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REVIEW

IMMUNOTHERAPY FOR EPITHELIAL TUMORS OF THE THYMUS

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ABSTRACT

Thymomas and carcinomas of the thymus gland, also known as epithelial tumors of the thymus (TT) are rare malignant neoplasms, but are the most common solid tumors of the anterior mediastinum. The incidence does not exceed 1.3–1.7 per million inhabitants per year. In Europe, about 1,500 new cases are registered annually, and the average age of patients is around 40–50 years.

Originating from the epithelial component of the thymus, the primary lymphoid organ, they are accompanied by a high risk of developing autoimmune disorders due to their unique biology. Indeed, up to 30 % of TETS patients suffer from autoimmune disorders (AID), the most common of which is myasthenia gravis (MG). AID are detected not only during the diagnosis of a tumor, but also during follow-up. With rare exceptions, there are no specific targets for targeted therapy in TETS. Immune checkpoint inhibitors (ICIs) halt the ability of tumor cells to evade immune surveillance, enhancing their killing. Unprecedented achievements of immunotherapy (IT) in the treatment of metastatic non-small cell lung cancer (NSCLC) and melanoma have made it reasonable to study the effectiveness of prescribing ICI in patients with TETs. The prevalence of AIR in different morphological subtypes of TETs may influence the decision to conduct IT due to the increased risk of toxicity. The review summarizes current data on the effectiveness of IT in thymoma and thymus cancer (TC) and discusses several unresolved problems associated with the use of ICI in TETs.

The purpose of this review is to present up-to-date data on the issue under discussion and possible prognostic biomarkers for IT, and to highlight the problems associated with autoimmune disorders (AID).

In our opinion, a deep understanding of the molecular genetic and immune landscape of thymus epithelial tumors and the interaction of ICI with the immune system is the key to improving the effectiveness and preventing the side effects of autoimmune IT. A comprehensive solution to existing problems will undoubtedly open up new possibilities for the drug treatment of this rare and difficult disease.

Keywords: thymus epithelial tumors (TETs), thymoma, thymic carcinomas (TC), immune checkpoint inhibitors (ICIs), autoimmune disorders (AID), immunotherapy (IT) toxicity

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ИММУНОТЕРАПИЯ ЭПИТЕЛИАЛЬНЫХ ОПУХОЛЕЙ ВИЛОЧКОВОЙ ЖЕЛЕЗЫ

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РЕЗЮМЕ

Тимомы и карциномы вилочковой железы, также известные как эпителиальные опухоли тимуса (ОТ), являются редкими злокачественными новообразованиями, но также наиболее частыми солидными опухолями переднего средостения. Заболеваемость не превышает 1,3–1,7 на миллион жителей в год. В Европе ежегодно регистрируется около 1500 новых случаев, а средний возраст заболевших составляет от 40 до 50 лет.

Происходя из эпителиального компонента тимуса – первичного лимфоидного органа, они из-за своей уникальной биологии сопровождаются высоким риском развития аутоиммунных расстройств. Действительно, до 30 % больных ОТ страдают аутоиммунными расстройствами (АИР), наиболее частым из которых является миастения гравис (МГ). АИР выявляются не только при диагностике опухоли, но и во время последующего наблюдения. За редким исключением в ОТ отсутствуют специфические мишени для таргетной терапии. Ингибиторы иммунных контрольных точек (ИИКТ) подавляют способность опухолевых клеток уклоняться от иммунного надзора, усиливая их киллинг. Беспрецедентные достижения иммунотерапии (ИТ) в лечении метастатического немелкоклеточного рака легкого (НМРЛ) и меланомы сделали обоснованным изучение эффективности назначения ИИКТ пациентам с ОТ. Распространенность АИР при разных морфологических подтипах ОТ может повлиять на решение о проведении ИТ из-за повышенного риска токсичности. В обзоре обобщены современные данные об эффективности ИТ при тимоме и раке тимуса (РТ) и обсуждаются несколько нерешенных проблем, связанных с использованием ИИКТ при ОТ.

Цель данного обзора – представить современные данные по обсуждаемому вопросу и возможные прогностические биомаркеры для ИТ и осветить проблемы, связанные с аутоиммунными расстройствами (АИР).

По нашему мнению, глубокое понимание молекулярно-генетического и иммунного ландшафта эпителиальных опухолей вилочковой железы и взаимодействия ИИКТ с иммунной системой является ключом к повышению эффективности и предотвращению побочного аутоиммунного действия ИТ. Всестороннее решение существующих проблем, несомненно, позволит открыть новые возможности лекарственного лечения этого редкого и трудного заболевания.

Ключевые слова: эпителиальные опухоли тимуса (ОТ), тимомы, рак тимуса (РТ), ингибиторы иммунных контрольных точек (ИИКТ), аутоиммунные расстройства (АИР), токсичность иммунотерапии (ИТ)

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INTRODUCTION

Epithelial tumors of the thymus (TETs) are rare and potentially aggressive malignant neoplasms of the anterior mediastinum. The incidence does not exceed 1.3–1.7 per million inhabitants per year; in Europe, about 1,500 new cases are registered annually, and the average age of patients is from 40 to 50 years [1]. Based on the morphological structure, namely the proportion of two components of the thymus gland – immature lymphocytes and epithelial cells – the WHO classification distinguishes two types of epithelial tumors: thymoma and thymus cancer and six main morphological subtypes: thymomas A, AB, B1, B2, B3 and TC [2]. The epithelial component is the only one in which a malignant tumor develops. At the consensus meeting of the ITMIG (International Thymic Malignancy Interest Group) in 2011, the WHO classification was approved as a standard for clinical practice [3]. Less common than thymoma, thymus cancer accounts for about 10–15 % of and is largely associated with the development of distant metastases and poor prognosis. TCis most often represented by squamous cell carcinoma. Tumor cells of thymus carcinomas express cluster determinants CD5+ and CD117/KIT+, determined by immunohistochemical examination (IHCE) and have specific molecular features that distinguish them from thymoma and squamous cell lung cancer [4].

The clinical course of TETs is determined by the nature of the growth of the neoplasm. Encapsulated tumors corresponding to stage I according to the Masaoka-Koga (M-K) surgical classification account for 65 %, while invasive tumors of stage II-IV account for 35 % of cases [5; 6]. Surgical intervention is a key stage of treatment for TETs stage I, II and even III, since radical removal of the tumor, along with stage [5; 6] and morphological structure [3], is the most important independent prognostic factor in terms of survival [6-8]. Tumor recurrence, depending on the stage of the disease, should be expected in 8–33 % of patients with thymoma and in 25–59 % of patients with TC [9]. Regimens of combined chemotherapy (CT) based on platinum preparations remain the standard method of treatment of inoperable, refractory and metastatic forms of the disease. The possibilities of modern CT are known to be limited, while the response rate ranges from 69 % for thymoma to 42 % for TC [9; 10]. In addition, some effectiveness of targeted drugs from the group of tyrosine kinase inhibitors, such as sunitinib [11] and everolimus [12], has been demonstrated. Less often, the c-KIT and PI3KCA genes, as well as epigenetic signaling pathways, are used as targets [13]. The expected 5-year overall survival(s) for thymoma is 80 %, and for TC – 40 % [14].

ICIs have changed the paradigm of cancer treatment, becoming the standard treatment for melanoma, NSCLC and bladder cancer [15]. The role of immunotherapy (IT) in the treatment of TETs has not been definitively studied, primarily due to the high frequency of autoimmune conditions leading to a high risk of toxicity.

The purpose of this review is to present up-to-date data on the issue under discussion and possible prognostic biomarkers for IT, and to highlight the problems associated with autoimmune disorders (AID).

Thymus physiology and oncogenesis

The thymus gland is the central organ of the immune system that ensures the development of immune tolerance. After formation in the bone marrow, immature thymocytes mature in the thymus as a result of interaction between cortical and medullary epithelial cells of the thymus gland. The presentation of tissue-specific autoantigens through the main histocompatibility complex of class II (MHC-II) is regulated by two transcription factors: the AIRE genes (autoimmune regulator) and Fez (Fez family zinc finger 2) [16]. The passage of T-thymocytes through the thymus cortex and corticomedullary junction implies phenotypic modifications affecting the functioning of T-lymphocytes. Immature T-lymphocytes reacting with MHC-II are able to penetrate into the thymus medulla, while non-interacting T-cells are eliminated. Both dendritic cells and medullary epithelial cells are found in the medulla of the thymus gland. Medullary epithelial cells expressing AIRE undergo various changes and undergo apoptosis, releasing tissue-specific autoantigens for thymus dendritic cells. T-lymphocytes reacting against tissue-specific autoantigens undergo apoptosis, providing immune tolerance [16]. This process occurs mainly in childhood, but is sometimes present in adults and probably goes further into the process of carcinogenesis [4].

Autoimmune disorders and TETs

Autoimmune disorders (AID) need to be differentiated from paraneoplastic syndromes. Their patho-

physiology, clinical course and impact on survival are different. Paraneoplastic syndromes, as a rule, arise as a result of the production of hormones, cytokines or peptides by tumor cells, which leads to metabolic disorders and the induction of autoantibodies produced by tumor cells. Thus, the successful treatment of the tumor should eliminate the clinical manifestations of paraneoplastic syndromes, regardless of whether airs can stop due to a violation of the regulation of the function of the thymus gland and imperfect selection of immature T-lymphocytes.

AIDs are present in more than 30 % of observations from [16]. The most common syndrome is myasthenia gravis (MG), the frequency of which ranges from 17 % in thymoma A to 71 % in thymoma B2 [7]. In addition, endocrine, rheumatological, gastrointestinal, renal, and skin lesions are recorded [17]. The data from RYTHMIC (Réseau tumeurs THYMiques et Cancer), one of the largest TET registries in Europe, demonstrate a 20.2 % prevalence of AIR with more than one disorder in 3.8 % of patients. The majority of patients had MG – 69.6 %, followed by: Hood syndrome – 5.6 %, systemic lupus erythematosus – 4.4 %, thyroiditis – 3.4 % and pure erythrocyte aplasia – 2.8 %. As for the morphological subtypes, the prevalence of AID more than 40 % was established with thymoma B2-45 % and B3-41 % [18]. Thymomas AB, B1 and B2 are rich in lymphocyte agglomerates, which explains their more frequent relationship with AIR compared to thymoma B3 and RT. Nevertheless, several studies have described a high prevalence of autoimmune conditions in thymoma B3 [7; 18]. It is important to note that TC is rarely associated with AID [19]; the absence of MG in thymus carcinoma has been reported [20], possibly due to the presence of immature T cells. The high prevalence of air in TETs and the appearance of autoimmune symptoms after diagnosis [18] requires extremely careful monitoring of the condition of patients during IT.

Molecular features of TETs and AID

The unique biology of thymus tumors gives special interest to the study of autoimmune processes due to the strong association with AID, especially with MG. In fact, knowledge about the molecular characteristics of MG associated with thymoma is limited. It is well known that antibodies against the acetylcholine receptor (AchR) are mandatory for the development of MG, anti-AchR are able to block the postsynaptic membrane, as well as reduce the amount of AchR in the neuromuscular junction, which leads to a decrease in the reaction to acetycholine, clinically manifested by paroxysmal weakness and fatigue of skeletal muscles [21]. Immunoregulation disorders and tolerance caused by the tumor microenvironment, probable mechanisms of the pathogenesis of tumor-related AID, primarily MG.

Several studies have investigated whether various acetylcholine subunits are expressed in the thymus and whether some of them are associated with the development of MG associated with thymoma. Low levels of expression of AIRE (autoimmune regulator) and AID by tumor cells correlate with a higher risk of MG [22]. Moreover, the relative levels of Foxp3 (forkhead box P3) RNA expression were significantly higher in the tumor tissue samples of patients without AID compared with patients suffering from MG and/or other AID. It should be noted that AIRE and Foxp3 are transcription factors that play an important role in the differentiation of T-reg lymphocytes, which play an important role in suppressing immunity, contributing to tumor growth [23]. Interestingly, AIRE may be associated with specific genomic changes, for example, an imbalance of the NF-kappaB/AIRE signaling pathway observed in MG associated with thymoma [23].

One of the largest molecular studies of TETs was conducted within the framework of TCGA (The Cancer Genome Atlas). The analysis of 117 TETs revealed a higher frequency of aneuploidy in the thymomas of patients with MG [13]. In addition, the expression levels of the α-subunit of AchR (CHRNA1 – neuronal acetylcholine receptor subunit alpha-1) were higher in tim samples of patients suffering from MG. A medium-sized neurofilament (NEFM – neurofilament medium chain) is a protein with similar immunogenic properties to CHRNA1 and titin, mainly overexpressed in the tim A and AB subgroups, accompanied by MG. As for TC, despite their more aggressive biological behavior, several tumor suppressor genes were found in them: CYLD, CBFB, CDH1, CDH11, CTCF and ZFHX3, as well as a higher mutational load of the tumor (TMB) compared to thymomas [13]. The presented results confirm the conclusions that TC and thymoma differ in their genetic and epigenetic profiles. Indeed, the results of a grandiose transcriptomic analysis of 2,560 genes in 194 samples TETs the recent one revealed two different clusters of genes that distinguish TC from thymoma [24].

In a Chinese study of 105 patients suffering from MG, an increase in inflammatory responses was found, in contrast to patients without AIR. It should be noted that in the latter, a mutation of the GTF2I gene was detected significantly more often [25]. In fact, the presence of the GTF2I mutation correlates with better survival rates and, perhaps, its carriers can become candidates for IT. The GTF2I mutation was detected in 82 % of tim A and 74 % of tim AB, but rarely in aggressive subtypes, especially in RT, in which repeated mutations of known malignant tumor genes were detected, including TP53, CYLD, CDKN2A, BAP1 and PBRM1 [13]. At the same time, the expression of the GTF2I gene, which is very important, is associated with severe toxicity in IT, so there is an obvious need for further study of GTF2I as a biomarker [26].

Finally, to differentiate thymoma from thymus cancer and to understand the pathogenesis of MG, several other biomarkers have been studied: IGFBP1, KLF15, PDK4 and HIF3A. Other AIRS, such as encephalitis or polymyositis, correlate with an increase in anti-Hu antibodies, Ma2 antibodies and CRP5 antibodies or a violation of the regulation of the T-cell receptor (TCR) and an increase in the expression of MHC-I in muscle fibers, but the landscape of AID and MG is still unknown [27].

The strategy of TETs immunotherapy

In recent years, ICIs have revolutionized the treatment strategy and prognosis of several solid tumors. In previously treated patients, the appointment of ICIs gave a 5-year overall survival rate of 34 % in advanced melanoma, 28 % in renal cell carcinoma and 16 % in NSCLC [15], which led to the approval of anti-PD1 inhibitors (anti-Programmed cell Death protein 1), anti-PDL1 inhibitors (anti-Programmed Death Ligand 1) and anti-CTLA4 inhibitors (anti-Cytotoxic T Lymphocyte Antigen 4) for the treatment of metastatic forms of the disease. Given the prolonged effect of ICIs in many solid tumors, high hopes are pinned on IT of epithelial tumors of the thymus gland [4].

Immune-related predictive biomarkers

Several biomarkers have been tested as predictors of IT effectiveness, however, only two have been approved as biomarkers of response to the appointment of ICIs: I) PD-L1 expression in tumor cells and II) tumor mutation load (TMB), which is determined by the number of non-synonymous single-nucleotide variants in the coding region of the tumor genome. Tumors with high TMB contain more neoantigens that enhance the immune response, which leads to an increase in the effectiveness of IT, as shown in previous studies. In addition, activation of the immune system requires a high content of tumor-infiltrating lymphocytes (TILs) to achieve a better response to treatment [28].

PD-L1 expression is observed in more than 90 % of epithelial cells of the normal thymus gland and has been extensively studied in TET due to the aggressiveness of their biological behavior. On the material from 100 tim and 69 TC, high expression of PD-L1 and FOXP3+T reg was associated with a higher degree of malignancy of neoplasms. In other studies, PD-L1 expression in thymoma varied from 23 % to 92 % of tumor cells, and in TC – from 36 % to 100 % of tumor cells. Indeed, a number of clinical and pathological features, namely: young age, the common stage of the disease according to the M-K classification, the impossibility of radical removal and neoadjuvant therapy of thymoma, correlated with high expression of PD-L1. On the contrary, the correlation with morphological subtypes remains unclear. Reliable data on survival rates have not yet been presented, given that in some studies high PD-L1 expression correlated with better survival, and in others with poor outcomes. In addition to PD-L1 expression, the severity of TILs tumor tissue infiltration was studied, although on limited material. R. Higuchi and colleagues studied the expression of PD-L1 and the severity of TILs in surgical preparations in 39 patients with thymomas and RT. PD-L1 expression above 1 % was registered in 54 % of samples with different distribution among TETs subtypes: B2> B3> PT> B1> AB> A. A high infiltration (84 %) of CD8+ among CD3+ TILs was determined, which was evenly distributed among all cases. High PD-1 expression in TILs was found in 23–62 % of PTCS, without any predictive or prognostic significance [29-31].

Interestingly, TMB in TETs is one of the lowest among malignant tumors. The question of whether PD-L1 is the best predictive biomarker remains controversial due to the deterioration of the condition of many patients, despite IT. A more favorable therapeutic effect is better with aggressive thymomas of B2 or B3 subtypes, although the high prevalence of AID makes it difficult to use ICIs.

IT effectiveness in clinical trials

ICIs have been studied in several clinical studies on TETs. In one phase II group study, 40 patients with recurrent TC were treated with pembrolizumab, a humanized antibody IgG4 targeted at the PD-1 receptor. Patients with a history of air were not included in the study. The overall response rate (ORR) was observed in 22.5 % of cases. Disease control was achieved in 30 (75 %) patients with a median response time of 3 years. The median progression-free survival (PFS – progression free survival) was 4.2 months, and the median overall survival(s) was 24.9 months. One-year PFS and OS reached 29 % and 71 %, respectively, and 5-year OS was 8 %. High, at least 50 %, PD-L1 expression in tumor cells was observed in 10 (25 %) patients, which was associated with longer survival: median PFS 24 vs. 2.9 months; median S was not reached compared to 15.5 months. When PD-L1 was expressed by tumor cells less than 50 %, only 3 out of 27 patients with a response was achieved. The IFN-γ signature evaluated by Nanostring analysis correlated with the response to pembrolizumab therapy, on the contrary, the TP53 mutation registered in 36 % of tumors was associated with lower PD-L1 expression and shorter s. Interestingly, after a relapse of the disease, 4 patients, one of them 2 years after the completion of therapy with pembrolizumab, pembrolizumab was prescribed repeatedly with 2 responses to treatment [32].

J. Cho and colleagues conducted a second clinical trial with a similar design, examining the efficacy of pembrolizumab in 26 patients with recurrent TC and in 7 patients with recurrent thymoma: subtype B1-4, subtype B2/B3-1 and subtype B3-1). Three patients had a history of MG. ORR was 19.2 % in patients with TC and 28.6 % in patients with thymoma. Similarly, out of 26 patients with RT, 5 (19 %) achieved a partial response, and 14 (54 %) stabilized the disease. Tumors with high PD-L1 expression responded better to treatment. The median duration of response in patients with thymoma was not reached, in patients with TC was 9.7 months. Median PFS was 6.1 months in both groups. The median OS was 14.5 months for TC sufferers and was not achieved in patients with thymoma (Table 1) [33].

Avelumab is a human antibody IgG1 against PD-L1 was studied in 7 patients with thymoma and 1 MRI without a history of autoimmune conditions. The following morphological subtypes were registered among patients with thymoma: B3-2, B2/B3-1, B2-2 and B1-1. An objective response was obtained in four (57 %) of 7 patients with thymoma, including a confirmed partial response in 2 (29 %) patients. It should be noted that a significant decrease in tumor size was observed after one dose of avelumab in three patients [34].

Finally, a Japanese phase II study evaluated the role of nivolumab in the treatment of patients with inoperable or recurrent thymus carcinomas. Of these, 11 patients registered stabilization of the disease, including five patients for 24 or more weeks. Median PFS and median S were 3.8 months and 14.1 months, respectively. Further inclusion of patients in the study was terminated prematurely at the first stage due to the fact that none of them achieved an objective response [35].

Enhanced autoimmune toxicity

Activation of immunity increases the risk of developing undesirable side effects associated with IT

Table 1. Clinical studies on the subject of thymus epithelial tumors immunotherapy

Author/ year	*Phase/N*	Therapeutic agent	RR/DCR (%)	Median PFS (mon.)	Median of OS (mon.)	irAEs ≥ 3 st. (%)
Giaccone et al. (33)	II/ 40 TC	Pembrolizumab	23/76 %	4.2	24.9	15 %
Cho et al. (34)	II/ 40 TC и 7T	Pembrolizumab	19/73 % 29/100 %	6.1	14.5 Not achieved	15.4 % 71.4 %
Katsuya et al. (36)	II/ 13 TC	Nivolumab	0/38 %	3.8	11.3	13 %
Heery et al. (35)	I/7 T 1 PT	Avelumab	5 %	50	-	63 %

Notes: N – number of patients; TC – thymus cancer; T – thymoma; RR/DCR – objective response; PFS – progression-free survival; OS – overall survival; irAEs – adverse events associated with immunotherapy.

(irAE – immune-related adverse events). The frequency of treatment-related adverse events in the studies under consideration is relatively high compared to the results of IT of other malignant neoplasms, such as melanoma, NSCLC, squamous cell carcinoma of the head and neck and urothelial carcinoma, where the frequency of irAE of 3 or more severity ranges from 3 % to 9.7 % [36].

Among 40 patients in the study of G. Giaccone et al., who received pembrolizumab, 6 (15 %) developed serious AIDs, and 4 (10 %) had more than one condition: polymyositis and myocarditis in two cases; pancreatitis, hepatitis and diabetes mellitus in one case; bullous pemphigoid in one case (autoimmune exfoliation of the epidermis); in one case, polymyositis and hepatitis; and, finally, one case of a significant increase in the level of hepatic transaminases. Three patients had to stop treatment due to severe toxicity. Patients suffering from myocarditis and polymyositis, as well as bullous pemphigoid, needed the appointment of corticosteroid hormones for the relief of conditions [33]. It should be noted that one patient with developed myositis, myocarditis and initial MG had a complete response for 40 months [32].

In another study, 5 (71 %) of 7 patients with thymomas and 4 (15 %) of 26 patients with TC had irAE of 3 or more severity, including hepatitis – 12.1 %, myocarditis – 9.1 % and MG – 6.1 %, which 1 patient had initially; in addition, thyroiditis was recorded, antineutrophil cytoplasmic antibodies associated with rapidly progressive glomerulonephritis, colitis and myoclonus. Treatment was discontinued by 8 (24.2 %) patients. Therapy of undesirable toxic reactions, as a rule, was based on the appointment of corticosteroid hormones and immunoglobulins [33].

Among patients treated with nivolumab, serious airs were observed in two cases: an increase in the level of transaminases and adrenal insufficiency [35]. Among patients treated with avelumab, undesirable side effects associated with IT of all degrees were noted in 5 (63 %) patients [34].

Of particular concern is the frequency of myocarditis, since myocarditis accompanies TETs in less than 1 % of cases [32]. Myocarditis is observed in 5 % of TC patients and in 43–57 % of patients with thymoma included in clinical trials of ICI therapy [26; 34; 35]. This fact has been confirmed in several ongoing studies of IT of epithelial tumors of the thymus gland [36].

Myositis was observed in 8 % of patients with TC treated with pembrolizumab, and more than half of patients with thymoma included in the study to increase the dose of avelumab [26]. Muscle toxicity is explained by the existence of TCR clones and increased expression of MHC-I in muscle fibers with inflammatory infiltrates of macrophages and lymphocytes after treatment with ICIs. It should be noted that in patients who developed myositis, no specific antibodies were detected before and after ICI therapy [37].

MG often concomitant TETa as undesirable side effects associated with IT was noted in 3–14 % of TET patients treated with pembrolizumab [26; 33]. As explained above, the development of MG requires antibodies against AhR, as well as antibodies to MuSK and Lrp4 [37]. Interestingly, pure aplasia of erythrocytes, described as the most common AIR after MG in studies on IT of epithelial tumors of the thymus gland, was not recorded.

Ongoing clinical trials

With thymoma of the B1/B2 subtype, IT is not prescribed due to the high prevalence of AIR [4] and should not be carried out without a comprehensive discussion of the risks at a multidisciplinary oncological consultation. Currently, several clinical studies are being conducted on the effectiveness of the use of ICI both in monotherapy and in combination. In Europe, EORTC (European Organization for Research and Treatment of Cancer) and the European Platform for Thoracic Oncology have launched a phase II study of NIVOTHYM to study the effectiveness of nivolumab or its combination with ipilimumab in patients with progressive, refractory thymoma B3 subtype or TC with planned strict registration of AIR (NCT03134118). MD Anderson Cancer Center is conducting a Phase I/II study using pembrolizumab for TC and thymomas (NCT03295227). The National Cancer Institute (NCI) has developed a phase II protocol to evaluate the efficacy and toxicity of IT avelumab in thymoma and TC, (NCT03076554) (Table 2).

The preliminary results of the CAVEATT protocol, a study on the combined administration of avelumab with axitinib, have recently been published, showing a partial response and stabilization of the disease in 40 % and 60 %, respectively, with a median PFS of 7.9 months and an acceptable toxicity profile [38]. In addition, combinations of ICI with tyrosine kinase inhibitors sunitinib or lenvatinib, or with an indoleamine 2,3-dioxygenase-1 inhibitor (IDO – indoleamina 2,3-di-

oxigenasa-1) epacadostatot are being studied due to the importance of these signaling pathways in TET. It should be noted that in patients receiving a combination of pembrolizumab and epacadoscate before discontinuation of the study, no unexpected results obtained in melanoma were recorded [32]. A new studied combination in TET therapy is the bispecific single-domain Fc-fused antibody (PD-L1/CTLA4) KN046 (NCT04469725). Finally, data on the advantages of neoadjuvant and adjuvant approaches to IT of solid tumors formed the basis of studies to assess their effectiveness in the treatment of OT, for example, in relation to pembrolizumab (NCT03858582) (Table 2).

Existing IT pitfalls

Since patients with TET have an increased risk of developing treatment-related adverse events, this is an important aspect that should be taken into account when selecting candidates for IT. Some approaches are needed to reduce the risk of irAEs and increase the IT safety of epithelial tumors of the thymus gland.

Depending on the histological characteristics for each morphological subtype, the probability of developing AIR is different. The degree of infiltration by lymphocytes of the tumor differs from B1 – rich in lymphocytes to B3 – poor in lymphocytes. In addition, different molecular profiles are associated with each morphological subtype [13]. It is known that previously detected autoantibodies against AhR and B-cell lymphopenia studied in thymoma correlate with a higher risk of myositis when avelumab is prescribed [39]. In addition, overexpression of CHRNA1 and RYR3 (Ryanodine receptor type 3) is present in thymomas with a MG clinic [13], which is associated with the ability of tumor cells to secrete functional proteins that mimic non-tumor cells [37]. A distinctive feature of such tumors is their association with autoimmunity, carried out through overexpression of

Table 2. Ongoing clinical studies of immunotherapy of thymus epithelial tumors

NCT/ phase	Title, patients number (*N*)	Therapeutic agent	Tumor type	Final study checkpoints
NCT03076554/II	NCI, *N* = 55	Avelumab	TC, thymoma	Safety, response intensity
NCT03134118/II	NIVOTHYM, *N* = 50\50	Nivolumab/ nivolumab + iplimumab	TC, thymoma B3	PFS
NCT03295227/I–II	MD Anderson Cancer Center, *N* = 30	Pembrolizumab	TC, thymoma	Dose limiting toxicity
NCT04321330/ II	ML41253, *N* = 34	Atezolizumab	TC	Response intensity
NCT04417660/II	Maryland, *N* = 38	Bintrafa Alfa	TC, thymoma	Response intensity
NCT03463460/II	NCI, *N* = 40	Pembrolizumab + Sunitinib	TC	Response intensity
NCT04710628/ II	PECATI, *N* = 43	Pembrolizumab + Lenvatinib	TC, thymoma	PFS
NCT02364076/II	Georgetown University, *N* = 45	Pembrolizumab + Epacadostat	TC	Response intensity
NCT03583086/ I–II	Vanderbilt-Ingram Cancer Center, *N* = 177	Nivolumab + Vorolanib	TC	Safety, response intensity.
NCT04234113/ I- Ib	Sotio, *N* = 96	Pembrolizumab and SO-C101 (IL-15/IL-15R α)	TC	Dose limiting toxicity
NCT04469725/II	Jiangsu, *N* = 66	KN046 (PD-L1/CTLA4 bispecific single domain Fc protein antibody)	TC	Response intensity
NCT03858582/II	Samsung Medical Center, *N* = 40	Pembrolizumab in combination with neoadjuvant and adjuvant chemotherapy	TC, thymoma	Marks pathological response

Notes: TC: thymus cancer; PFS (progression-free survival): progression-free survival.

muscle autoantigens and increased aneuploidy [13].

There are data on the problems of re-prescribing ICI to patients with developed irAE against the background of previous IT. In some retrospective studies, up to 55 % of such cases of irAE were noted, but not as pronounced as in the initial treatment [40]. However, this scenario has not been sufficiently studied in thymoma due to the high probability of developing air. Careful monitoring and molecular profiling of AIR in TETs open up opportunities for the inclusion of patients with this pathology in clinical trials. This tactic has been studied in melanoma patients receiving ipilimumab; of the 30 patients with progressive melanoma suffering from various AID, such as Graves' disease, Crohn's disease and rheumatoid arthritis, 27 % had an exacerbation of AID, 33 % had the development of new irAEs, while half of the patients were treated without exacerbation of old and the emergence of new autoimmune conditions [41]. Finally, as a new approach, a combination of ICI with selective immunosuppressants has been proposed to prevent outbreaks of air [42], which should be studied in depth in TETs.

CONCLUSION

Immunotherapy is a new approach to the treatment of common epithelial tumors of the thymus gland, although its introduction into clinical routine practice seems to be a challenging due to the special biology of these malignant neoplasms. Despite the fact that the frequency of treatment-related adverse events is higher in thymoma compared to thymus carcinoma, patients with thymus cancer are also at risk of developing immune toxicity. Nevertheless, the re-appointment of ICIs is possible, but requires very careful monitoring of autoimmune disorders. New combinations of IT and targeted therapy seem promising. In our opinion, a deep understanding of the molecular genetic and immune landscape of thymus epithelial tumors and the interaction of ICIs with the immune system is the key to improving the effectiveness and preventing the side effects of autoimmune IT. A comprehensive solution to existing problems will undoubtedly open up new possibilities for the drug treatment of this rare and difficult disease.

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