TRAb) should be measured. TRAb are increased in Graves' hyperthyroidism, but not in painless thyroiditis [66].

ICPI-RELATED PRIMARY ADRENAL INSUFFICIENCY (PAI)

Checkpoint blockade associated adrenal insufficiency is a potentially life-threatening complication of hypophysitis or adrenalitis in this patient group. Its symptoms are unspecific and include nausea, fatigue, appetite loss, abdominal pain, weight loss, hypotension, and hypoglycemia [18]. Life-threatening adrenal crisis, if untreated, may also occur and lead to shock and death [14]. Hyponatremia and hyperkalemia are frequently due to the presence of glucocorticoid and mineralocorticoid deficiency, while hypoglycemia and hypercalcemia are rare [6]. The overall incidence is low and appears more frequently when patients are treated with PD1 antibodies (0–4.3% with pembrolizumab and 0–3.3% with nivolumab) than with CTLA-4 inhibitors (ipilimumab 0.3-1.5%) [66]. The pathogenesis of ICPi-related PAI is unclear [14].

ICPI-RELATED DIABETES MELLITUS

Diabetes mellitus (DM) was present in less than 1% of patients treated with immune checkpoint inhibitors. Almost all cases of ICPi-related DM are caused by anti-PD-1 therapy. The patients commonly follow a fulminant course, with diabetic ketoacidosis and a rapid destruction of beta-cells. The pathophysiologic mechanism and predictive biomarkers have not yet been determined. The result of ICPi-related DM is permanent insulin-dependence (type 1 diabetes mellitus, T1DM). Patients with ICPi-related T1DM have a propensity to have relatively low levels of hemoglobin A1C (HbA1C), in comparison to the degree of hyperglycemia at presentation. This points to the rapidity of hyperglycemia progression [14, 76]. It is important to note that ICPi-induced diabetes tends to be irreversible [27]. Therefore, such symptoms as polyuria, polydipsia and weight loss should indicate a possibility of T1DM development [13].

MANAGEMENT AND PREVENTION OF ENDOCRINE ADVERSE EVENTS

Because ICPi modulates immune responses, high-dose corticosteroid treatment is suggested for some adverse effects. β-blockers appear to be adequate in managing the thyroiditis in the thyrotoxic phase. The manifestations of hypothyroidism are so unspecific that using them in deciding on the initiation of thyroid replacement therapy would be unsafe. It is proposed to introduce levothyroxine when the TSH levels are > 10mUI/L, as is commonly recommended in adult primary hypothyroidism. In case of central hypothyroidism, the introduction of thyroxine should be based on the FT4 levels, when they fall below the lower limit of the normal range, irrespectively of the TSH levels. The decision whether ICPi treatment should be continued, should not be based on the appearance of endocrine toxicity, excluding situations of life-threatening endocrine toxicity that are unsuitable for effective therapy [36]. This decision should be grounded in the risk involved in withdrawing therapy in patients under treatment for controlled or responsive malignant tumor. There are no indications to stop ICPi therapy in patients with grade 1 (mild) hypophysitis. In case of a higher degree of toxicity, it is recommended to discontinue the therapy and include systemic high-dose glucocorticoids. In case of clinical enhancement, immunotherapy can be resumed in combination with appropriate hormone replacement therapy (HRT) [30].

It is difficult to systematize objective recommendations to avoid severe endocrine adverse effects. Clinicians should choose an individual and specific to each patient treatment regimen. Current guidelines, research data and clinical experience can be used to limit adverse effects of therapy. As hypopituitarism, thyroid dysfunction, and diabetes mellitus are the three primary types of endocrine toxicity, TSH, FT4, cortisol, ACTH and glucose measurements should be done before starting ICPi treatment. Creation of objective recommendations for follow-up seems to be problematic due to frequently missing information on the timing of onset of the side effects from large trials [36].

Figure 1A and B show suggested endocrine parameters that should be monitored in patients during monoclonal antibody treatment.

CONCLUSIONS

Many molecular targeted therapies approved by the FDA have demonstrated remarkable clinical success in the treatment of various cancer types. Among them, we distinguish specific mAbs. However, we should be aware of the potential side effects in the endocrine system that can be dangerous for the patients. Immune checkpoint inhibitors, such as anti-CTLA-4 and anti-PD-1, or its ligand PD-L1, can cause a variety of autoimmune adverse effects. Among the most common ones are hypopituitarism, thyroid dysfunction, adrenal insufficiency and diabetes mellitus. It is necessary to monitor the general condition of patients and appropriate diagnostic parameters. This will allow choosing individual anticancer therapy and proper ICPi-related endocrinopathy treatment.

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