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ENDOCRINE TOXICITY OF IMMUNE CHECKPOINT INHIBITORS IN CLINICAL PRACTICE

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ABSTRACT

Relevance: *Immunological control points significantly changed cancer therapy worldwide after registering a new class of inhibitor drugs. Based on clinical studies, this type of treatment was associated with better survival in sensitive patients than cytostatic therapy. Checkpoint inhibitors exert their effect by regulating the immune response to malignant cells, blocking the usual inhibitory pathways of T-cell regulation. The receptors of cytotoxic T-lymphocytic antigen-4 (CTLA-4) and programmed cell death protein (PD-1) or its associated ligand (PD-L-1) are the target of inhibitors. CTLA-4 acts at an early stage of triggering an antigenic response, and PD-1 and PD-L-1 act by modulating interaction with peripheral tissue*

However, treatment with checkpoint inhibitors (ICTs) is accompanied by a wide range of immune mediated adverse events associated with the activation of the immune system. Despite the positive effect on survival, side effects with endocrine effects were noted in about 10% of patients.

The study aimed to *assess the incidence of immune mediated adverse events from the thyroid gland in clinical practice in patients with different localization of malignant tumors in the first and subsequent lines of therapy with checkpoint inhibitors.*

Methods: *The study utilized anamnestic, laboratory, and instrumental tests. Laboratory analysis included determining the blood levels of TSH, T3, T4, ACTH, and cortisol. Data analysis was carried out using the Microsoft Excel program.*

Results: *The frequency of development of immune mediated thyroiditis against the background of therapy with blockers of control points of the immune pathway in our observation was 29%. The debut of thyroid disorders was diagnosed in the first 12-16 weeks of therapy, beginning with hyperthyroidism against the background of thyroid destruction, followed by a transition to persistent hypothyroidism after 1-3 months.*

Conclusion: *When analyzing the safety profile of ICTs in patients in our study, immune mediated adverse reactions did not differ in frequency and spectrum from world practice. The spec-trum of toxicity did not depend on the localization of the tumor. Early diagnosis of thyroid lesions necessary for optimal and effective treatment can be carried out using laboratory tests. Knowing the timing of the development of adverse events during ICT therapy allows timely diagnosing and correcting complications from the thyroid to continue effective therapy.*

Keywords: *immune mediated endocrinopathy, immunotherapy, checkpoint inhibitors (ICTs).*

Introduction: The emergence of such highly effective drugs as checkpoint target blockers has increased the duration of the recurrence-free period but posed new challenges to oncologists and endocrinologists [1]. The thyroid gland is most frequently affected by tumor therapy with drugs that inhibit immune signal transduction checkpoints due to the peculiarities of the immune status of this organ [1, 2]. It has been confirmed that normal thyroid tissue expresses PD-L1 and PD-L2 proteins [3]. Immune checkpoint inhibitors (ICT) can increase the level of pre-existing antibodies [2] and, in addition, reduce immune tolerance even in normal thyroid tissue, leading to the development of thyroiditis [3, 4]. Endocrine tissue does not regenerate and has a very small volume, so immune destruction has great consequences for the secretion of major hormones [5]. The development of clinically significant immune mediated adverse reactions may require discontinuing antitumor therapy and prescription of immunosuppressants, so early diagnosis and timely therapy of complications serve as important criteria for successful antitumor therapy [6].

Registration of a new class of ICT inhibitor drugs has significantly changed the approach to cancer therapy worldwide. In clinical trials, the survival rate of patients susceptible to this type of treatment increased compared to cytostatic therapy.

ICTs regulate the immune response to malignant cells by blocking regular inhibitory pathways of T-cell regulation [7].

The PD-1 glycoprotein was first identified in 1992 by a group of Japanese researchers who subsequently recognized its key role in T-cell activity regulation.

PD-L1 (B7-H1) was identified in 2000 by two independent groups in lymphoid tissue, including T-cells, APCs, dendritic cells, macrophages/monocytes, and B cells. PD-L1 is also found in non-lymphoid cells such as vascular endothelial cells, thyroid cells, muscle cells, hepatocytes, placental cells, mesenchymal stem cells, and pancreatic islet cells [8]. The following year PD-L2 was identified [9].

However, ICT treatment is accompanied by a wide range of immune-mediated adverse events (imAE) associated with the activation of the immune system.

Endocrine-mediated side effects occur in approximately 10% of patients [5]. These include hypophysitis, thyroid dysfunction, insulin deficiency, diabetes mellitus, and primary adrenal insufficiency. Diabetes mellitus and primary adrenal insufficiency are rare endocrine pathologies associated with therapy with control point target blockers but can be fatal if not detected and treated in time [10]. Hypophysitis leading to central adrenal insufficiency is particularly associated with anti-CTLA-4 therapy, whereas thyroid dysfunction is often associated with anti-PD-1 therapy [11].

Yamauchi et al. study [2] analyzed five consecutive cases of thyroid dysfunction associated with Nivolumab therapy. All patients developed thyrotoxicosis within four weeks of the first Nivolumab administration and normalized within four weeks of initiation in three of five patients. Two patients discontinued therapy with Nivolumab because of concomitant adverse events.

Most endocrinopathies exhibit nonspecific symptoms, which creates a diagnostic challenge. The most common side effect of ICT is fatigue. Because of this, symptoms may be overlooked or attributed to other causes. Diagnosis is also complicated by the extensive use of corticosteroids, antiemetics (together with ICT), and episodes of severe disease secondary to immunosuppression, which complicates diagnostic testing [5].

Our study investigated the frequency of endocrinopathies when using ICT in patients with different localization of the malignant tumor and compared the incidence of thyroid imAE in real clinical practice with research data and medical statistics.

All data was obtained from the medical records of patients who received Pembrolizumab and Nivolumab at the Republican Clinical Oncology Dispensary named after Prof. M.Z. Sigal of the Ministry of Health of Tajikistan from May 2019 to May 2021. Data are current as of March 1, 2022.

The study aimed to assess the incidence of immune-mediated adverse events from the thyroid gland in clinical practice in patients with different localization of malignant tumors in the first and subsequent lines of therapy with checkpoint inhibitors.

Materials and Methods: The study utilized anamnestic, laboratory, and instrumental tests. Laboratory analysis included determining the blood levels of TSH, T3, T4, ACTH, and cortisol. Data analysis was carried out using the Microsoft Excel program.

Before treatment, all patients underwent a comprehensive examination, including collecting their complaints and anamnesis, objective examination, CT/MRI of the thorax and abdomen or whole-body PET-CT, ultrasound of the neck organs, and endocrine system functionality assessment by blood serum hormone indices. Other methods (ultrasound, scintigraphy, consultation with an Endocrinologist, etc.) were used when examining patients with thyroid dysfunction.

The therapy efficacy was evaluated every six courses of treatment or when clinical signs of progression appeared. The maximum number of immunotherapy courses was 35 injections. Response to treatment was assessed using iRECIST 1.1 criteria.

A total of 55 patients aged 24 to 79 were enrolled (the mean age was 55.9%); 13 (23.6%) were above 65. The men-women ratio was close to one – 25 and 30 (45.4% and 54.6%, respectively).

Distribution of patients by diagnosis was as follows: head and neck squamous cell cancer – 11, urothelial cancer – 7, clear cell renal adenocarcinoma – 2, squamous cell cervical cancer – 4, melanoma – 14, small cell lung cancer – 1, ovarian cancer (in the framework of the RCT) – 7, lung squamous cell cancer (in the framework of the RCT) – 9.

ICT therapy was administered in a mono regimen to 36 patients; the other 19 received ICT with chemotherapy (ChT) in the Etoposide + Cisplatin or Paclitaxel + Carboplatin regimens. ChT was administered in cycles, 4 to 6 courses, as per the clinical guidelines.

The median hospital stay was one day. The median follow-up of patients was 13.5 months (1 to 27 months of follow-up). The median follow-up period after imAE development was 90 days.

Results: Sixteen (29%) patients in the study developed immune-mediated endocrinopathies. Patients in the ICT + ChT group had thyroid disorders, and one developed immune-mediated hypophysitis. The results are reflected in Table 1.

Table 1 - Development of endocrinopathies against the background of systemic antitumor therapy in the study

imAE	Endocrine disorders in the ICT group (all) (n)	Endocrine disorders in the ICT+ ChT group (all) (n)	Endocrine disorders in the ICT group (3rd-4th de-gree) (n)	Endocrine dis-orders in the ICT+ ChT group (3-4 de-grees) (n)	Total
Hypothyroidism	7	6	0	0	13
Hyperthyroidism	2	0	0	0	2
Hypophysitis	0	1	0	1	1
Total	9	7	0	1	16

In two patients, a moderate degree of hyperthyroidism developed at 12 weeks of ICT therapy, which required medication correction. The clinical picture manifested as tachycardia, unstable hemodynamics, and required therapy with β-blockers.

Secondary adrenal insufficiency in one case was due to 3rd-degree hypophysitis with a pronounced clinical picture (hypotension, unstable hemodynamics, electrolyte disturbances) combined with 2nd-degree hypothyroidism. The patient required hospitalization.

Hypothyroidism was noted in most cases (81.2%).

Patients mainly complained of weakness and fatigue in the study (Table 2).

Table 2 - Complaints against the background of ICT therapy in the study

Symptoms and Signs	Men (n)	Women (n)
Headache	0	0
Fatigue or weakness	3	4
Vision impairment	0	0
Tachycardia	1	1
Total	4	5

In most patients, hypothyroidism was asymptomatic or had manifestations of a mild degree and did not require medical correction. A moderate degree of hypothyroidism developed in 2 patients with a clinical picture in the form of weakness and fatigue, and after consultation with an Endocrinologist, the patients were prescribed L-thyroxine replacement therapy.

When analyzing complications in patients treated at the Republican Clinical Oncology Dispensary named after Prof. M.Z. Sigal of the Ministry of Health of Tajikistan, the median time to development of imAE was approximately the same – 12 weeks (CI 95% 1-5), which corresponds to the literature data [4]. The results are reflected in Table 3.

Table 3 - Duration of immune-mediated endocrinopathies against the background of ICT therapy in comparison with literature data [4]

The drug	Number of patients (n)	Time to the beginning of the imAE (weeks)		Time until the end of the imAE (weeks)	
		literature data	own data	literature data	own data
Pembrolizumab	10	12-16	17	48	59
Nivolumab	6	12-16	12	38	28

The main difference was the time to resolve the phenomenon: a short and rapid course was noted with Nivolumab (average time – 38 vs. 48 weeks).

The average percentage of thyroid function abnormalities against anti-PD-1 monotherapy amounts to 10% [7] and does not affect the subsequent immunotherapy. No imAE registered in our patients required cancellation of anti-PD-1 therapy.

Takeaways:

1. The frequency of immune-mediated thyroiditis against the background of therapy with immune checkpoint blockers in our study was 29%.

2. The debut of thyroid disorders was diagnosed in the first 12-16 weeks of therapy, beginning with hyperthyroidism against the background of thyroid destruction, followed by a transition to persistent hypothyroidism in 1-3 months.

3. Analysis of the ICT safety profile demonstrated the expected spectrum of adverse reactions.

Discussion: Typically, hypothyroidism begins with a transient phase, which may be asymptomatic or manifested by nonspecific symptoms similar to those of the underlying disease – weakness, weight loss, tachycardia, changes in hair and nails [1, 12], followed by persistent subclinical or overt hypothyroidism. On this basis, a spectrum of complaints was defined for subsequent analysis.

When interpreting the laboratory results, one should consider the possibility of secondary thyroid lesions due to hypophysitis [1, 4, 5].

Hypophysitis occurred infrequently in the study – in 1.8% of cases, which correlates with the data of other authors: max frequency is from 1.2% to 0.9% [12]. A sensitive and specific indicator of hypophysitis is an enlargement of the pituitary gland on radiographs, which can precede the clinical diagnosis of hypophysitis by several weeks.

A multidisciplinary team of physicians is recommended to provide optimal treatment and maintain quality of life. An endocrinologist will be of value to this team.

Thyroid function should be monitored before and during systemic antitumor therapy.

Regular laboratory screening of thyroid function with tests is recommended at baseline, before each dose of immunotherapy, every 6-12 weeks for the first six months after completion of treatment. Expansion of the examination scope is required if abnormalities or an increase in symptoms are detected.

Treatment of endocrine disorders is independent of the immune inhibitor that causes these events.

Conclusion: When analyzing the safety profile of ICT in patients in our study, immune-mediated adverse reactions did not differ in frequency and spectrum from world practice. The spectrum of toxicity did not depend on the localization of the tumor. Early diagnosis of thyroid lesions necessary for optimal and effective treatment can be carried out using laboratory tests.

Knowing the timing of the development of adverse events during ICT therapy allows timely diagnosing and correcting complications from the thyroid to continue effective therapy.

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АҢДАТПА

КЛИНИКАЛЫҚ ТӘЖІРИБЕДЕ ИММУНДЫҚ БАҚЫЛАУ НҮКТЕСІ ИНГИБИТОРЛАРЫНЫҢ ЭНДОКРИНДІК УЫТТЫЛЫҒЫ

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Өзектілігі: *ингибиторлық препараттардың жаңа класын тіркеуге байланысты иммунологиялық бақылау нүктелері бүкіл әлемде қатерлі ісік терапиясы айтарлықтай өзгерді. Клиникалық зерттеулерге сүйене отырып, емдеудің осы түріне сезімтал науқастарда цитостатикалық терапиямен салыстырғанда өмір сүрудің жоғарылауы дәлелденді. Бақылау нүктесінің ингибиторлары өздерінің әсерін қатерлі жасушаларға иммундық реакцияны реттеу, Т-жасушаларын реттеудің әдеттегі тежеу жолдарын блоктау арқылы көрсетеді. Цитотоксикалық т-лимфоцитарлық антиген-4 (CTLA-4) және бағдарламаланған жасуша өлімі ақуызының (PD-1) немесе онымен байланысты лигандтың (PD-L-1) рецепторлары ингибиторлардың нысаны болып табылады. CTLA-4 антигендік реакцияны бастаудың ерте сатысында әрекет етеді, ал PD-1 және PD-L-1 перифериялық тінмен өзара әрекеттесуді модуляциялау арқылы әрекет етеді.*

Алайда, бақылау нүктесінің ингибиторларымен (акт) емдеу иммундық жүйенің белсендірілуіне байланысты иммундық жанама жағымсыз құбылыстардың (ион) кең спектрімен бірге жүреді. Өмір сүруге оң әсер еткеніне қарамастан, пациенттердің шамамен 10% -. эндокриндік әсерлері бар жаңама әсерлер байқалды.

Зерттеудің мақсаты *– Бақылау нүктесінің ингибиторларымен емдеудің бірінші және кейінгі желілерінде қатерлі ісіктердің әртүрлі локализациясы бар емделушілерде клиникалық тәжірибе жағдайында қалқанша безінің иммундық-делдалдық жағымсыз құбылыстарының даму жиілігін бағалау.*

Әдістер: *Жұмыс анамнездік, зертханалық және аспаптық зерттеу әдістерін қолдану арқылы орындалды. Зертханалық талдау қандағы TSH, T3, T4, ACTH, кортизол деңгейін анықтауды қамтиды. Мәліметтерді талдау Microsoft Excel бағдарламасы арқылы жүргізілді.*

Нәтижелер: *иммундық жолдың бақылау нүктелерін блокаторлармен емдеу аясында иммундық тиреоидиттің даму жиілігі біздің бақылауымызда 29% құрады. Қалқанша безінің бұзылуының дебюті терапияның алғашқы 12-16 аптасында диагноз қойылды, қалқанша безінің бұзылуы аясында гипертиреоздан басталды, содан кейін 1-3 айдан кейін тұрақты гипотиреозға көшті.*

Қорытынды: *Біздің зерттеуімізде пациенттердегі АКТ қауіпсіздік профилін талдау кезінде иммундық әсер ететін жағымсыз реакциялар жиілігі мен спектрі бойынша әлемдік тәжірибеден ерекшеленбеді. Уыттылық спектрі ісіктің локализациясына байланысты емес. Оңтайлы және тиімді емдеу үшін қалқанша безінің зақымдануын ерте диагностикалау қажет, оны зертханалық зерттеулер арқылы жүзеге асыруға болады. АКТ терапиясы кезінде қолайсыз құбылыстардың даму уақытын білу қалқанша безінің терапиясынан болатын асқынуларды уақтылы диагностикалауға және түзетуге мүмкіндік береді және тиімді терапияны жалғастыруға мүмкіндік береді.*

Түйін сөздер: *иммундық эндокринопатия, иммунотерапия, бақылау нүктесінің ингибиторлары (акт).*

АННОТАЦИЯ

ЭНДОКРИННАЯ ТОКСИЧНОСТЬ ИНГИБИТОРОВ ИММУННЫХ КОНТРОЛЬНЫХ ТОЧЕК В КЛИНИЧЕСКОЙ ПРАКТИКЕ

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Актуальность: *В связи с регистрацией нового класса препаратов-ингибиторов иммунных контрольных точек (ИКТ) существенно изменилась терапия рака во всем мире. На основе клинических исследований было доказано увеличение выживаемости по сравнению с цитостатической терапией у пациентов, чувствительных к этому виду лечения. Ингибиторы контрольных точек проявляют свой*

эффект, регулируя иммунный ответ на злокачественные клетки, блокируя обычные тормозные пути регуляции Т-клеток. Рецепторы цитотоксического Т-лимфоцитарного антигена-4 (CTLA-4) и белка запрограммированной гибели клеток (PD-1) или связанного с ним лиганда (PD-L-1) являются мишенью ингибиторов. CTLA-4 действует на ранней стадии запуска антигенного ответа, а PD-1 и PD-L-1 действуют, модулируя взаимодействие с периферической тканью

Однако применение ИКТ сопровождается широким спектром иммуно-опосредованных нежелательных явлений, связанных с активацией иммунной системы. Несмотря на положительное влияние на выживаемость, были отмечены побочные эффекты с эндокринными эффектами примерно у 10% пациентов.

***Цель исследования** – оценить частоту развития иммунноопосредованных нежелательных явлений со стороны щитовидной железы в условиях клинической практики у пациентов с со злокачественными опухолями различной локализации в первой и последующих линиях терапии ИКТ.*

***Методы:** Работа выполнена с использованием анамнестических, лабораторных и инструментальных методов исследования. Лабораторный анализ включал определение уровней ТТГ, Т3,Т4, АКТГ и кортизола в крови. Анализ данных проводился с помощью программы Microsoft Excel.*

***Результаты:** Частота развития иммуноопосредованного тиреоидита на фоне терапии ИКТ в нашем наблюдении составила 29%. Дебют нарушений щитовидной железы диагностировался в первые 12-16 недель терапии, начинался с гипертиреоза на фоне деструкции щитовидной железы с последующим переходом в стойкий гипотиреоз через 1-3 мес.*

***Заключение:** При анализе профиля безопасности ИКТ у пациентов в нашем исследовании иммуноопосредованные нежелательные реакции не отличались по частоте и спектру от мировой практики. Спектр токсичности не зависел от локализации опухоли.*

Для оптимального и эффективного лечения необходима ранняя диагностика поражений щитовидной железы, которую возможно проводить методом лабораторного анализа.

Знание сроков развития нежелательных явлений во время терапии ИКТ позволяет своевременно диагностировать и корректировать осложнения со стороны щитовидной железы и продолжать эффективную терапию.

***Ключевые слова:** иммуноопосредованная эндокринопатия, иммунотерапия, ингибиторы контрольных точек (ИКТ).*

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