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Effect of Chemo- and Immunotherapy of Hemoblastosis on The Endocrine System

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Abstract

Chemo- and immunotherapy of hemoblastoses, including leukemia, lymphoma and myeloma, are associated with the development of a wide range of acute and delayed endocrinopathies. The pathogenesis of these conditions is multifactorial and includes direct cytotoxic action, autoimmune activation, systemic inflammation and secondary effects of transplantation. The article summarizes data on the frequency, pathogenesis and clinical manifestations of endocrinopathies in oncohematological patients. Practical recommendations for their screening and monitoring, as well as on issues of fertility preservation are presented.

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Keywords: Hemoblastoses, chemotherapy, immunotherapy, checkpoint inhibitors, CAR-T therapy, hematopoietic stem cell transplantation, endocrine complications, hypothyroidism, hypophysitis, autoimmune diabetes, gonadal insufficiency.

Introduction

The scientific novelty of the article consists in a comprehensive analysis of endocrine complications of chemo- and immunotherapy of hemoblastoses with clarification of their mechanisms, risk factors and clinical manifestations, as well as in substantiating practical approaches to diagnostics and monitoring to improve the effectiveness of treatment and the quality of life of patients.

The problem of hemoblastoses (leukemia, lymphoma and myelomas) is one of the most pressing in modern oncohematology. Intensification of therapy, including chemotherapy, targeted drugs, immunotherapy and hematopoietic stem cell transplantation (HSCT), has led to a significant increase in patient survival [1]. However, this is associated with increasing attention to the remote consequences of treatment, in particular, damage to the endocrine system.

The endocrine system is exposed to multiple effects of cytostatic and immunomodulatory agents:

1. Alkylating agents and total TVB radiation (TBI) used as conditioning before HSCT is associated with a high risk of gonadal failure, hypothyroidism and growth failure in children.

2. Immunotherapy, especially checkpoint inhibitors (anti-CTLA-4, anti-PD-1/PD-L1), often leads to the development of autoimmune endocrinopathies: thyroiditis, hypophysitis, adrenal insufficiency and type 1 diabetes mellitus. The frequency of these complications reaches 20% and higher [2].

In patients who have undergone HSCT, the incidence of endocrine complications in the long term reaches 60-70%. The most common disorders are hypogonadism, hypothyroidism, hypopituitarism, as well as metabolic changes, including obesity and osteoporosis.

Therefore, endocrine toxicity is an integral part of the spectrum of complications of modern therapy of hemoblastoses. Its timely diagnosis and correction are of crucial importance for the quality of life, preservation of reproductive potential and prevention of severe complications. The purpose of this article is to summarize current data on the impact of antitumor therapy on the endocrine system and discuss the prospects for managing this cohort of patients.

The impact of antitumor therapy of hemoblastoses on the endocrine system is multifactorial. The main pathogenetic mechanisms include:

1. Direct cytotoxic damage. Alkylating agents (eg., cyclophosphamide, busulfan) and platinum-containing drugs have a direct damaging effect on the germinal epithelium of the gonadal and thyroid cells, leading to the development of hypogonadism, premature ovarian failure, and hypothyroidism [3].

2. Radiation exposure. Total body irradiation (TBI) used in pre-transplant conditioning causes damage to the hypothalamic-pituitary system and thyroid gland. In children and adolescents, this manifests as growth retardation, growth hormone deficiency, and secondary hypothyroidism [4].

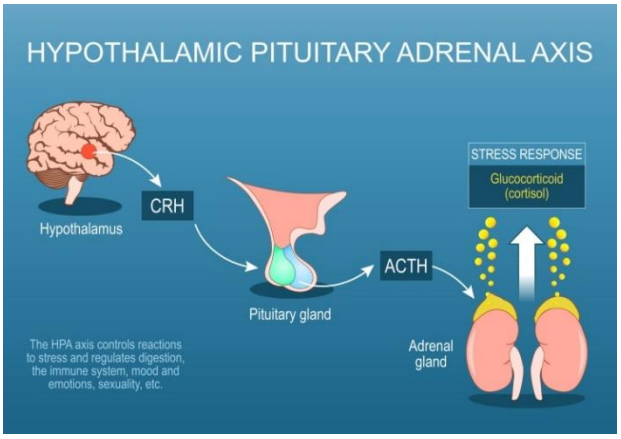

Fig. 1 - Diagram of the interaction of the hypothalamus and pituitary gland

3. Immune-mediated reactions. Checkpoint inhibitors (anti-CTLA-4, anti-PD-1/PD-L1) disrupt peripheral tolerance mechanisms, which initiates autoimmune inflammation of endocrine organs. This most often leads to autoimmune thyroiditis , hypophysitis, and type 1 diabetes mellitus [5].

4. Cytokine-mediated damage. Cytokine release syndrome (CRS) develops during CAR-T therapy. This syndrome can indirectly affect the hypothalamic-pituitary axis, thyroid function, and glycemic control [6].

5. Cumulative effect of therapy. The combined use of chemotherapy, immunotherapy and HSCT significantly increases the risk of developing multiple endocrinopathies. According to the results of cohort studies, most patients who have undergone this treatment experience at least one endocrine dysfunction within 10 years after therapy [7].

Table 1 - The main mechanisms of endocrine disorders in the treatment of hemoblastoses

Mechanism	**Preparations/methods**	**Major endocrine complications**
Direct cytotoxicity	Alkylating agents, platinum	Hypogonadism, hypothyroidism
Radiation therapy (TBI)	TV irradiation	Growth hormone deficiency, hypopituitarism , hypothyroidism
Immune -mediated reactions	Checkpoint inhibitors	Autoimmune thyroiditis , hypophysitis, type 1 diabetes
Cytokine-mediated action	CAR-T therapy, CRS	Thyroid dysfunction, carbohydrate metabolism disorders
Cumulative impact	HT + IT + TGSK	Multiple endocrinopathies

Thyroid dysfunction is one of the most common endocrine complications associated with the use of checkpoint inhibitors (CPIs), particularly anti-PD-1/PD-L1 and anti-CTLA-4. It may manifest as thyroiditis with an initial phase of thyrotoxicosis, which subsequently develops into hypothyroidism, or as isolated hypothyroidism. The clinical picture includes fatigue, weight changes, thermoregulatory disorders, and palpitations. For early detection, monitoring of TSH and free T4 levels every 4-6 weeks at the start of therapy, as well as determination of thyroid antibodies, are recommended. peroxidase when symptoms appear.

Hypophysitis, associated mainly with anti-CTLA-4 and combination immunotherapeutic regimens, manifests itself as headache, asthenia, arterial hypotension and anorexia. Secondary adrenal insufficiency, secondary hypothyroidism and hypogonadism may develop. If hypophysitis is suspected, it is

necessary to urgently assess the concentration of morning cortisol, ACTH, TSH/free T4, LH/FSH. MRI of the pituitary gland is indicated to confirm the diagnosis.

The use of ICT can induce autoimmune diabetes mellitus, characterized by rapid development of insulin deficiency, often with ketoacidosis. Clinical signs include polydipsia, polyuria, and rapid weight loss. Insulin therapy is usually required from the onset of the disease. Glucose monitoring at each visit is mandatory. If hyperglycemia is detected, determination of C-peptide and islet cell antibodies is recommended.

Primary adrenal insufficiency is a rare but reported complication of IBS. Secondary adrenal insufficiency, on the other hand, often develops as a consequence of hypophysitis. Symptoms include weakness, hypotension, hyponatremia, and hyperkalemia (in the primary form). Diagnostic screening includes morning cortisol and ACTH levels. If cortisol levels are low, an ACTH stimulation test is indicated.

Chemotherapy (particularly alkylating agents) and total TV irradiation (TBI) have a cumulative gonadotoxic effect. In women, this leads to a decrease in ovarian reserve and premature menopause, and in men - to azo / oligospermia and decreased testosterone levels. Before starting therapy, an assessment of fertility and a discussion of methods for preserving it (cryopreservation of gametes / tissues) are necessary.

Intensive systemic therapy, HSCT and long-term corticosteroid use increase the risk of decreased bone mineral density, osteopenia /osteoporosis and pathological fractures. In children, this may lead to growth disturbances. Risk factor assessment, densitometry (DXA) and correction of vitamin D and calcium deficiency are recommended.

After intensive care and HSCT, metabolic disorders are often observed in surviving patients: weight gain, dyslipidemia, and insulin resistance. These conditions increase long-term cardiovascular risk and require systematic monitoring, as well as timely lifestyle modification and drug therapy.

CAR-T therapy is associated with a high risk of developing cytokine release syndrome (CRS). High levels of proinflammatory cytokines can cause secondary endocrine disturbances, including impaired glycemic control and effects on the hypothalamic-pituitary axis. Data on the long-term endocrine effects of CAR-T therapy remain fragmentary. In the acute phase of CRS, careful monitoring of metabolic parameters is necessary.

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Table 2 - Endocrine complications of chemo- and immunotherapy: clinical manifestations, onset time and diagnostic methods

Organ / system	Typical clinical manifestations	Time of occurrence	Recommended examinations
Thyroid gland	Fatigue, weight change, tachycardia (thyrotoxicosis), then hypothyroidism	Within a few weeks to months after the start of ICI; also later	TSH, free T4 , TPO antibodies (if indicated)
Pituitary	Headache, weakness, arterial hypotension, deficiency of ACTH/TSH/LH-FSH	More often in the first months of ICI therapy (especially with anti-CTLA-4)	Morning cortisol, ACTH, TSH/s-T4, LH/FSH, MRI of the pituitary gland if suspected
Pancreas (β-cells)	Polydipsia, polyuria, rapid weight loss, risk of DKA	May occur acutely (weeks-months) with ICI	Blood glucose, C-peptide, autoantibodies (GAD, etc.)
Adrenal glands	Weakness, hypotension, hyponatremia	In primary cases - after several months; in secondary cases - in the context of hypophysitis	Morning cortisol, ACTH; ACTH test if indicated
Gonads	Menstrual irregularities, premature menopause, azo / oligospermia , decreased fertility	Dependent on dose and type of chemotherapy; often during treatment and in the early late period	LH, FSH, estradiol /testosterone, AMH (ovarian reserve), spermogram
Bones / Height	Osteopenia , decreased bone density, in children - growth retardation	Late effects (months-years) after HSCT and corticosteroids	DXA, 25(OH)D levels, calcium, PTH
Metabolism/Body weight	Obesity in survivors , dyslipidemia , insulin resistance	Remotely after therapy/HSCT	Lipid profile, glycated Hb, OGTT when indicated
CAR-T/CRS	Glycemic disturbances, acute systemic manifestations, potential late effects	Acute in CRS; late - under study	Glucose monitoring, inflammation indicators; multidisciplinary monitoring

The frequency of endocrine complications arising during antitumor therapy has significant variability. It depends on the type of treatment, the patient's age, the cumulative dose of drugs and the presence of concomitant factors:

1. Chemotherapy and hematopoietic stem cell transplantation (HSCT). The use of alkylating agents (cyclophosphamide, busulfan) and total body irradiation (TBI) in conditioning regimens before HSCT is associated with a high risk of gonadal insufficiency. According to studies, in women, the incidence of premature ovarian

failure after high-dose therapy and TBI reaches 65–85% [3]. In men, hypogonadism and azoospermia occur in 50–70% of cases, which correlates with the dose and age at the start of treatment [8]. In children who have undergone HSCT, the risk of endocrine disorders is especially high. According to a cohort study, by the 10-year follow-up period, at least 60% of patients have one or more endocrine complications, such as hypothyroidism, hypogonadism, and growth retardation [4].

2. Immunotherapy (checkpoint inhibitors). Checkpoint inhibitors (CPIs), including anti-PD-1, anti-PD-L1, and anti-CTLA-4, cause autoimmune endocrinopathies. Thyroid disorders are the most common: according to a meta-analysis, hypothyroidism is recorded in 6–10% of patients, and thyrotoxicosis in 3–5% [2]. Hypophysitis most often develops during therapy with ipilimumab (anti-CTLA-4) and occurs in 5–17% of patients [5]. Cases of autoimmune diabetes mellitus are rare (about 1%), but are characterized by the rapid development of ketoacidosis [9]. Risk factors for the development of endocrine complications during immunotherapy are a combination of several CPIs, a high cumulative dose, and a history of autoimmune diseases.

3. CAR-T therapy. Data on the incidence of endocrine disorders after CAR-T therapy are currently limited. In the acute phase, caused by cytokine release syndrome (CRS), glycemic control and hypothalamic-pituitary system function disorders may be observed. Remote consequences have not been sufficiently studied, but isolated cases of secondary hypogonadism and growth disorders in children have been described [10].

General risk factors for the development of endocrine toxicity include:

- young age at the start of therapy (especially in children, where there is a risk of delayed growth and puberty);
- female gender (due to the high sensitivity of the ovarian reserve to cytostatic and radiation load);
- use of high cumulative doses of alkylating agents;
- the use of total body irradiation;
- combination immunotherapy;
- the presence of a predisposition to autoimmune diseases.

Thus, endocrine toxicity is a frequent and clinically significant complication of antitumor treatment of hemoblastoses. Its risk is especially high in children and young adult patients, as well as when using intensive conditioning regimens and combination immunotherapy.

Effective diagnosis and monitoring of endocrine disorders in patients with hematological malignancies require a systematic approach that depends on the type of therapy, patient age and associated risks.

Before starting highly toxic therapy (high-dose chemotherapy, HSCT, immunotherapy, CAR-T), basic endocrine screening is necessary. This includes collecting anamnesis, assessing fertility, measuring TSH, free T4, morning cortisol, LH/FSH, and testosterone or estradiol. For women of reproductive age, anti-Müllerian hormone (AMH) analysis is important to assess ovarian reserve. Glycated hemoglobin/glucose levels are also assessed. This approach allows identifying baseline abnormalities and establishing reference values for further dynamic monitoring.

Monitoring should be risk-oriented, with the frequency and set of tests adapted to the specific treatment regimen. A multidisciplinary approach, including an oncologist/hematologist, endocrinologist and reproductive specialist , is mandatory.

Recommendations for immunotherapy (ICT):

1. Measurement of TSH and free T4 is recommended prior to initiation of therapy and then regularly, every 4–6 weeks for the first 3–6 months. If symptoms occur: immediately. The frequency of monitoring may be increased when using combination regimens.
2. In the presence of symptoms such as fatigue, headache, hypotension, hyponatremia, it is necessary to immediately assess the levels of morning cortisol and ACTH. If hypophysitis is suspected: add the analysis of TSH/free T4, LH/FSH and prolactin, and also perform an MRI of the pituitary gland.
3. Blood glucose monitoring at each visit. In case of persistent hyperglycemia: additional analysis of C-peptide and autoantibodies , as well as consultation with an endocrinologist.

If hormonal deficiency is confirmed, replacement therapy (eg, cortisone or L-thyroxine) should be started immediately and interruption of ICT therapy should be considered.

Recommendations for HSCT and radiation:

1. Evaluation of sexual function, thyroid hormones, and growth and pubertal development status in children is mandatory. Discussion of fertility preservation options is essential.
2. Patients who have undergone HSCT require lifelong monitoring of the endocrine system. Annual monitoring of sexual and thyroid functions is recommended. More

frequent examinations are recommended in the presence of risk factors (TBI, high doses of alkylating agents).

3. In patients receiving long-term corticosteroids or undergoing HSCT, bone mineral density assessment (BMD) and monitoring of vitamin D and calcium levels are recommended.

Recommendations for CAR-T therapy:

1. During the period of cytokine release syndrome, careful monitoring of glucose and electrolytes is necessary. If signs of endocrine disorders are detected, cortisol and other hormone levels are assessed.

2. Since the long-term effects of CAR-T therapy have not been adequately studied, patients should be included in lifelong monitoring programs with periodic assessment of thyroid and reproductive functions, as well as metabolic parameters.

Table 3 - Recommended examinations and monitoring frequencies for different types of therapy

Purpose of the survey	**Before therapy (basic set)**	**During therapy**	**After therapy / long term**	**Note / When to examine immediately**
Thyroid function (TSH, fT4)	All patients	ICI: every 4–6 weeks ; immediately if symptoms occur	Annually (or more often if there are deviations)	If symptoms occur (weakness, weight change, tachycardia) immediately
Adrenal / pituitary (morning cortisol, ACTH; TSH, fT4; if pituitary MRI is suspected)	Morning cortisol in risky individuals	If symptoms occur (hypotension, severe fatigue) immediately	In case of confirmed dysfunction, long-term observation	If symptoms/suspected hypophysitis occur, immediately
Glucose/metabolism (glucose, HbA1c; if necessary C-peptide, antibodies)	Glucose/HbA1c in patients with risk factors	ICI/CAR-T: glucose testing at every visit; additional testing when elevated	Periodic (annually or as clinically indicated)	In case of polydipsia/polyuria/ RV, immediate examination
Sexual function/fertility (LH/FSH, estradiol /testosterone, AMH, spermogram)	Mandatory in reproductive age before TGSC/chemotherapy	For symptoms / fertility preservation plan	monitoring ; refer to fertility specialist	Fertility Preservation Consultation Before Highly Toxicity Therapy
Bones (DXA, 25(OH)D)	Assess risk factors; baseline 25(OH)D	During long-term corticosteroid therapy, routine assessment	Periodically in high-risk individuals ; treatment when osteopenia is detected	In case of fractures/risk factors, prescribe DXA
General long-term screening after HSCT/CAR-T	Basic endocrine kit	According to indications, symptoms	Lifetime surveillance, annually or at risk; include in survivorship clinic	In case of symptoms/pathology, urgent coordination with an endocrinologist

Management of patients with endocrine disorders caused by antitumor therapy requires a balanced and timely approach. In the presence of a clinical picture

indicating adrenal insufficiency, it is important to promptly determine the level of morning cortisol. If low values are detected, especially against the background of pronounced symptoms, cortisol replacement therapy should be started immediately, without waiting for the results of stimulation tests. It is important to consider that many endocrine disorders induced by checkpoint inhibitors (ICIs) can be permanent. In this regard, it is necessary to inform patients about the potential need for lifelong hormone replacement therapy.

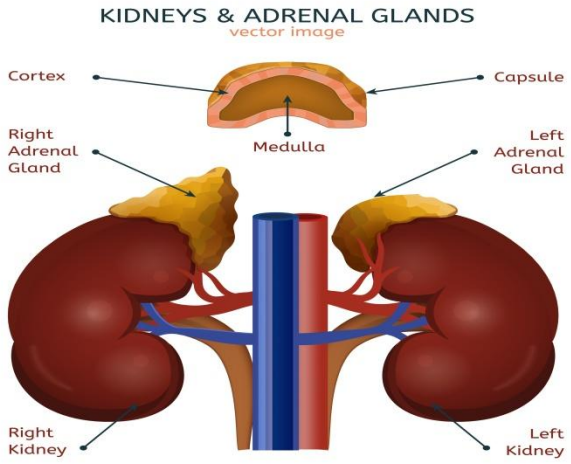

Fig. 2 - Schematic representation of the adrenal glands on the kidneys

To optimize the patient management process, it is advisable to implement local algorithms and checklists. These tools will allow oncologists and hematologists to systematize patient examinations, identifying the necessary tests before and during therapy, as well as establishing clear criteria for timely referral to an endocrinologist. This approach ensures effective interdisciplinary interaction and improves long-term treatment outcomes.

Endocrine toxicity is a frequent and clinically significant complication of antitumor therapy. Its timely diagnosis and correction are crucial for quality of life, preservation of reproductive potential and prevention of severe consequences.

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