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Modern View on the Influence of Antitumor Therapy on the Activity of the Thyroid Gland

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ABSTRACT

Chemotherapy, targeted and immune therapy of malignant tumors affect the endocrine system, including its steroidal and non-steroidal components, including the thyroid gland, as well as the outcomes of treatment of neoplasms associated with hormonal and metabolic changes [Hartmann K., 2015]. This article presents a review of the literature on the effect of anticancer therapy on thyroid function.

Relevance. Many patients experience newly diagnosed or chronic thyroid disease when diagnosed with cancer. Some of these diseases are identified by chance, as a result of an examination for a neoplasm, at the same time, they can also be a direct result of the therapy that patients receive. Proper diagnosis and treatment of thyroid diseases are important for the results of therapy and rehabilitation of patients with malignant tumors. Thus, undiagnosed hypothyroidism or hyperthyroidism often occurs with symptoms associated with the toxicity of the therapy used, which can lead to an erroneous reduction in the dose of medication by the oncologist or temporary suspension of treatment [Riksfjord Hamnvik O.P., Reed Larsen P., Marqusee E., 2021]. Anticancer drugs used in oncology practice can lead to thyroid dysfunction, which manifests itself clinically as hypothyroidism or thyrotoxicosis (hyperthyroidism). In oncological practice, for the diagnosis of malignant neoplasms, radiation imaging methods using a radiopaque preparation are widely used, which most often leads to thyroid dysfunction. Early symptoms that may raise an occupational alert for thyrotoxicosis include palpitations or nervousness in patients. They may experience hunger, heat intolerance, and sweating. There may be an increase in the frequency of defecation (with or without diarrhea). A severe form of thyrotoxicosis or "thyroid storm" may be accompanied by fever, tachycardia, nausea, vomiting, diarrhea, and anxiety. Possible weight loss, first appeared atrial fibrillation, tremor, systolic hypertension. Ophthalmopathy often manifests itself, requiring consultation with an ophthalmologist. Treatment of thyrotoxicosis is more complex and should usually be carried out in conjunction with an endocrinologist [Janssen M., Charehbili A., Dijkgraaf E.M. et al., 2015]. Compensation for the symptoms of thyrotoxicosis is achieved by the appointment of thyreostatic

agents [Tomer Y., Blackard J.T., Akeno N., 2017]. Objectively, hyperthyroidism is characterized by an increased level of circulating thyroid hormones (T4 and T3) and a decrease in the level of thyroid-stimulating hormone (TSH) in the blood serum. Thyrotoxicosis can be an independent disease in a cancer patient. Much less often, an increased level of thyroxine, according to Y. Tomer et al. [14], can be provoked by drugs (intravenous radiopaque preparation, interferon alfa). Diagnostic testing includes laboratory testing of the levels of TSH, free thyroxine (T4) and triiodothyronine (T3), thyroid stimulating immunoglobulins (TSIs), which are markedly elevated in Graves' disease [Sherman S.I., 2013]. At the same time, there may be some difficulties associated with both the interpretation of the results of analyzes and thyroscintigraphy, and the treatment of thyroid diseases due to a possible exacerbation of Graves' disease caused by the appointment of a radiopaque drug and interferons. When visualizing the thyroid gland, a characteristic pattern of the distribution of radionuclides in the thyroid gland is observed: homogeneous absorption confirms Graves' disease, while single or multiple discrete foci of the radiopharmaceutical indicate nodular toxic goiter. Hot nodules are almost always benign, however, there are reports of cases of their content in the morphological study of thyroid cancer foci. It is important to diagnose hyperthyroidism after iodine contrast studies. In addition, thyrotoxicosis can be caused by drugs such as heroin, methadone, clofibrate, barbiturates, rifampicin, dothiepin. Among the side effects of chemotherapy on the thyroid gland, we highlight hypothyroidism, which is a common side effect for most new antitumor agents that affect the thyroid gland at the level of the so-called regulatory axis of the gland: hypothalamic-pituitary-thyroid. Typical symptoms of hypothyroidism: depression and apathy, drowsiness, weakness, fatigue, tearfulness, insomnia, memory impairment and concentration, poor cold tolerance, muscle weakness, arthralgia, parasthesia. Hypothyroidism is indicated by a low level of thyroid hormones in the blood serum. Patients have normal or low free T4, elevated TSH (except in cases of pituitary insufficiency), and low T3. In these patients, as well as in all patients with abnormal TSH, an assessment of free thyroxine and T3 is indicated. Total T4 and T3 levels are less reliable because some drugs, such as estrogen and estrogen-containing contraceptives, as well as tamoxifen citrate, methadone hydrochloride, fluorocyl, mitotane, androgens, anabolic steroids, nicotinic acid, and glucocorticoids. But, as before, the measurement of the total level of T3 is the most used test, since many laboratories cannot measure the free T3 [Gafiullina A.D., 2019].

O.P. Riksfjord et al recommend routine thyroid function testing in patients receiving anticancer agents [3]. The diagnosis of primary hypothyroidism is confirmed by elevated TSH and subnormal free T4 levels. However, in subclinical hypothyroidism, the free T4 concentration remains normal, while the TSH concentration rises (in contrast to subclinical hyperthyroidism, when TSH is below normal). Measuring total or free T3 is also useful for documenting possible hyperthyroidism, especially if free T4 is normal and thyroid-stimulating hormone is suppressed. The first diagnostic test for hypothyroidism is serum TSH. Elevated levels indicate that the patient has primary hypothyroidism, regardless of the cause or severity of the disease. Normal TSH levels in non-diseased individuals range from 0.4 to 4.0 mIU/L [21]. For patients with hypothyroidism, treatment usually begins with levothyroxine replacement therapy at an initial dose of 1.6 µg/kg. Subclinical hypothyroidism, in which patients have moderately elevated TSH levels and normal free T4 levels, can be observed in the absence of symptoms or comorbidities [11, 13, 14, 19-21]. The primary causes of hypothyroidism are most often: dysfunction of the thyroid gland due to autoimmune diseases, surgical removal of the thyroid gland, infiltration of

the gland tissue in amyloidosis, or rarely in cancer [1, 3]. For the purpose of differential diagnosis in primary hypothyroidism, antibodies to thyroxy peroxidase (TPO) can be used to distinguish an autoimmune disease from other diseases leading to hypothyroidism [Gafiullina A.D., 2019].

Some authors write that the development of thyroid dysfunction may be a marker of an increased likelihood of response to antitumor therapy. For example, overall survival and remission in patients with renal cell carcinoma who received sorafenib or sunitinib (tyrosine kinase inhibitors - TKIs) were better in those patients who developed hypothyroidism than in those who did not [3, 20, 21]. A similar pattern was found in autoimmune thyroid disease associated with increased tumor response to interleukin-2 therapy in the treatment of melanoma and kidney cancer [3, 20].

Anticancer drugs, which are widely used in the treatment of patients with malignant neoplasms, can have undesirable side effects on the thyroid gland and other endocrine glands, which, in turn, can affect the results of treatment and the quality of life of patients. Clinicians should be familiar with the undesirable effects of the drugs used on the endocrine glands, as well as their elimination. Difficult patients with hormonal disorders may be entitled to a multidisciplinary approach to solving the problem with the involvement of an experienced endocrinologist. There are no known strategies for the prevention of thyroid disease in patients receiving new anticancer drugs. An algorithm for the prevention and treatment of dysfunctions of the thyroid gland, as well as other endocrine glands, in cancer patients receiving antitumor drug therapy needs to be developed.

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