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A MODERN APPROACH TO T-CELL LYMPHOMA TREATMENT: DEMONSTRATING A THERAPEUTIC STRATEGY (A CLINICAL CASE)

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ABSTRACT

Relevance: *Primary central nervous system (PCCNS) lymphomas are a rare type of lymphoma, accounting for 2% of all CNS lymphomas, and are associated with a poor prognosis. According to data from the Republic of Kazakhstan EROB Information System, in 2023-2024, the «CNS lymphoma» diagnosis was morphologically confirmed in 13 individuals. Among primary CNS lymphomas, the ALK-negative subtype of anaplastic large-cell T-cell lymphoma is a highly malignant tumor with an aggressive clinical course. Treatment of such patients remains challenging, requiring an expanded evidence base and more clinical case reports.*

The study aimed to *demonstrate the effectiveness of combined chemo-targeted therapy with autologous bone marrow transplantation in a patient with ALK-negative anaplastic large cell CNS lymphoma (a T-cell lymphoma subtype) through a clinical case and literature review.*

Methods: *This article presents a literature review and a clinical case of a patient with T-cell lymphoma of the central nervous system. Diagnostic assessments included computed tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI) of the brain, as well as histopathological and immunohistochemical examination of postoperative tissue samples. The disease course and response to treatment are described.*

Results: *A patient with a provisional clinical diagnosis of «Primary anaplastic CNS lymphoma, ALK-negative subtype» underwent microsurgical tumor resection. Given the rare nature and localization of the tumor, a histopathological re-evaluation with immunohistochemical analysis of the postoperative specimen was performed. A therapeutic strategy was selected, including using the targeted agent brentuximab vedotin. This case illustrates the potential of combined chemo-targeted therapy in treating ALK-negative anaplastic CNS lymphoma, taking into account the tumor's biological characteristics and the patient's individual features.*

Conclusion: *The correct choice of treatment strategy depends on timely and accurate diagnosis, making diagnostic workup - including morphological and immunohistochemical evaluation - a key step in patient management. In recent years, the strategy of choice for improving prognosis and survival in such patients has been developing and implementing combined therapeutic approaches, incorporating both intensive chemotherapy regimens and modern targeted therapies.*

Keywords: *central nervous system (CNS) lymphoma, epidemiology, T-cell lymphomas, anaplastic large cell lymphoma (ALCL), targeted therapy.*

Introduction: Primary central nervous system lymphoma (PCNSL) is a rare and aggressive type of non-Hodgkin lymphoma (NHL) affecting the brain, meninges, eyes, and spinal cord [1]. PCNSL account for approximately 5% of all primary CNS tumors and 1% of all NHLs. According to population studies in Western Europe, North America, and Asia, the incidence of PCNSL ranges from 0.3 to 0.5 per 100,000 population [2]. According to the "Electronic Register of Cancer Patients of the Republic of Kazakhstan" Information System, in 2023–2024, CNS lymphomas were morphologically confirmed in 13 people.

Histologically, the most common type is diffuse large B-cell lymphoma (DLBCL), while T-cell lymphoma variants are rare, accounting for only 2% of all CNS lymphomas. A unique type of T-cell lymphoma is anaplastic T-cell lymphoma (ATCL). This lymphoma is divided into two subtypes depending on the expression of anaplastic lymphoma kinase (ALK): ALK-positive and ALK-negative [2,3].

ALK-positive ATCL is more common (70-80% of cases), whereas the ALK-negative form is rare and is characterized by a more aggressive course, diagnostic difficulties, and limited therapeutic options [3, 4].

In recent years, the use of combined treatment methods, including chemotargeted therapy and cell technologies, in the treatment of ATCL has been actively studied. This article presents a clinical case of a patient diagnosed with ALK-negative ATCL. The patient underwent successful microsurgical removal of the tumor followed by spe-

cific chemotargeted therapy, which resulted in a stable remission for 18 months.

The study aimed to demonstrate the effectiveness of combined chemo-targeted therapy with autologous bone marrow transplantation in a patient with ALK-negative anaplastic large cell CNS lymphoma (a T-cell lymphoma subtype) through a clinical case and literature review.

Materials and methods: To conduct a literature review, a systematic search of scientific literature was conducted in PubMed, Web of Science, and Scopus electronic databases, covering the period from January 2010 to January 2024.

The search was conducted using a combination of the following keywords and Medical Subject Headings (MeSH) terms: "T-cell anaplastic lymphoma," "ALK-negative status," and synonyms and derivatives of these terms (in English).

The analysis included publications that met the following inclusion criteria: articles published in peer-reviewed scientific journals with the full text available in English; articles containing data from randomized controlled trials, cohort studies, meta-analyses, and systematic reviews; and publications describing individual clinical cases. Exclusion criteria: incomplete publications (e.g., conference abstracts, presentations); articles not indexed in leading databases or published in journals with a low impact factor and questionable scientific reputation; articles with a citation index below the average for the subject during the search period according to Scopus/Web of Science.

The initial search yielded approximately 20 publications. After applying the inclusion and exclusion criteria, 16 of the most relevant sources were selected for analysis. Two researchers conducted the article selection.

The article also describes the clinical situation and medical history of a 47-year-old patient diagnosed with ALK-negative anaplastic large cell lymphoma. The following research methods were employed during the diagnostic search: positron emission tomography (PET), computed tomography (CT), magnetic resonance imaging (MRI), and immunohistochemical studies of morphological and histopathological material.

Clinical situation:

Patient information: A 47-year-old man was admitted to the Bone Marrow Transplant and Hematology Center of the Kazakh Research Institute of Oncology and Radiology for the first time with complaints of headache in the occipital region, nausea, muscle weakness in the left arm and leg.

Clinical data: The disease lasted for several months; examination revealed left-sided hemiparesis.

Diagnosis: Contrast-enhanced MRI of the brain revealed a 6.5 cm tumor in the right parietal lobe. Additional CT of the chest, abdomen, and pelvis, as well as bone marrow puncture, did not reveal a primary lesion or metastases. An intraparenchymal soft mass measuring 6.5×4.7 cm with unclear borders and a density of 40 HU was found in the right parietal lobe. Extensive perilesional edema and compression of the lateral ventricles around the first ventricle were noted (Fig. 1).

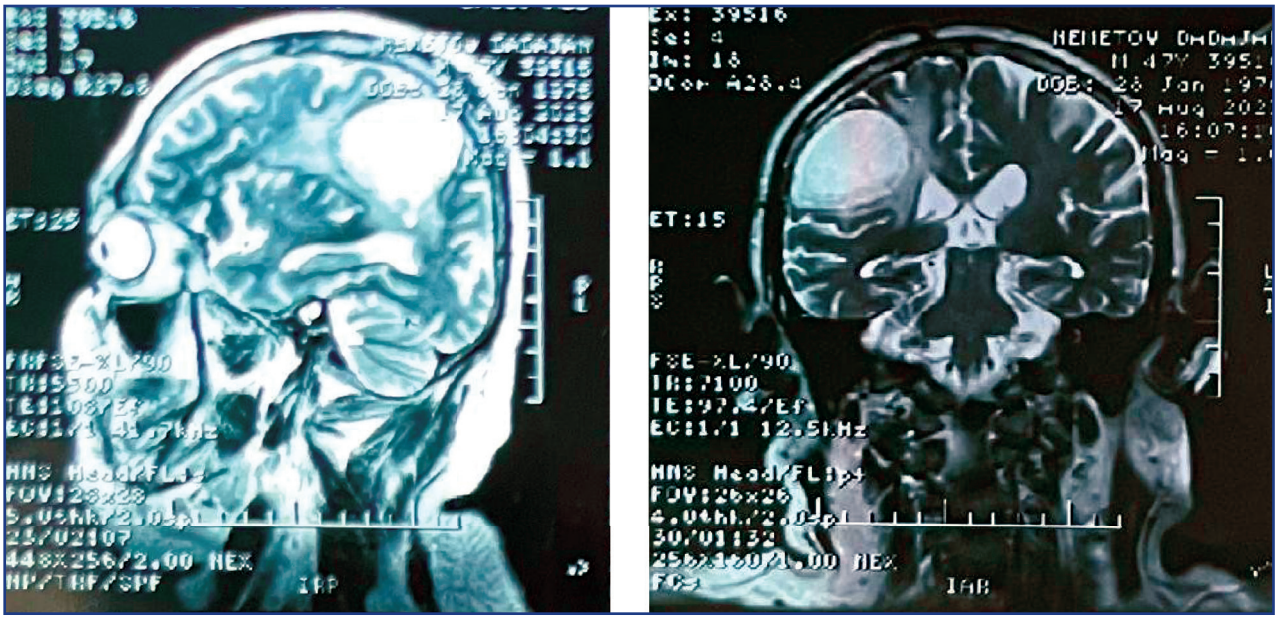

Figure 1 – MRI data from February 2023: a soft mass in the right parietal region, perilesional edema, and ventricular compression were determined.

Histological examination of the I-cell biopsy revealed diffuse infiltration of the brain tissue by atypical cells with large, hyperchromatic, ovoid, and bean-shaped nuclei characteristic of this tumor. The differential diagnosis included germ cell tumors and various large cell lymphomas. Immunohistochemical examination showed that the tumor cells were positive for CD45, CD30, and CD8 markers, but negative for the ALK marker. Based on the results obtained, the diagnosis of ALK-negative anaplastic large T-cell lymphoma (ALCL) was confirmed (Figure 2).

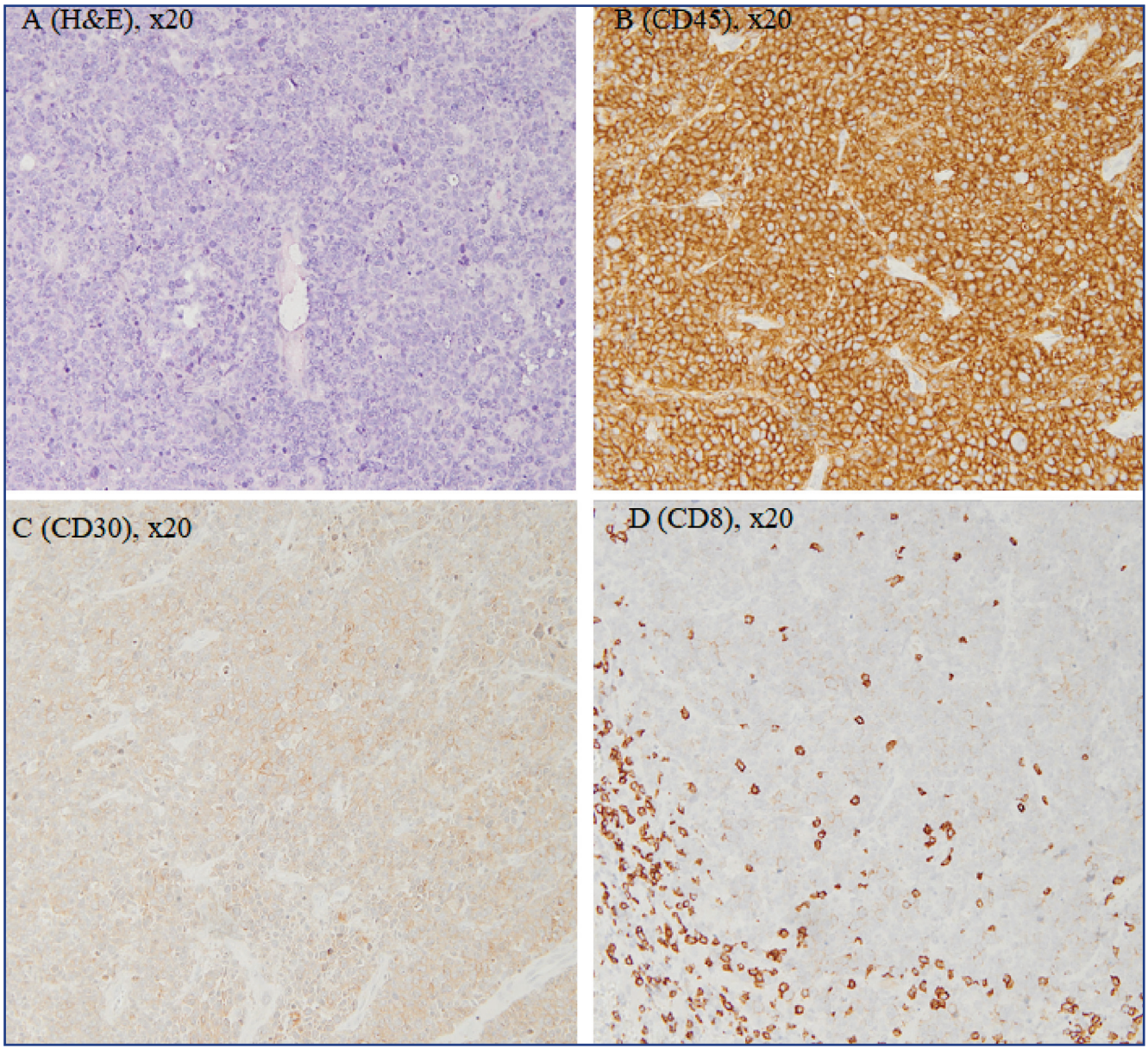

Figure 2 - (A) Diffuse proliferation of large atypical lymphoid cells. Intense diffuse immunostaining for CD45 (B), CD30 (C), and weakly positive immunostaining for CD8 (D)

PET-CT revealed accumulation of fluorodeoxyglucose F18 only in the brain; no other foci were detected. No tumor cells were detected in the cerebrospinal fluid.

Differential diagnosis includes glioblastoma, metastases from solid tumors, and brain lymphoma.

Treatment: The first tumor was completely removed microsurgically after 2 months. Pathological examination confirmed an ALK-negative ALCL. The tumor in the right parietal lobe was removed microsurgically using neuronavigation. Since the patient was diagnosed with ALK-negative ALCL, the treatment followed the Bre-HyperCVAD protocol considering the marker expression and status (cycles 1,3,5,7: brentuximab vedotin (1.8 mg/kg), cyclophosphamide (2×300 mg/m^2), vincristine (2 mg), doxorubicin (50 mg/m^2); cycles 2,4,6,8: brentuximab vedotin (1.8 mg/kg), methotrexate (1 g/m^2), cytarabine (2 g/m^2). A total of 8 cycles of chemotargeted therapy and autologous hematopoietic stem cell transplantation (autoHSCT) in a treosulfan-conditioned regimen were performed.

During chemotherapy, grade 1-2 side effects were registered: mild anemia and mild thrombocytopenia. Maintenance therapy: dexamethasone, leucovorin. After four courses of the Bre-HyperCVAD protocol, complete remission was achieved, and stem cells were collected in a volume of 5×10^6/kg. Conditioning was carried out on days 1–3 with treosulfan at a dose of 16 g/m^2, and autologous HSCT was performed on April 7, 2024 (Day 0). Neutrophil recovery was noted on Day 14.

Results: After completing combination therapy, including chemotargeted therapy according to the Bre-Hyper CVAD regimen (8 courses) and subsequent autologous bone marrow transplantation, a control MRI examination of the brain performed 12 months later revealed no signs of disease recurrence (Figure 3).

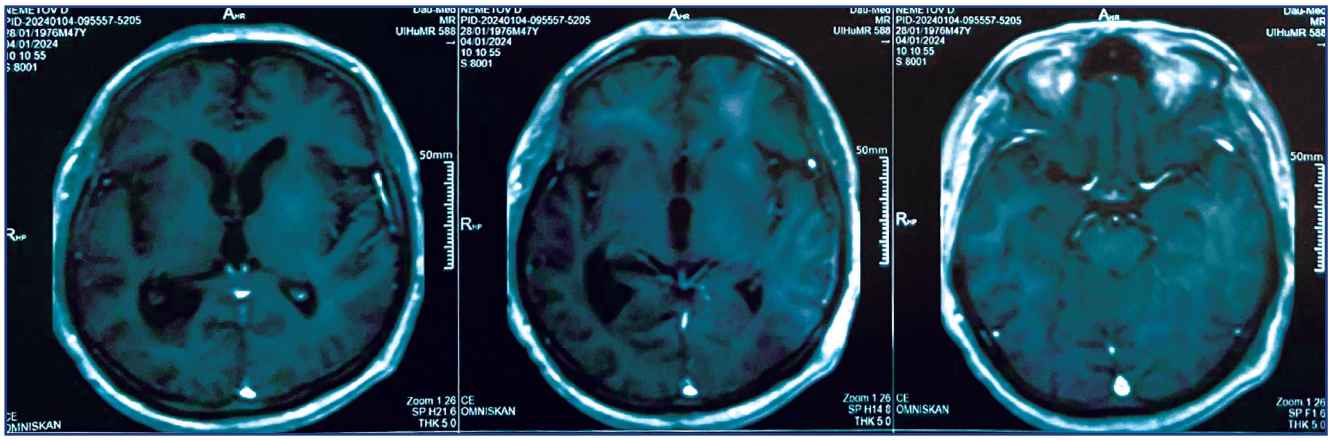

Figure 3 – Cystic mass (1.5×4.5 cm). Multiple vasogenic foci were detected in the white matter of the brain. Right-sided sinusitis. (April 2025)

Table 1 – Timeline of a clinical case of ALK-negative anaplastic large T-cell lymphoma

Date	Event
January 2023	The disease began with severe headaches in the occipital region. The patient consulted a neurologist and underwent outpatient treatment, which had a temporary effect.
February 2023	The symptoms worsened: headache, double vision, weakness in the left arm and leg. MRI revealed a large mass in the right parietal lobe.
April 2023	12.04 – Surgery performed: craniotomy of the right occipital lobe. The tumor was removed microsurgically using neuronavigation. 15.04 – Pathomorphological examination: According to the results of the IHC study, the morphology and immunophenotype corresponded to non-Hodgkin's lymphoma. CD45 exhibited a diffuse positive reaction, while CD20 was positive in rare B-lymphocytes, and CD79a was positive in B-lymphocytes. CD3 was positive in T-lymphocytes, CD99 was negative, FLI1 was focally positive, panceratin (AE1/AE3) was negative, and CD138 was positive in single plasma cells.
May 2023	03.05 – repeated IHC study was performed at KazNIIOiR: CD20, PanCK, PAX5, CD3, CD138, ALK, CD15, CD4, Granzyme B, CD5, CD79a – negative; MUM1, CD45, CD30, CD8, p63 – positive. Conclusion: Tumor morphology and immunophenotype corresponded to ALK-negative anaplastic large cell lymphoma. 25.05 – MRI of the brain (with contrast): hypervascular formations, edema, and displacement of brain structures were determined in the right frontal-parietal region and left frontal region.
June 2023	11.06 – Results of MDT at KazNIIOiR: treatment according to the Bre-HyperCVAD scheme was recommended; the patient underwent 1 course.
July 2023	09.07 – 2nd course according to the Bre-HyperCVAD scheme
August 2023	06.08 – 3rd course according to the Bre-HyperCVAD scheme
September 2023	11.09 – Mobilization of stem cells (5 million cells collected)
October 2023	15.10 – 4th course according to the Bre-HyperCVAD scheme
November 2023	25.11 – 5th course according to the Bre-HyperCVAD scheme
December 2023	25.12 – 6th course according to the Bre-HyperCVAD scheme
January 2024	18.01 – 7th course according to the Bre-HyperCVAD scheme
February 2024	20.02 – 8th course according to the Bre-HyperCVAD scheme
March-April 2024	09.03 – Pre-transplant preparation started: conditioning regimen RIC-treosulfan 16 mg/m² on days 1-3. 24.03 – The patient underwent autologous hematopoietic stem cell transplantation (autoHSCT) (Day 0) 07.04 – On D+14, restoration of neutrophils was recorded.
April 2025	MRI of the brain: no signs of relapse found.

Discussion: According to the literature, fewer than 20 confirmed cases of ALK-negative CNS ALCL have been registered worldwide, predominantly in patients over 40 years old, with a male predominance [5, 6]. The disease presents with nonspecific symptoms, including headache, aphasia, weakness, and confusion. An MRI of the brain often reveals solitary or multifocal lesions [7,8]. Morphologically, this lymphoma is characterized by large, atypical cells with horseshoe-shaped nuclei expressing CD30. Immunohistochemical studies reveal the presence of T-cell markers (CD4, CD43, Granzyme B), but ALK expression is absent. In some patients, genetic studies have revealed *TP53 gene deletions, complex karyotypes, and DUSP22 rearrangements (including DUSP22-IRF4),* which may impact the disease prognosis [9-13].

The standard approach to treating PCNSL is a combination of rituximab with high-dose methotrexate and cytarabine. During the consolidation phase, autologous bone marrow transplantation is performed using a myeloablative or non-myeloablative regimen, which enhances treatment effectiveness and facilitates long-term remission [14]. Previously, radiation therapy to the brain was used in the consolidation phase, as well as additional (boost) radiation directed at the tumor [15]. Given the rarity of PCNSL and its aggressive course, the search for effective treatment methods for this patient group is an urgent problem [16]. Although the ability of brentuximab vedotin (BV) to penetrate the blood-brain barrier (BBB) has not been proven, its penetration through the BBB is theoretically possible as a result of systemic spread of lymphoma to the CNS [17, 18].

According to the literature, BV is effective in treating systemic T-cell lymphomas. However, its use in PCNSL is limited and has been described in only a few clinical cases. Combination approaches, such as BV plus high-dose methotrexate or HyperCBAD (modified HyperCVAD with BV instead of vincristine), have been successfully used in two patients with refractory ALCL involving the CNS and in one patient with CD30-positive DLBCL [19-20].

T. Mitsunobu et al. described a case of ALK-negative ALCL in an 11-year-old boy. The boy presented with secondary CNS involvement and was treated with intensive chemotherapy consisting of BV and high-dose methotrexate in the induction phase, sequentially [20].

In 2016, W. *Delacruz* et al. reported two clinical cases. The first clinical case is a patient with stage IV ALCL with cranial nerve involvement. This patient experienced disease progression during first-line treatment with CHOP (cyclophosphamide, vincristine, doxorubicin, prednisone) and second-line HyperCVAD. However, a positive response was observed after using BV instead of vincristine (HyperCBAD regimen). The second patient was a man with stage IV DLBCL with leptomeningeal involvement. The disease progressed during first-line treatment with R-CHOP and second-line treatment with R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin). However, the combination of BV with topotecan showed significant improvement [19].

In addition to histological type and ALK positivity, the study of CD30 expression in lymphoma has resulted in the development of important therapeutic approaches. Currently, numerous clinical trials are underway to develop more effective treatment regimens that utilize BV in combination with other drugs, such as chemotherapy or immunotherapy. Additionally, various approaches are employed to target CD30-positive cells. These include the use of bispecific antibodies and chimeric antigen receptor (CAR) T-cell therapy [21].

Conclusion: Treatment of PCNSL is a challenging task for oncohematologists. The choice of treatment tactics is made taking into account the tumor localization, its morphological structure, the presence of perifocal edema, the presence or absence of genetic abnormalities, immunophenotype, and often the patient's comorbidities. T-cell PCNSL, particularly ALK-negative ALCL, is a rare disease, and its treatment options are limited. However, active research is currently underway to develop new treatment strategies for ALK-negative ALCL, including modifications of existing treatment regimens. In this clinical setting, we demonstrated the effectiveness of BV and chemotargeted therapy in combination with an integrated approach that includes autologous hematopoiesis. Nevertheless, despite the development of new, promising methods for treating ALCL, the prognosis for these patients remains unfavorable. In this regard, studying the pathological mechanisms of the disease, collecting data on patients with this rare disease, monitoring the course of the disease, and analyzing its outcomes will pave the way for the development of successful treatment strategies and the widespread use of existing therapeutic options, thereby increasing the life expectancy of patients in this group.

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АҢДАТПА

Т-ЖАСУШАЛЫ ЛИМФОМАНЫ ЕМДЕУДЕГІ ЗАМАНАУИ ТӘСІЛ: ТЕРАПИЯЛЫҚ СТРАТЕГИЯНЫ КӨРСЕТУ (КЛИНИКАЛЫҚ ЖАҒДАЙ)

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Өзектілігі: *Орталық жүйке жүйесінің біріншілік лимфомалары (ОЖЖБЛ) - лимфомалардың сирек кездесетін түрлерінің бірі болып табылады, олар ОЖЖ-нің барлық лимфомаларының 2%-ын құрайды және болжамы қолайсыз болып есептеледі. Қазақстан Республикасындағы ЭРОБ Ақпараттық Жүйесінің деректеріне сәйкес, 2023-2024 жылдары «ОЖЖ лимфомасы» диагнозы морфологиялық түрде 13 адамда расталған. ОЖЖБЛ ішінде анапластикалық лимфома киназа (АЛК)-теріс анапластикалық Т-жасушалы лимфома - жоғары дәрежелі қатерлі ісік түрі, ағымы агрессивті болады. Мұндай науқастарды емдеу мәселелері әлі толық шешілмеген, бұл өз кезегінде дәрелді деректер қорын кеңейтуді және клиникалық бақылаулар санын арттыруды талап етеді.*

Зерттеудің мақсаты *– клиникалық жағдай мен әдеби деректер негізінде ОЖЖ-нің АЛК-теріс анапластикалық ірі жасушалы лимфомасы (АІЖЛ) – Т-жасушалық лимфомамен ауыратын науқаста химио-таргеттік біріктірілген терапияны аутологиялық сүйек кемігінің трансплантациясымен қатар қолданудың тиімділігін көрсету.*

Әдістері: *Мақалада ОЖЖ-нің Т-жасушалық лимфомасы бар науқастың клиникалық жағдайы мен әдеби шолу сипатталған. Осындай зерттеу деректері ұсынылған: компьютерлік томография (КТ), позитронды-эмиссиялық томография (ПЭТ), бас миына жасалған магниттік-резонанстық томография (МРТ), сондай-ақ операциядан кейінгі материалға жүргізілген патоморфологиялық және иммуногистохимиялық зерттеу. Аурудың динамикасы мен емге жауабы баяндалған.*

Нәтижелері: *«ОЖЖ-нің біріншілік анапластикалық лимфомасы, АЛК-теріс түрі» деген клиникалық диагнозы бар науқасқа микрохирургиялық жолмен ісік алынып тасталғаннан кейін, аурудың сирек кездесетін нұсқасы мен ісіктің орналасуын ескере отырып, операциядан кейінгі материалға патоморфологиялық және иммуногистохимиялық зерттеу жүргізіліп, препараттарды қайта қарау жүзеге асырылды. Емдеу тактикасы ретінде таргеттік препарат – брентуксимаб ведотинді қамтитын біріктірілген ем таңдалды. Ұсынылған клиникалық жағдай АЛК-теріс түріндегі ОЖЖ-нің анапластикалық лимфомасын емдеуде ісіктің биологиялық ерекшеліктері мен науқастың жеке жағдайын ескере отырып, химио-таргеттік біріктірілген терапияны қолданудың әлеуетін көрсетеді.*

Қорытынды: *Дұрыс ем тактикасын таңдау дәл диагноздың уақытында қойылуына тікелей байланысты, сондықтан диагностика – науқасты жүргізу алгоритміндегі негізгі буын болып табылады. Осыған орай, морфологиялық және иммуногистохимиялық зерттеулер жүргізу аса маңызды. Мұндай науқастардың болжамын жақсарту және өмір сүру көрсеткіштерін арттыру мақсатында соңғы жылдары емдеудің таңдаулы стратегиясы ретінде қарқынды химиотерапиялық схемалар мен заманауи таргеттік препараттарды қамтитын біріктірілген емдеу тәсілдерін әзірлеу және қолдану ұсынылып отыр.*

Түйін сөздер: *орталық жүйке жүйесінің біріншілік лимфомалары (ОЖЖБЛ), эпидемиология, Т-жасушалық лимфомалар, анапластикалық ірі жасушалы лимфома (АІЖЛ), таргеттік терапия.*

АННОТАЦИЯ

СОВРЕМЕННЫЙ ПОДХОД К ЛЕЧЕНИЮ Т-КЛЕТОЧНОЙ ЛИМФОМЕ: ДЕМОНСТРАЦИЯ ТЕРАПЕВТИЧЕСКОЙ СТРАТЕГИИ (КЛИНИЧЕСКИЙ СЛУЧАЙ)

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Актуальность: *Первичные лимфомы центральной нервной системы (ПЛЦНС) являются редким видом лимфом, встречаются в 2% от всех лимфом ЦНС и являются прогностически неблагоприятными. Согласно данным Информационной Системы ЭРОБ*

в Республике Казахстан, в 2023-2024 годах диагноз «лимфома ЦНС» был морфологически подтвержден у 13 человек. Среди первичных лимфом центральной нервной системы, ALK-негативная анапластическая крупноклеточная лимфома (АККЛ) является высокозлокачественной опухолью с агрессивным характером течения. Вопросы лечения таких пациентов остаются нерешенными, что требует расширения доказательной базы и большего количества клинических наблюдений.

***Цель исследования** – на примере клинического случая и литературных данных показать эффективность применения химио-таргетной комбинированной терапии в сочетании с аутологичной трансплантацией костного мозга у пациента с Т-клеточной лимфомой (АККЛ ЦНС).*

***Методы:** В статье описан литературный обзор и клинический случай пациента с Т-клеточной лимфомой ЦНС. Представлены данные исследований: компьютерная томография, позитронно-эмиссионная томография, магнито-резонансная томография головного мозга, а также патоморфологическое исследование с иммуногистохимическим исследованием послеоперационного материала. Описана динамика заболевания, ответ на лечение.*

***Результаты:** Пациент с направительным клиническим диагнозом «Первичная анапластическая лимфома ЦНС, ALK-негативный подтип», после микрохирургического удаления опухоли. Учитывая редкий вариант заболевания, локализацию образования, был проведен патоморфологический пересмотр препаратов с иммуногистохимическим исследованием послеоперационного материала и выбрана тактика терапии с включением таргетного препарата брентуксимаб ведотин. Представленный случай показывает потенциал применения комбинированной химиотаргетной терапии в лечении АККЛ ЦНС с учётом биологических особенностей опухоли и индивидуальных особенностей пациента.*

***Заключение:** Выбор верной тактики лечения зависит от своевременно уставленного точного диагноза, что делает диагностику ключевым звеном в алгоритме ведения пациента, в связи с чем необходимо проведение морфологического, иммуногистохимического исследования. С целью улучшения прогноза и показателей выживаемости таких пациентов, в последние годы стратегией выбора является разработка и применение комбинированных лечебных подходов, включающих как интенсивные химиотерапевтические схемы, так и современные таргетные препараты.*

***Ключевые слова:** лимфома центральной нервной системы (ЦНС), эпидемиология, Т-клеточные лимфомы, анапластическая крупноклеточная лимфома (АККЛ), таргетная терапия.*

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