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MODERN APPROACH TO THE TREATMENT OF T-CELL LYMPHOMA: A CLINICAL CASE OF USING HIGH-DOSE CHEMO- AND TARGETED THERAPY

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ABSTRACT

Relevance: *T-cell lymphomas are rare, aggressive non-Hodgkin lymphomas. Therapy for T-cell lymphomas remains a challenge for oncologists. In recent years, immunotherapy has developed greatly in the treatment of cancer. PD-L1 expression correlates with an unfavorable prognosis in many cancers; therefore, the prognostic value of PD-L1 levels in non-Hodgkin lymphomas is relevant.*

The study aimed to *determine the level of PDL-1 expression in T-cell lymphomas using TPS and CPS analyses, and to analyze the correlation between expression levels and clinical and pathological features, as well as patient treatment outcomes.*

Methods: *A retrospective study of pathomorphological material from primary patients with T-cell lymphomas was conducted from 2015 to 2020. PD-L1 expression was determined using a modified combined positive score (CPS) and tumor share index (TPS). Clinical, laboratory, and instrumental data, as well as the results of therapy for patients included in the study, were collected.*

Results: *The study included 40 patients; the average age was 48 years (range 18-76). 55% of patients were men, 45% were women. In 60% of cases, patients were under 60 years old. All patients received therapy according to the CHOP regimen (cyclophosphamide 750 mg/m² on Day 1, doxorubicin 50 mg/m² on Day 1, vincristine 1.3 mg/m² on Day 1, and prednisolone 60 mg/m2 on Days 1-5). Complete remission was achieved in 12 patients, disease progression was observed in 19 patients, and 6 patients died from disease progression. PDL-1 overexpression was detected in 37 patients. Statistical correla-tion of PDL-1 expression with late-stage disease ($p = 0.001$), high IPI index ($p = 0.001$), high relapse rate ($p = 0.001$), and high serum LDH level ($p = 0.001$) was observed. PD-L1 expression was a prognostic factor affecting therapy outcome and prognosis.*

Conclusion: *The significant increase in PDL-1 expression is a key prognostic factor and a predictor of poor response to standard therapy. The combination of two research types, CPS and TPS, more effectively detects PDL-1 expression, which is optimal given the biology of the tumor process. Immune therapy is a promising therapeutic option.*

Keywords: *epidemiology, T-cell lymphomas, immune therapy, PDL-1 expression.*

Introduction: Non-Hodgkin lymphomas (NHL) rank sixth among men and fifth among women worldwide among all oncological diseases, comprising both B-cell and T-cell variants of the condition [1]. T-cell lymphomas are a rare and aggressive type of NHL, with the most common forms being peripheral T-cell lymphomas (PTCL), ALK-positive and ALK-negative subtypes, Sézary syndrome, mycosis fungoides, nasal-type T/NK-cell lymphomas, and others [2]. For all types of T-cell lymphomas, except for Sézary syndrome and mycosis fungoides, disease staging is performed according to the Ann Arbor classification and the International Prognostic Index (IPI), which determines the disease prognosis [3, 4].

In contrast to B-cell lymphomas, for which various treatment options are available, the treatment of T-cell lymphomas remains a challenge for oncologists [5, 6]. Despite the availability of similar therapeutic options and treatment strategies, the prognosis of T-cell lymphomas varies depending on histological subtype, molecular variants, and the patient's clinical condition. Therefore, identifying new biomarkers may expand therapeutic options and help determine disease prognosis.

In recent years, immune therapy with immune checkpoint inhibitors (ICIs) has made significant advances in the treatment of many cancers [7]. Tumor immune regulation occurs through PD-1, PD-L1, and PD-L2 ligands in three stages: immune surveillance, immune homeostasis, and immune evasion [8].

PD-L1 is a ligand that is highly expressed not only on malignant cells in various solid tumors, but also on T-lymphocytes, B-lymphocytes, and antigen-presenting cells (APCs), and becomes further activated upon immune cell

stimulation [9]. PD-L2 is expressed by comparatively fewer cell types than PD-L1, primarily on APCs [10-11].

According to some researchers, PD-L1 expression correlates with poor prognosis, underscoring the importance of studying its prognostic significance in NHL [12]. Currently, there is no standardized interpretation of PD-L1 expression in NHL, which significantly complicates its analysis [13].

In this study, we evaluated the level of PD-L1 expression in T-cell lymphomas using a modified approach based on two methods of expression analysis: the Combined Proportional Score (CPS), which measures PD-L1 expression on both tumor cells and immune cells within the tumor microenvironment, and the Tumor Proportional Score (TPS), which measures PD-L1 expression on tumor cells only. We also compared the results of immunohistochemical PD-L1 expression analysis with other clinicopathological characteristics and patient treatment outcomes.

The study aimed to determine the level of PD-L1 expression in T-cell lymphomas using TPS and CPS analyses, and to analyze the correlation between expression levels and clinical and pathological features, as well as patient treatment outcomes.

Materials and Methods: A retrospective study was conducted using histological material from patients diagnosed with T-cell lymphoma during 2015-2020. A total of 40 patients were included in the study. All patients had a confirmed diagnosis of a T-cell lymphoma variant and underwent excisional biopsy. Medical records were analyzed for clinical and laboratory data and treatment outcomes. Treatment outcomes were categorized according to the Lugano classification [14].

Cases were classified based on the variant of T-cell lymphoma in accordance with the 2022 WHO classification of hematopoietic and lymphoid tumors [15]. Immunohistochemical staining for PD-L1 was performed using polyclonal PD-L1 antibodies (Biospes) according to the manufacturer's instructions, with appropriate positive and negative controls.

PD-L1 analysis in T-cell lymphomas is complex, as PD-L1 expression is also present in the tumor microenvironment. PD-L1 expression was evaluated using two assessment methods: a modified Combined Positive Score (CPS) and the Tumor Proportion Score (TPS) [16].

Figure 1 shows the ratio of the total number of PD-L1-positive tumor cells to lymphocytes and macrophages, as well as the total number of viable tumor cells.

TPS analysis calculates the ratio of PD-L1-positive tumor cells to the total number of tumor cells in the sample (Figure 1).

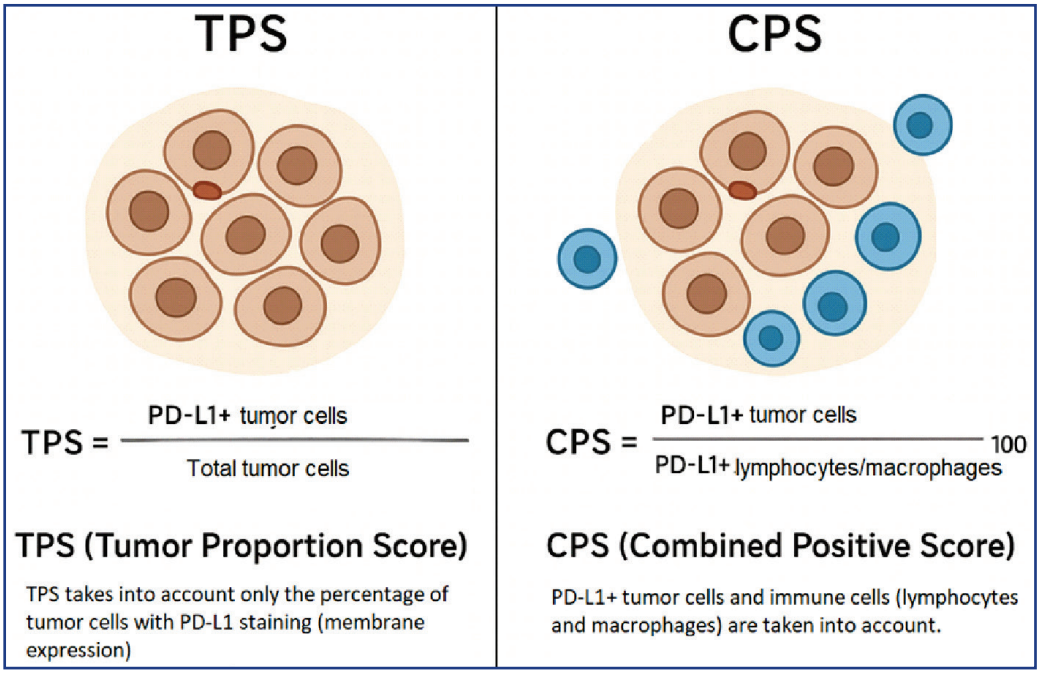

Figure 1 – Comparison of PD-L1 scoring systems.
Source: ChatGPT. Generated illustration [On-line resource]. Available at: https://chatgpt.com/c/68ad47b6-7ee0-8325-941c-6e8dbc30fe41 (accessed: 26.08.2025)

The threshold for CPS analysis was set at 5% of cells expressing cytoplasmic and/or membranous PD-L1. Cases were considered positive with either low expression (≥5% to <50% of cells) or high expression (≥50% of cells) [17, 18].

For TPS, the result – expressed as a percentage (0-100%) – indicated the level of expression: low expression was defined as <1% or ≥1%, and high expression as ≥50% [19].

Statistical Analysis: Data were analyzed using IBM SPSS Statistics for Windows, Version 27.0 (Armonk, NY: IBM Corp.). Qualitative data were expressed as absolute numbers and percentages. Quantitative data were expressed

as mean ± standard deviation for parametric data after testing for normality using the Shapiro-Wilk test (n < 50).

The chi-squared test or Fisher's exact test was used to compare qualitative variables across two or more groups. Fisher's exact test value was 0.906.

Relapse-free survival (RFS) was measured in months from the date of complete response to the date of death, relapse, or last follow-up visit.

Overall survival (OS) was measured in months from the date of diagnosis to the date of death or last follow-up visit. Survival data were analyzed using the Kaplan-Meier method.

Cox regression analysis was used to identify independent factors that could jointly affect survival. The p-value was considered significant if it was less than 0.05 at the 95% confidence interval.

The Local Ethics Committee of Asfendiyarov Kazakh National Medical University reviewed and approved this study (Protocol No. 5(82) dated 24.04.2019). The authors declare adherence to the World Medical Association's Declaration of Helsinki.

Results: The study included 40 patients with T-cell lymphomas (Table 1). The median age of the patients was 48 years (ranging from 18 to 76 years). Men accounted for 55% of the patients, and women 45%. In 60% of the cases, patients were under 60 years of age. Serum lactate dehydrogenase (LDH) levels were elevated in 67.5% of patients, and extranodal involvement was observed in 70% of cases. 85% of cases were at an advanced stage (stage III or IV according to the Ann Arbor classification). 57% of cases had a high-intermediate or high IPI score.

Among the 40 patients included in the study, 19 were diagnosed with PTCL, 6 with anaplastic large-cell lymphoma (ALK-negative), 5 with anaplastic large-cell lymphoma (ALK-positive), 8 with mycosis fungoides, and 2 with Sézary syndrome.

Table 1 – Characteristics of the Study Patients (n=40)

Indicator	Absolute number, n	Relative quantity, %
Sex		
Male	22	55
Female	18	45
Age		
≤60	28	70
>60	12	30
Lactate dehydrogenase Level (normal: 135-214 U/L)		
Normal	16	33
Elevated	27	67
Disease Spread		
Nodal	12	30
Extranodal	28	70
Ann Arbor Stage		
I, II	13	32
III, IV	27	68
IPI Risk Group		
Low	5	13
Low-intermediate	12	30
High-intermediate	15	37
High	8	20
PD-L1 Expression		
Low	6	15
High	34	25
Response to Therapy		
Complete remission	12	30
Partial remission	7	17.5
Stable disease	2	5
Disease progression	19	47.5
Relapse after 1st-line therapy		
Yes	4	33.3
No	8	66.6

All patients included in the study received therapy according to the CHOP regimen (cyclophosphamide 750 mg/m^2 on day 1, doxorubicin 50 mg/m^2 on day 1, vincristine 1.3 mg/m^2 on day 1, and prednisone 60 mg/m^2 on days 1-5). Regarding treatment response, 12 patients achieved complete remission, 19 experienced disease progression, and 6 died of disease progression.

PD-L1 expression was detected in the majority of cases in the study. In 4 patients, expression was below 5% and

was classified as negative. One patient showed low expression (Figure 2).

High PD-L1 expression was observed in 35 patients (Figure 3). Lack of PD-L1 expression in 2 cases may be due to low-quality material.

PD-L1 Expression and Clinicopathological Features: According to the statistical analysis, high PD-L1 expression was significantly associated with: advanced disease stage (p=0.001), high IPI score (p=0.001), high relapse rate (p=0.001), and elevated serum LDH level (p=0.001).

No statistically significant association was found between PD-L1 expression and sex (p=0.73) or age (p=0.152) (Table 2).

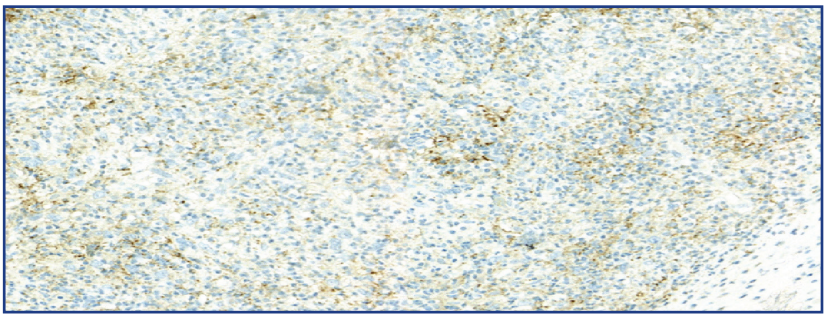

Figure 2 – Low PD-L1 Expression in T-cell Lymphomas

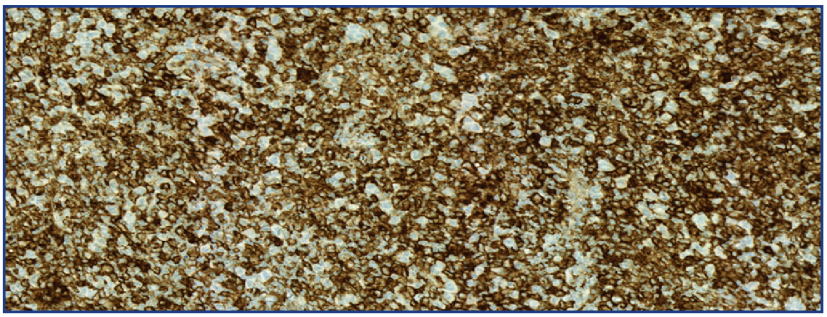

Figure 3 – High PD-L1 Expression in T-cell Lymphomas

Table 2 – Association of PD-L1 Expression with Clinical Features

Indicator	Low/Absent PD-L1 Expression (n=6)	High PD-L1 Expres-sion (n=34)	P-value
Sex			
Male	3	19	p<0.73
Female	3	15	
Age			
≤60	3	25	p<0.152
>60	3	9	
LDH level			
Normal	4	12	p<0.001
Elevated	2	25	
Ann Arbor Stage			
I, II	3	10	p<0.001
III, IV	3	24	
IPI Risk Group			
Low, low-intermediate	5	12	p<0.001
High-intermediate, high	1	22	
Relapse after 1st-line therapy			
Yes	0	4	p<0.001
No	6	2	

The estimated 1-year and 5-year progression-free survival (PFS) rates for the study cohort were 92.2% and 58.5%, respectively.

PD-L1 expression was found to be a prognostic factor: 5-year overall survival (OS) was 29% in patients with high PD-L1 expression and 84.8% in patients with low PD-L1 expression (p=0.001) (Figure 4).

Discussion: T-cell lymphomas are rare malignant neoplasms characterized by aggressive progression and the development of resistance to standard chemotherapy protocols [20]. Currently, novel agents such as brentuximab ve-

dotin, romidepsin, and pralatrexate are being used in the treatment of T-cell lymphomas [21]. Autologous bone marrow transplantation is performed at the consolidation stage [22]. The effectiveness of T-cell lymphoma therapy remains low, necessitating the search for new markers to accurately predict disease prognosis and treatment outcomes [23].

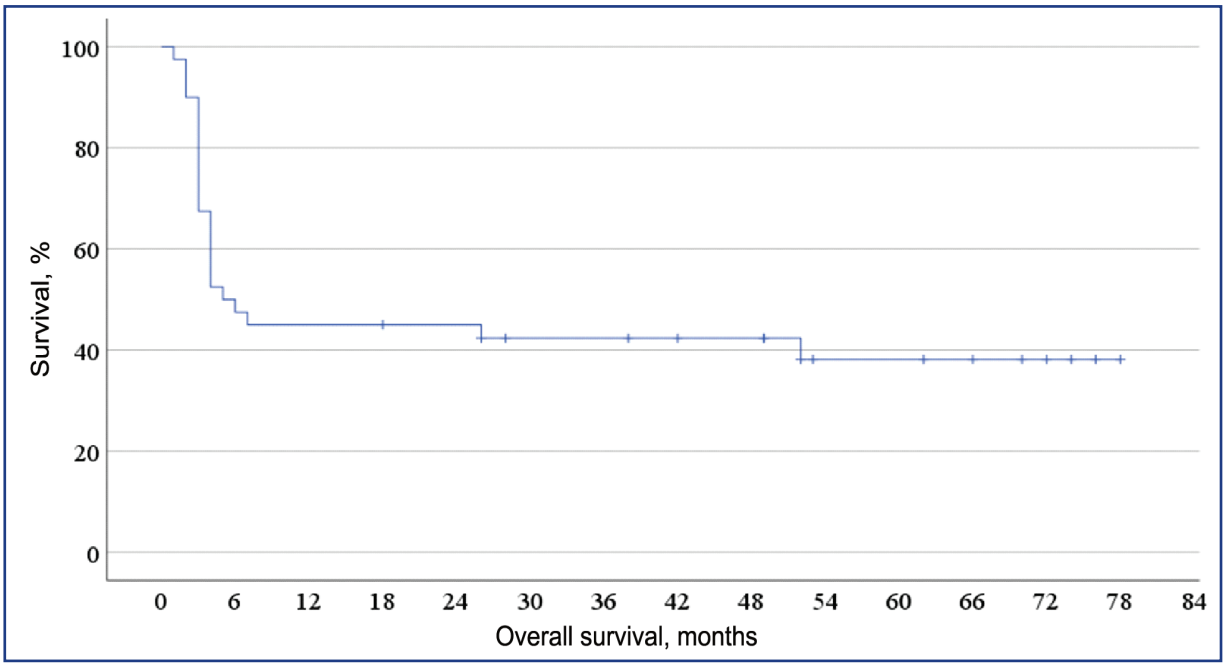

Figure 4 – Association Between Overall Survival and PD-L1 Expression Level

PD-L1 is expressed on the majority of hematopoietic cells at various stages of maturation and is constitutively expressed on T cells, B cells, macrophages, and dendritic cells. This ligand is additionally activated and induced by mitogenic stimulation and IFN-γ, resembling the expression pattern of the PD-1 receptor. High expression of this ligand has been identified in most hematologic malignancies, including primary mediastinal large B-cell lymphoma, Epstein-Barr virus (EBV)-associated lymphomas, T-cell/histiocyte-rich large B-cell lymphoma, plasmablastic lymphoma, extranodal NK/T-cell lymphoma, and Burkitt lymphoma [24]. This may be due to genomic aberrations at the 9p24.1 locus or to EBV proteins, which can upregulate PD-L1 expression [25-27].

To date, ICI drugs have been approved for the treatment of relapsed and refractory classical Hodgkin lymphoma (cHL), primary mediastinal large B-cell lymphoma, and the nasal-type T/NK-cell lymphoma variant [28-29].

M. Xie et al. (2019) believe that increased infiltration by PD-1+ tumor-infiltrating lymphocytes (TILs) is a favorable prognostic factor in diffuse large B-cell lymphoma, but not in HL. In follicular lymphoma, PD-1+ expression is higher than in other B-cell lymphoma subtypes; however, its prognostic significance remains controversial [30]. PD-L1 expression is highly heterogeneous across peripheral T-cell lymphoma subtypes.

P.K. Panjwani et al. (2018) evaluated PD-L1 expression in 702 patients with lymphoma and identified PD-L1-positive cells in 80% of both ALK-positive and ALK-negative anaplastic large-cell lymphomas (ALCL) [32].

In 2021, Y. Shi et al. assessed PD-L1 expression levels. PD-L1 expression ≥50% was identified in 78.9% of nasal-type T/NK-cell lymphomas, 71.4% of ALK+ ALCL, 38.5% of ALK-negative ALCL, and 35.7% of PTCL cases [33].

There are complexities in analyzing PD-L1 expression, including assessing PD-L1 levels in tumor tissue and the microenvironment, evaluating the specificity of different PD-L1 antibody clones for immunohistochemistry (IHC) analysis, and technical aspects such as tissue fixation, processing, and antigen retrieval [34]. Various commercially available companion/complementary diagnostic tests are available for PD-L1 IHC analysis. A companion diagnostic test can determine a patient's eligibility for anti-PD-L1 therapy. Validity, threshold values, and data registration methods vary across platforms [13]. As for PD-L1 cellular localization, complex measurement systems are used. The Tumor Proportion Score (TPS) measures the proportion of tumor cells expressing PD-L1 among all tumor cells. The modified Combined Positive Score (CPS) correlates the number of positive tumor and immune cells with the total cell count.

There is no clear consensus on which threshold level is relevant for distinguishing positive and negative results. The threshold for positive PD-L1 expression across studies ranged from 1% to 50% [35].

Conclusion: Increased PD-L1 expression correlates with prognostically unfavorable clinical variants and a low response to standard therapy. The combination of two assessment methods demonstrated an effective approach for determining PD-L1 expression, which is considered

an optimal option given the biology of the tumor process and the abundance of PD-L1 in microenvironmental cells. The detection of PD-L1 expression not only on cancer cells but also in their microenvironment confirms that ICIs are a promising treatment approach. However, to standardize PD-L1 assessment methods in NHL and the evaluation criteria for expression, more prospective multicenter studies with larger sample sizes are required.

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АҢДАТПА

МАҚАЛА ТАҚЫРЫБЫ Т-ЖАСУШАЛЫҚ ЛИМФОМАЛАРДАҒЫ PDL-1 ЭКСПРЕССИЯСЫН ТАЛДАУ: КЛИНИКОПАТОЛОГИЯЛЫҚ БОЛЖАМДЫҚ ФАКТОРЛАРМЕН КОРРЕЛЯЦИЯ

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Өзектілігі: *Т-жасушалық лимфомалар Ходжкиндік емес лимфоманың сирек кездесетін агрессивті түрі болып табылады. Т-жасушалық лимфомалардың терапиясы онкологтар үшін күрделі мәселе болып қала береді. Соңғы жылдары иммундық терапия ісік ауруын емдеуде айтарлықтай дамыды. PD-L1 экспрессиясы көптеген қатерлі ісіктердегі қолайсыз болжаммен корреляцияланады, сондықтан Ходжкиндік емес лимфомалардағы PD-L1 деңгейлерінің болжамдық мәнін зерттеу өзекті болып табылады.*

Зерттеудің мақсаты: *TPS және CPS талдауына негізделген Т-жасушалық лимфомалардағы PDL-1 экспрессиясының деңгейін анықтау, экспрессия деңгейінің клиникалық және патологиялық белгілермен және пациенттерді емдеу нәтижелерімен корреляциясын талдау.*

Әдістері: *Т-жасушалық лимфомасы бар бастапқы пациенттердің патоморфологиялық материалын ретроспективті зерттеу 2015 жылдан 2020 жылға дейін жүргізілді. PD-L1 экспрессиясы модификацияланған біріктірілген оң балл (CPS) және ісік үлесінің индексі (TPS) арқылы анықталды. Зерттеуге енгізілген науқастардың клиникалық, зертханалық және аспаптық деректері, терапия нәтижелері жиналды.*

Нәтижелері: *Зерттеуге 40 пациент қатысты, науқастардың орташа жасы 48 жасты (18-ден 76 жасқа дейін) құрады. Науқастардың 55%-ы ерлер, 45%-ы әйелдер. 60% жағдайда науқастар 60 жасқа толмаған. Барлық емделушілер CHOP режиміне сәйкес терапия алды (циклофосфамид 750 мг/м^2 1 күн, доксорубицин 50 мг/м^2 1 күн, винкристин 1,3 мг/м^2 1 күн және преднизолон 60 мг/м^2 1-5 күн). 12 науқаста толық ремиссияға қол жеткізілді, 19 науқаста аурудың өршуі байқалды, 6 науқас аурудың өршуінен қайтыс болды. 37 науқаста PDL-1 жоғары экспрессиясы анықталды. PDL-1 экспрессиясының аурудың кеш сатысымен (p=0,001), жоғары IPI индексімен (p=0,001), жоғары қайталану жылдамдығымен (p=0,001) және сарысудағы ЛДГ деңгейінің жоғары деңгейімен (p=0,001) статистикалық корреляция анықталды. PD-L1 экспрессиясы терапия мен болжамның нәтижесіне әсер ететін болжамдық фактор болды.*

Қорытынды: *PDL-1 экспрессиясының анық жоғарылауы аурудың болжамында маңызды және стандартты терапияға төмен жауап береді. CPS және TPS зерттеулерінің екі түрін біріктіру PDL-1 өрнектерін тиімдірек анықтайды, бұл ісік процесінің биологиясын ескере отырып, оңтайлы. Иммундық терапия перспективалы терапиялық нұсқа болып табылады.*

Түйінді сөздер: *эпидемиология, Т-жасушалық лимфомалар, иммундық терапия, PDL-1 экспрессиясы.*

АННОТАЦИЯ

АНАЛИЗ ЭКСПРЕССИИ PDL-1 ПРИ Т-КЛЕТОЧНЫХ ЛИМФОМАХ: КОРРЕЛЯЦИЯ С КЛИНИКО-ПАТОЛОГИЧЕСКИМИ ПРОГНОСТИЧЕСКИМИ ФАКТОРАМИ

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Актуальность: *Т-клеточные лимфомы являются редким, агрессивным видом неходжкинских лимфом. Терапия Т-клеточных лимфом остается вызовом для онкологов. В последние годы в лечении онкологических заболеваний большое развитие получила*

иммунная терапия. Экспрессия PD-L1 коррелирует с неблагоприятным прогнозом при многих онкологических заболеваниях, в связи с этим, исследование прогностического значения уровня PD-L1 при неходжкинских лимфомах является актуальным.

***Цель исследования** – определить уровень экспрессии PDL-1 при Т-клеточных лимфомах, на основании анализа TPS и CPS, провести анализ корреляции уровня экспрессии с клинико-патологическими признаками и исходами лечения пациентов.*

***Методы:** Было проведено ретроспективное исследование патоморфологического материала первичных пациентов с Т-клеточными лимфомами, в период с 2015 по 2020 год. Экспрессия PD-L1 определялась с помощью модифицированного комбинированного положительного балла (CPS) и индекса доли опухоли (TPS). Был проведен сбор клинических, лабораторно-инструментальных данных, результата терапии пациентов, включенных в исследование.*

***Результаты:** В исследование было включено 40 пациентов, средний возраст пациентов составил 48 лет (от 18 до 76 лет). 55% пациентов мужчины, женщин составило 45%. В 60% случаев пациенты были младше 60 лет. Все пациенты получали терапию по схеме CHOP (циклофосфамид 750 мг/м^2 1 день, доксорубицин 50 мг/м^2 1день, винкристин 1.3 мг/м^2 1день, и преднизолон 60 мг/м^2 1-5 дни). У 12 пациентов была достигнута полная ремиссия, у 19 пациентов – прогрессирование заболевания, 6 пациентов умерли от прогрессирования заболевания. Гиперэкспрессия PDL-1 была обнаружена у 37 пациентов. Определена статистическая корреляция экспрессии PDL-1 с поздней стадией заболевания ($p = 0,001$), высоким индексом IPI ($p = 0,001$), высокой частотой рецидивов ($p = 0,001$), и высоким уровнем сывороточной ЛДГ ($p = 0,001$). Экспрессия PD-L1 являлась прогностическим фактором влияющим на исход терапии и прогноз.*

***Заключение:** Определенно повышенная экспрессия PDL-1 значима в прогнозе заболевания и низким ответом на стандартную терапию. Комбинация двух видов исследования CPS и TPS эффективнее выявляет экспрессию PDL-1, что является более оптимальным с учетом биологии опухолевого процесса. Иммунная терапия является многообещающей терапевтической опцией.*

***Ключевые слова:** эпидемиология, Т-клеточные лимфомы, иммунная терапия, экспрессия PDL-1.*

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