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THE SIDE EFFECTS OF IMMUNE CHECKPOINT INHIBITOR THERAPY ON THE THYROID GLAND

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Abstract. Survival of patients with advanced-stage cancers remains poor despite significant successes in targeted and chemotherapy. Immunotherapy is a systemic method of treatment that has expanded the possibilities of drug therapy for malignant tumors. Immunotherapy's side effect significantly differs from chemotherapeutic drugs and targeted therapy.

One of the most common side effects is a toxic effect on the endocrine system, particularly the thyroid gland.

Aim of the research. Conduct a systematic analysis of scientific literature on the side effects of immune checkpoint inhibitors on the thyroid gland.

Materials and methods. A scientific search was conducted in Pubmed, Scopus, and Web of Science databases. The following search terms were used: "immune checkpoint inhibitors," "immunotherapy," "thyroid gland," and "side effects."

Research results. Both PD-1/PD-L1 inhibitors and CTLA-4 inhibitors can cause thyroid dysfunction (hyperthyroidism or hypothyroidism). One of the meta-analyses reported no difference in the incidence of thyrotoxicity between the two drug groups. However, other meta-analyses have shown that this phenomenon is more common in patients treated with PD-1/PD-L1 inhibitors than with CTLA-4 inhibitors. In addition, scientists proved that hypothyroidism occurred statistically more often (3.8% of patients) than hyperthyroidism (1.7%). Hypothyroidism was more common in PD-1 inhibitor users than hyperthyroidism (7.0% vs. 3.2%, respectively). Patients with a history of autoimmune thyroid disease have a high risk of disease exacerbation after initiating immune checkpoint inhibitor therapy. The side effect of immune checkpoint inhibitors is developed mainly in women. The first laboratory signs of hypothyroidism are observed after 2-4 courses of immunotherapy. In most cases, the disease is asymptomatic, but in rare cases, it turns into permanent hypothyroidism and even thyroid crisis. The leading causes of destruction of the thyroid gland due to immune checkpoint inhibitors are damaged by autoantibodies or the production of thyroid-stimulating antibodies.

Levothyroxine is prescribed at 0.8–1.6 μg/kg/day for treating hypothyroidism with clinical symptoms. For elderly patients and patients with cardiac pathology, the initial dose of the drug should be no more than 25-50 μg. Treatment with immune checkpoint inhibitors is usually continued. Treatment of thyrotoxicosis depends on the pathological mechanism that caused it. Most often, beta-blockers (atenolol and propranolol) are used to eliminate the symptoms of thyrotoxicosis. A feature of thyroiditis is its ability to transition into hypothyroidism, which can become permanent.

Conclusions. The development of thyroid dysfunction is the most common consequence of autoimmune damage. PD-1 inhibitors are the most common cause of this condition. Usually, the disorders are asymptomatic and have the first degree of severity. Timely appointment for hormone replacement therapy allows the effective continuation of immunotherapy. However, some conditions may be refractory to such treatment, requiring steroid therapy and discontinuation of immunotherapy.

Keywords: immune checkpoint inhibitors, side effects, immunotherapy, thyroid gland.

Introduction. Survival of patients with advanced-stage cancers remains poor despite significant successes in targeted and chemotherapy. Immunotherapy is a systemic method of treatment that has expanded the possibilities of drug therapy for malignant tumors [1]. Inhibition of T cells occurs due to the competition of cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) with CD28 for binding to the B7 protein on the antigen-presenting cell [2]. In addition to CTLA-4, PD-1 (programmed cell death protein) is expressed in T cells. This protein can also be detected in macrophages, thymocytes, and mature B cells. Suppression of T-lymphocyte function occurs due to interaction with PD-L1 (ligand of programmed cell death) on tumor cells. In addition to T-lymphocytes, PD-1 can be detected in the tumor microenvironment. Pathological pathways PD-1/PD-L1 and CTLA-4 contribute to the proliferation and spread of tumor cells. In turn, by blocking signaling pathways, it is possible to achieve an anticancer effect. Monoclonal antibodies capable of blocking immune checkpoints and leading to the activation of T cells are called immune checkpoint inhibitors [3].

The Food and Drug Administration (FDA) has approved three main groups of drugs for immunotherapy of malignant neoplasms: PD-1 inhibitors (nivolumab, pembrolizumab, dasarlimab, cemiplimab), PD-L1 inhibitors (durvalumab, atezolizumab, avelumab), and CTLA-4 inhibitors (ipilimumab). They are widely used to treat non-small cell and small cell lung cancer, kidney cancer, melanoma, ovarian, bladder, head and neck tumors. The antiproliferative effect of immunotherapy occurs at different levels. CTLA-4 inhibitors increase the proliferation of T cells in lymph nodes. PD-1/PD-L1 blockers have a more significant effect on the tumor microenvironment. As a result, immunotherapy's side effects significantly differ from chemotherapy drugs and targeted therapy [4].

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Research rationale. One of the most common side effects is a toxic demage to the endocrine system, particularly the thyroid gland [5]. Combining drugs from different groups significantly increases the risk of developing immune-related adverse events [6, 7].

Aim of the research. Conduct a systematic analysis of scientific literature on the side effects of immune checkpoint inhibitors on the thyroid gland.

Materials and methods. A scientific search was conducted in Pubmed, Scopus, and Web of Science databases. The following search terms were used: "immune checkpoint inhibitors," "immunotherapy," "thyroid gland," and "side effects."

Research results and discussion. Most doctors are cautious about prescribing immunotherapy because of the high risk of developing endocrine toxicity and autoimmune reactions. The final pathogenesis of the toxic effect of immune checkpoint inhibitors has not been established. Still, several theories can explain this phenomenon—for example, the appearance of autoantibodies and type II or IV hypersensitivity reactions [8].

Patients with a history of autoimmune diseases (type I diabetes, thyroiditis, psoriasis, rheumatoid arthritis, etc.) require special attention. Immune checkpoint inhibitors can cause exacerbation of the disease and deterioration of the general condition of patients. The primary treatment method for endocrine toxicity of immunotherapy is the appointment of hormone replacement therapy [9]. Depending on the severity of the immune-related toxic phenomenon, treatment with inhibitors of immune checkpoints is continued or stopped until the blood hormone levels normalize. Usually, endocrine toxicity of the first or second degree does not require discontinuation of immunotherapy. The mechanisms responsible for the development of endocrine toxicity require in-depth research to establish the risk of this complication.

Both PD-1/PD-L1 inhibitors and CTLA-4 inhibitors can cause thyroid dysfunction (hyperthyroidism or hypothyroidism). One of the meta-analyses reported no difference in the incidence of thyrotoxicity between the two drug groups. However, other meta-analyses have shown that this phenomenon is more common in patients treated with PD-1/PD-L1 inhibitors than with CTLA-4 inhibitors. In addition, scientists proved that hypothyroidism occurred statistically more often (3.8% of patients) than hyperthyroidism (1.7%). Hypothyroidism is more common in patients with PD-1 inhibitors than in hyperthyroidism (7.0% vs. 3.2%, respectively) [5, 10].

Patients with a history of autoimmune thyroid disease have a high risk of disease exacerbation after initiating immune checkpoint inhibitor therapy. Abdel-Wahab et al. [11] investigated the frequency of worsening of autoimmune thyroiditis after administration of any dose of immune checkpoint inhibitors. Scientists have established that in 17% of patients, hypothyroidism worsened immediately after the start of immunotherapy. The majority of these patients received pembrolizumab or nivolumab. Immune-mediated adverse events were controlled by adjusting the dose of hormone therapy.

Graves' disease and Hashimoto's autoimmune thyroiditis can develop due to genetic susceptibility caused by polymorphisms in CTLA-4/PD-1 genes. It causes changes in the immune response. However, the mechanisms of thyroid dysfunction are not clearly defined [12].

The role of autoantibodies is considered not clear. Antithyroid antibodies are not detected in all patients who received immune checkpoint inhibitors and had a side effect of thyroid gland dysfunction. Osorio et al. [13] reported that antithyroid antibodies are present in most patients. However, de Filette et al. [14] obtained opposite data and found that most patients with thyroid dysfunction do not have antibodies to thyroperoxidase. As a result, the theory of an antibody-independent mechanism of injury has been put forward. However, all scientists agree with the statement about developing destructive thyroiditis caused by cytotoxic T cells. These cells cause and maintain inflammation in the thyroid gland.

Immune-related damage to the thyroid gland includes hyperthyroidism, hypothyroidism, or thyroiditis. The side effect of immune checkpoint inhibitors is observed mainly in women. The first laboratory signs of hypothyroidism are observed after 2–4 courses of immunotherapy. In most cases, the condition is asymptomatic, but in rare cases, it turns into permanent hypothyroidism [15]. Kataoka et al. [16] reported that sporadic patients may develop thyroid storms. Khan et al. [17] described a myxedema crisis due to nivolumab administration. Martens et al. [18] reported Graves' disease with an elevated level of antibodies to the thyroid-stimulating hormone (TSH) receptor but with normal thyroid function.

Elevated levels of TSH and low levels of free thyroxine indicate hypothyroidism. In addition to laboratory signs, clinical symptoms (weakness, bradycardia, constipation, intolerance to cold, and dry skin) is evidence of decreased thyroid function [19]. In addition, secondary hypothyroidism can result from hypophysitis and pituitary insufficiency.

An elevated free thyroxine level and a low TSH level indicate hyperthyroidism. Clinical signs of increased thyroid function are anxiety, tremors, tachycardia, intolerance to hot, increased sweating, and frequent defecation [19]. However, this condition can be the result of advanced thyroid cancer. Therefore, it is necessary to carry out differential diagnosis.

The leading causes of destruction of the thyroid gland due to the use of immune checkpoint inhibitors are damaged by autoantibodies (this phenomenon is mainly temporary) or due to the production of thyroid-stimulating antibodies. The last option causes Graves' disease and is permanent. Radio iodine scanning is performed for differential diagnosis of the specified types of hyperthyroidism. Autoimmune thyroiditis is indicated by antibodies against thyroperoxidase and thyroglobulin [20]. Thyroid hormone levels should be measured before starting treatment with immune checkpoint inhibitors and then every six weeks during treatment [21].

Treating thyroid dysfunction is prescribed depending on whether the free thyroxine level is increased or decreased. With asymptomatic hypothyroidism corresponding to the first degree of severity, drug therapy is usually not prescribed. Levothyroxine is prescribed at 0.8–1.6 μg/kg/day for treating hypothyroidism with clinical symptoms. For elderly patients and patients with cardiac pathology, the initial dose of the drug should be no more than 25–50 μg [22, 23]. Treatment with immune checkpoint inhibitors is usually continued. Blood tests for thyroid hormones should be repeated every 6–8 weeks until

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TSH and free thyroxine levels normalize. After this, laboratory testing will be performed every three months.

Treatment of thyrotoxicosis depends on the pathological mechanism that caused it. Antithyroid drugs can block the synthesis of thyroxine and ease the course of Graves' disease. However, they do not work during the thyrotoxic phase of thyroiditis, when the main factor affecting the blood thyroxine concentration is the destruction of the thyroid gland`s cells. Most often, beta-blockers (atenolol and propranolol) are used to eliminate the symptoms of thyrotoxicosis. A feature of thyroiditis is its ability to transition into hypothyroidism, which can become permanent. Therefore, it is necessary to regularly perform laboratory tests to determine the level of TSH and free thyroxine hormones. In case of increased TSH, replacement therapy with levothyroxine is started [22, 23].

Indications for using steroid therapy are Graves' ophthalmopathy when the withdrawal of immune checkpoint inhibitors does not help stop the disease. Glucocorticoids are also used in elderly patients with severe thyrotoxicosis against cardiovascular diseases in the anamnesis [24]. Al Mushref et al. [25] demonstrated that developing autoimmune thyroid disorders in patients receiving immune checkpoint inhibitors for treating melanoma did not affect overall survival.

Conclusions. Immune checkpoint inhibitors demonstrate their effectiveness in treating malignant neoplasms. The development of thyroid dysfunction is the consequence of autoimmune damage. PD-1 inhibitors are the most common cause of this condition. Usually, the disorders are asymptomatic and have the first degree of severity. Timely appointment for hormone replacement therapy allows the effective continuation of immunotherapy. However, some conditions may be refractory to such treatment, requiring steroid therapy and discontinuation of immunotherapy. Oncologists and family doctors should be aware of the side effects of immune checkpoint inhibitors on the thyroid gland.

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ПОБІЧНА ДІЯ ТЕРАПІЇ ІНГІБІТОРАМИ ІМУННИХ КОНТРОЛЬНИХ ТОЧОК НА ЩИТОПОДІБНУ ЗАЛОЗУ

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Вступ. Системним методом лікування, який розширив можливості медикаментозної терапії злоякісних пухлин є імунотерапія.

Одним із найбільш частих побічних ефектів даної групи препаратів є токсичний вплив на щитоподібну залозу.

Мета. Провести системний аналіз наукової літератури щодо побічної дії інгібіторів імунних контрольних точок на щитоподібну залозу.

Матеріали і методи. Науковий пошук проводився в базі даних Pubmed, Scopus, Web of Science.

Результати. Дисфункцію щитоподібної залози можуть викликати інгібітори PD-1/PD-L1 та CTLA-4. Гіпотиреоз зустрічається частіше в порівнянні з гіпертиреозом (3,8% проти 1,7%). Пацієнти з аутоімунним захворюванням щитоподібної залози в анамнезі мають високий ризик загострення захворювання після початку терапії інгібіторами імунних контрольних точок. Побічний ефект спостерігається переважно в жінок. Перші лабораторні ознаки гіпотиреозу виникають після 2-4 курсів імунотерапії. Зазвичай захворювання перебігає безсимптомно, однак у рідкісних випадках переходить у постійний гіпотиреоз та навіть тиреоїдну кризу. Основними причинами деструкції щитоподібної залози є пошкодження аутоантитілами.

При симптоматичному гіпотиреозі призначають левотироксин у дозі 0,8-1,6 мкг/кг/день. Лікування інгібіторами імунних контрольних точок зазвичай продовжують. Найчастіше для усунення симптомів тиреотоксикозу використовують бета-блокатори.

Висновки. Розвиток дисфункції щитоподібної залози є найбільш поширеним наслідком аутоімунного ураження. Найчастішою причиною даного стану є інгібітори PD-1. Зазвичай, розлади безсимптомні та мають перший ступінь тяжкості.

Ключові слова: інгібітори імунних контрольних точок, побічна дія, імунотерапія, щитоподібна залоза.

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