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NOT OTHERWISE SPECIFIED T-CELL LYMPHOMA: OUTCOMES OF A SINGLE CENTER STUDY

Background. The peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) is the most common subtype of peripheral T-cell lymphoma (PTCL). It constitutes approximately 25% of all PTCLs and accounts for more than 15% of all lymphomas. The results of the first Ukrainian prospective study of patients with PTCL-NOS are presented in the article. **The aim** of the study was to analyze the morbidity of PTCL patients and the treatment performed, to evaluate overall survival and progression-free survival, and to determine the factors that predict the treatment response. **Patients and Methods.** An analysis was performed on the data of 31 patients diagnosed with peripheral PTCL-NOS from February 2018 to the present. T-cell lymphoid neoplasms were diagnosed according to the 2016 WHO classification. The treatment regimens were in alignment with ESMO and NCCN guidelines. More than 90% of patients were prescribed anthracycline-based regimens (CHOP; CHOEP — cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone). An initial treatment was performed with CHOP-based regimens in 38.70% (n = 12) of patients, with the addition of etoposide in 58.06% of patients (n = 18). **Results.** The response was assessed according to the response criteria for malignant lymphoma (Cheson, 2008, 2014). The overall response to therapy was 58.06% (n = 18), with complete responses in 29.03% of patients and partial responses in 29.03% of patients. The stabilization of the disease occurred in 3.44%, while the disease progression in 41.37% of patients. The 12-month and 24-month survival rates were 75.44% and 50.81%, respectively. The 12-month and 24-month progression-free survivals were 47.68% and 33.1%, respectively. Ki-67 overexpression (> 65%) was a negative prognostic factor. **Conclusions.** The results of the treatment of PTCL obtained in a Ukrainian population study are similar to those in other European studies, all of which remain unsatisfactory. Further research is required to develop a new strategy for examination and therapy to improve treatment outcomes. The emphasis should be placed on the pragmatic clinical trials comparing the efficacy of first-line treatment in PTCL patients with both favorable and unfavorable clinical factors.

Keywords: T-cell lymphoma, not otherwise specified T-cell lymphoma, incidence, prognostic factor, response, survival.

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The peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) is the most common subtype of peripheral T-cell lymphoma (PTCL). It comprises approximately 25% of all PTCLs and accounts for more than 15% of all lymphomas. PTCL-NOS is a diagnostic category defined by the WHO as a highly heterogeneous group of mature post-thymic T-cell neoplasms.

This type of lymphoma is predominantly diagnosed in adults, with an average patient age of 60 years, and exhibits a higher incidence in men. According to the International T-Cell Lymphoma Project [1], PTCL-NOS is equally common in Europe and North America, while the incidence is slightly lower in Asia (34.3%, 34.4%, and 22.4%, respectively). Patients often present with B-symptoms, generalized lymphadenopathy, bone marrow infiltration, and extranodal involvement with a high or high-intermediate International Prognostic Index score in 50%—70% of cases. The late-stage diagnoses are a common occurrence. The prognosis is poor, with a 5-year overall survival (OS) of 20%—30% [2]. Most patients with PTCL-NOS are enrolled in prospective trials to study new approaches, new drugs, combinations, and new treatment strategies.

PTCL-NOS is a diagnosis of exclusion that includes several diseases that differ in biology, clinical manifestations, and outcomes. It is based on the presence of typical histopathological features of lymphoma, an abnormal T-cell immunophenotype, often with loss of CD5 and CD7, and a clonal T-cell receptor (TCR) gene rearrangement, and the absence of characteristic features consistent with other PTCL subtypes defined by the WHO classification, i.e. excluding other variants of PTCL. According to the available immunophenotypic and molecular markers ((CD20, CD4, CD8, CD3, and other T-cell markers (CD2, CD5, CD7, CD43), and Ki-67)), in fact, about 30% of PTCL are classified as PTCL-NOS. This disease is heterogeneous and has a wide cytological spectrum and multiple molecular aspects [3—5]. There are several varieties based on the level of the expression of surface antigen CD30 and the level of expression of GATA3 and TBX21 (T-bet). Various mutations of *TET2*, *IDH2*, *DNMT3A*, *RHOA*, and *CD28* as well as *VAV1*, *SYK*, *FER*, and *ERBB4* are studied. Although the distribution of PTCL-NOS based on various molecular markers holds clinical significance, it does not impact the planning and outcomes of the first-line treatment.

The International Prognostic Index (IPI) specially developed for the aggressive non-Hodgkin's lymphoma is used to determine the clinical stratification of PTCL-NOS. New prognostic score systems have been developed as well, such as the prognostic index for PTCL-NOS (PIT) [6] and modified PIT (m-PIT) [7]. Both scores have some common risk factors, namely age (> 60 years), ECOG (> 1), and increased lactate dehydrogenase (LDH) levels. PIT also takes into account bone marrow infiltration, while m-PIT includes expression of the proliferation-related protein Ki-67. The fourth prognostic index developed by the International T-Cell Lymphoma Project (ITCLP) includes age (> 60 years), ECOG (> 1), and thrombocytopenia (< 150 x 10^9/l) as the three most important parameters [8].

The main goal of the first-line therapy of PTCL-NOS should be to achieve deep remission and long-term control of the disease. The standard of the first-line treatment, according to numerous recommendations, is an anthracycline-based regimen [9—11]. The meta-analysis performed by Abouyabis et al. [12] showed that the use of chemo-regimens based on anthracycline as an induction strategy in PTCL-NOS patients can result in a complete response (CR) in 17%—70% of patients. However, the 5-year overall survival (OS) only falls within the range of 32% to 45%. A study conducted by the International T-Cell Lymphoma Project team found no statistically significant survival advantage in terms of OS for patients with PTCL-NOS who received anthracycline-containing regimens during induction over those who received non-

anthracycline-containing therapy. The 5-year progression-free survival (PFS) and OS were reported as 20% and 32%, respectively [4]. More intensive chemotherapy regimens have not been proven to be more effective when compared to the historical controls with CHOP [13].

The efficacy of adding etoposide to the CHOP regimen during induction therapy was investigated by the German cooperative group (Non-Hodgkin Lymphoma Study Group) [14]. In patients with PTCL-NOS treated with the CHOEP regimen (22% of patients), the 3-year PFS and OS were 41.1% and 53.9%, respectively.

It should be noted that the attempts to improve therapy outcomes in young patients by increasing the dosage of any drug included in the CHOEP regimen have proven unsuccessful. Additionally, the efficacy of the CHOEP regimen in patients aged over 60 years does not exceed that of the CHOP regimen, which should remain the standard approach to first-line therapy in this age group.

Considering the short duration of remission and the high risk of relapse even in cases with a positive response to treatment, consolidation with auto-SCT has been recognized as a therapeutic option for patients who have achieved at least a partial response (PR) to induction therapy.

In a prospective phase II Italian study reported by Sorradini et al. [15], which included 62 patients with PTCL, a high CR (89%) was demonstrated after auto-SCT with 12-year OS, disease-free survival, and PFS of 34%, 55%, and 30%, respectively. OS and PFS, for the subgroup of patients with PTCL-NOS (45% of the total number), were 37% and 25%, respectively. The Nordic Lymphoma Group applied the CHOEP-14 induction strategy in 160 patients with PTCL (excluding ALK + ALCL) [16]. The fifth or sixth course was used as stem-cell mobilization, while the course of high-dose therapy before auto-SCT consisted of carmustine, etoposide, cytarabine, and melphalan (or high-dose cyclophosphamide). The achieved CR was 51%; 5-year OS and PFS were 51% and 44% for all patients, respectively, while 5-year OS and PFS were 47% and 38% for patients with PTCL-NOS.

Therefore, these studies show that consolidation therapy with autologous stem cell transplantation (SCT) increases the likelihood of long-term survival in patients with PTCL. Nevertheless, it should be noted that a significant proportion of patients (16%—41%) experienced disease progression during induction therapy or in the immediate lead-up to transplantation, thereby precluding this course of treatment [10].

Brentuximab vedotin is a synthetic drug conjugate with chimeric (human and mouse) monoclonal antibodies to the CD30 lymphocyte surface antigen. Approximately 20%—25% of PTCL-NOS cases express CD30 in at least 50% of tumor cells [17, 18], which makes brentuximab vedotin a promising treatment for this subset of patients. In a phase II study published by Horwitz et al. [19], 35 patients with CD30-positive T-cell lymphoma, including 22 patients with PTCL-NOS, received brentuximab vedotin at a dose of 1.8 mg/kg every 3 weeks. CR was achieved in 24% of cases and PR in 18% including 33% of patients with PTCL-NOS, 14% of whom achieved CR, establishing a clear correlation between the expression of CD30 and the level of the response to treatment. Notably, positive responses to treatment were also observed in patients with no CD30 expression on tumor cells. Disease progression was recorded in 41% of patients. In another study done by a French group of scientists, the efficacy of brentuximab vedotin was demonstrated in 56 patients with T-cell lymphomas, 11 of whom had PTCL-NOS. OS was achieved in 27% of patients with PTCL-NOS, while CR was observed only in 18% of cases [20]. In contrast to the previously published data, this study demonstrated the possibility of a correlation between CD30 expression and response to treatment: better responses to brentuximab vedotin were observed along with higher levels of CD30 expression on tumor cells.

A prospective cohort study of patients with recently diagnosed TCL was conducted at the National Cancer Institute (Ukraine). The aim of the study was to analyze the morbidity of patients of this category and the treatment performed as well as to evaluate OS and PFS and determine factors that predict the treatment response.

Materials and Methods

The study included a group of primary patients with TCL who were under supervision and treatment in the Oncohematology Department of the National Cancer Institute (Ukraine). Patient recruitment began in February 2018 and continued until September 2023. The study was approved by the Institutional Ethical Committee. All patients signed the consent for processing their clinical and laboratory data for scientific purposes. The diagnosis was established pathomorphologically by the WHO classification of lymphoid neoplasms, 2016 [21]. Immunohistochemistry panel included CD20, CD3, CD10, BCL6, Ki-67, CD5, CD30, CD2, CD4, CD8, CD7, CD56, CD21, CD23, TCRβ, ALK, and TP63. The phenotype of PTCL-NOS was usually $CD4^+/CD8^-$ or TCRβ+ and the expression of CD7 and CD5 was low. Occasionally, CD30 was positive.

The response to therapy was evaluated by the Cheson criteria 2008, 2014 [22]. The data were collected both manually and through a local electronic database.

OS was measured from the date of diagnosis until death from any cause or the date of the last known contact for living patients. PFS was measured from the time of diagnosis to the disease progression, death from any cause, or the date of last known contact for living patients. The additional secondary endpoints included demographic, clinical, and epidemiological characteristics of study subjects.

The descriptive statistics was used for analysis, survival curves were calculated using the Kaplan — Meier method. The difference was considered statistically significant at $p < 0.05$. The data were processed using Statistica version 10.0.

Results

The study group included 92 patients with T-cell lymphomas, of whom 33.69% (n = 31) had PTCL-NOS which corresponds to the data published by the T-Cell Lymphoma Project [23].

The following characteristics were assessed to identify unfavorable prognosis: age, stage of the disease according to the Ann Arbor classification, lactate dehydrogenase (LDH) level, ECOG status, extranodal involvement, bone marrow involvement, serum albumin level, platelet count, hemoglobin level, serum total protein, Ki-67 expression level, and the presence of B-symptoms.

The majority of patients, 59.37% (n = 19), were aged between 45 and 64 years, while those over 65 constituted 18.37% of the cohort. The majority were men, accounting for 67.74% (n = 21). At the time of diagnosis, 58.06% (n = 18) of patients were in advanced stages (III—IV) of the disease. The median age at the time of diagnosis was 52.87 years (range 33—75 years). Patient characteristics were also comparable to those enrolled in the International T-Cell Lymphoma Project 4, but the mean age was younger (52.87 *vs*. 62 years, $p < 0.05$) and fewer patients were diagnosed with stage III/IV disease (58.06% *vs*. 74.0%), while the other parameters were comparable.

The extranodal involvement was present in 35.48% (n = 11) of patients, and bone marrow involvement in 19.35% (n = 6) of patients. A significant number of patients, 45.16% (n = 14), exhibited an ECOG status of ≥ 2 at the time of diagnosis. B-symptoms were present in 61.29 % (n = 19) of patients. The high level of LDH (above 450 U/L) was registered in 22.58% (n = 7) of patients. Low albumin levels (< 35 g/L) were identified in 16.12% (n = 5) of cases and low total protein levels (< 65 g/L) were found in 12.9%

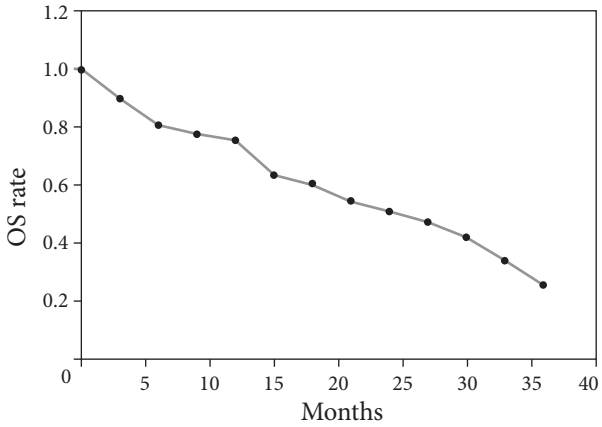

Fig. 1. OS rate of PTCL-NOS

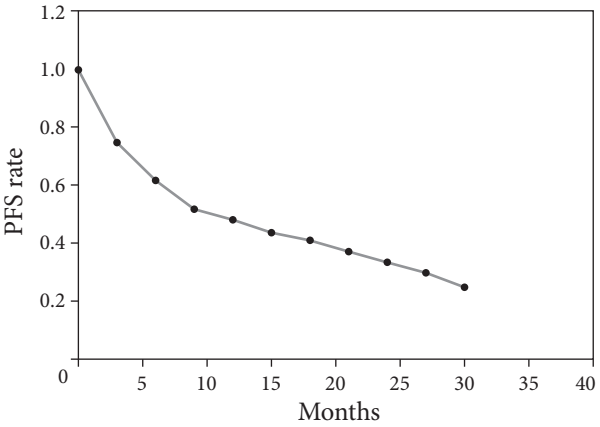

Fig. 2. PFS rate of PTCL-NOS

Table 1. **Patient clinical and demographic characteristics**

Characteristics (n = 31)	Number (%)
Average age at diagnosis (years)	52.87 (range 33—75)
Man	21 (67.74)
Woman	7 (32.25)
Early stage (I—II) by Ann Arbor	13 (41.94)
Late stage (III—IV) by Ann Arbor	18 (58.06)
ECOG <2	17 (54.84)
ECOG ≥2	14 (45.16)
Presence of B-symptoms	19 (61.29)
Absence of B-symptoms	12 (38.71)
Bone marrow involvement	6 (19.35)
Extranodal lesion	11 (35.48)
Increase in serum LDH	7 (22.58)
IPI	
0—1	18 (58.06)
2	2 (6.45)
≥3	11 (35.48)
Ki-67 > 65%	10 (32.25)
Ki-67 < 65%	21 (67.75)
Hb < 120 g/L	7 (22.58)
Platelets < 150 x 10^9/L	3 (9.67)
ANC > 6.5 x 10^9/L	8 (25.8)
Albumin < 35 g/L	5 (16.12)
Total protein < 65 g/L	4 (12.90)
ECOG	
0—1	25 (80.68)
2	4 (12.90)
≥ 3	2 (6.45)

(n = 4) of cases. Ki-67 expression was detected histologically in tumor cells of 32.25% (n = 10) of patients (Table 1).

30 patients were treated with curative intent, while 1 patient received treatment with a palliative goal. The treating physicians' selection of a specific first-line treatment was primarily influenced by factors including the TCL subtype, clinical data, and the patient's age.

Treatment regimens administered to patients were in alignment with the ESMO and NCCN guidelines and anthracycline-based regimens (CHOP; CHOEP — cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone) comprising more than 90%. Initial treatment was performed with CHOP-based regimens in 38.70% (n = 12) of patients, with the addition of etoposide in 58.06% of patients (n = 18). One patient received a combined regimen based on gemcitabine (3.22%). HDCT + auto-SCT was not performed as first-line consolidation treatment for patients in this group. Radiotherapy was performed in 4 patients. The initial plan for first-line therapy was completed in 64.51% of patients.

The responses were assessed according to the response criteria for malignant lymphoma (Cheson 2008, 2014). OR to therapy was 58.06% (n = 18), encompassing both CR and PR. CR was registered in 29.03% of patients, while PR

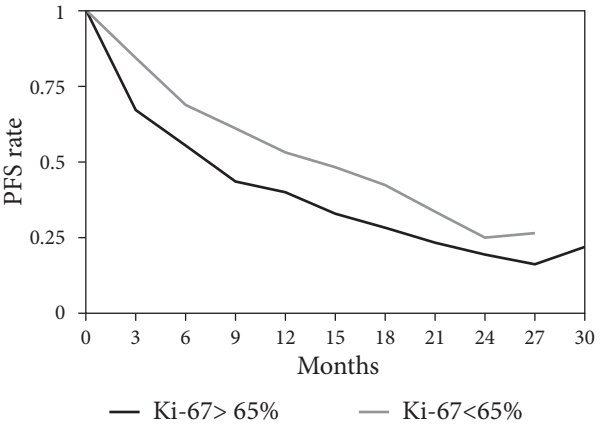

Fig. 3. PFS rate of PTCL-NOS depending on the Ki-67 level

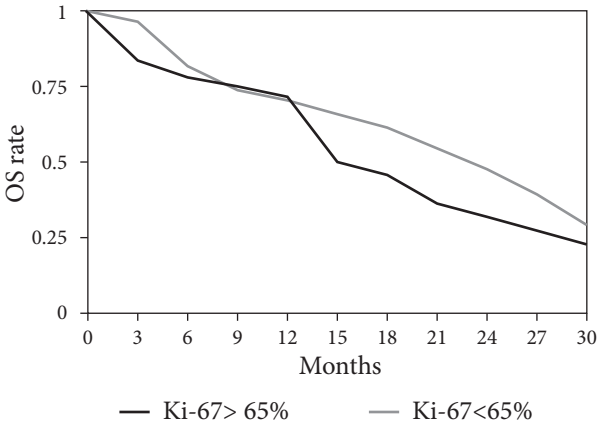

Fig. 4. OS rate of PTCL-NOS depending on the Ki-67 level

was observed in 29.03% of patients, stabilization of disease (SD) was observed in 3.44%, while disease progression occurred in 41.37% of patients. No response could be assessed in 6.45% (n = 2) patients. The best response was observed, on average, 132 days after diagnosis of PTCL, roughly corresponding to the completion of 6 cycles of chemotherapy.

In 32.25% (n = 10) of cases, disease relapse was registered. Of these, 16.12% (n = 5) of patients experienced an early relapse and 16.12% (n = 5) developed a late relapse during the observation period.

The average follow-up period in the cohort was 16.1 months (4.1—47.02 months). 12-month and 24-month survival rates were 75.44% and 50.81%, respectively. The survival rates are presented in Figs. 1 and 2. Currently, 61.29% (n = 19) of patients are alive under observation. 38.70% (n = 12) of patients died of the disease progression. The 12-month and 24-month PFS were 47.68% and 33.1%, respectively. Refractory disease or early relapse was registered in 12 (38.7%) patients, while late relapse occurred in 3 (9.67%) patients after first-line therapy during the follow-up period.

A correlation analysis of the influence of risk factors on the OR to treatment was performed (Table 2). Based on the Gamma coefficient, the expression level of the Ki-67 marker > 65% was established as a risk factor for negative treatment response in patients of this category. A reduction in the rate of complete or partial response to therapy was observed among patients who exhibited Ki-67 expression > 65% compared to patients with lower Ki-67 expression ($p = 0.0017$). Bone marrow lesions ($p = 0.87$), the presence of B-symptoms ($p = 0.8$), and increased LDH level ($p = 0.78$) did not show statistically significant changes.

Table 2. **Correlation analysis of risk factors affecting OR**

Risk factors	Number of observations	Gamma coefficient	*p*
Bone marrow involvement	31	–0.041322	0.870363
Presence of B-symptoms	31	–0.054054	0.809926
Level of LDH (> 450 μmol/L)	31	–0.057471	0.783911
Expression level of Ki-67 (> 65%)	31	–0.579487	0.001777

18-month OS and PFS were analyzed on the basis of these risk factors. 18-month OS was higher in patients with Ki-67 expression < 65% (60.9% *vs.* 45.5%, log-rank test $p = 0.12$) and overall survival (47.3% *vs.* 31.9%, log-rank test $p = 0.21$). Survival rates depending on the level Ki-67 are presented in Figs. 3 and 4. Bone marrow involvement, the presence of B-symptoms, increased LDH levels, and the addition of etoposide did not affect OS.

Discussion

This dataset constitutes the largest Ukrainian population data on PTCL despite being derived from a single-center experience.

The National Cancer Institute provides treatment to people from all over Ukraine. PTCL demonstrates notable epidemiologic variations across geographic regions. According to the International T-Cell Project, the most common types of PTCL are PTCL-NOS, AITL, ALCL (ALK−), ALCL (ALK+), and NK/T-cell lymphoma. In Europe, PTCL-NOS and AITL are more common than other subtypes, as corroborated by several studies. According to the International T-Cell Lymphoma Project [2], PTCL-NOS is equally common in Europe and North America, while the incidence is slightly lower in Asia (34.3%, 34.4%, and 22.4%, respectively). However, in our analysis, PTCL-NOS was observed in the majority of patients and accounted for 33.69% of all cases. The key limitation of the study is the small number of patients, attributed to the rarity of the pathology and the single-center design of the study.

Patient characteristics were comparable to those of patients enrolled in the International T-Cell Lymphoma Project 4, except for a younger mean age (52.87 years *vs.* 62 years) [23]. The shorter life expectancy of the Ukrainian population compared to their European counterparts may account for this. Additionally, fewer III/IV stages of the disease were recorded (58.06% *vs.* 74.0%), while the other indicators remained comparable.

The treatment regimens administered to patients were in alignment with the ESMO and NCCN guidelines, with anthracycline-based regimens (CHOP; CHOEP — cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone) comprising more than 90%. Etoposide was incorporated into the treatment for 58.06% of younger patients (< 65 years). However, no effect on OS was observed with or without the addition of etoposide in the first-line treatment ($p = 0.3$ and $p = 0.15$, respectively).

While the OR rate was in line with the results of the complete study (2016) [24], some data are difficult to compare. Given the rarity of the pathology, most clinical studies examine peripheral T-cell lymphomas as a whole, without subtype specification. OS rates in our study are consistent with the international data presented in the T-Cell Project where the 24-month survival rate was 58% [23].

The International Prognostic Index (IPI) was first introduced in 1993 to identify patients with aggressive NHL who are at increased risk of treatment failure, relapse, and death. The model included age, LDH level, ECOG status, stage, and extranodal involvement. In 2004, an Italian group (Intergruppo Italiano Linfomi) proposed a new prognostic model (modified prognostic index for TCL (mPIT)) based on a retrospective multicenter clinical analysis of 385 patients with PTCL [18] The new model included age, LDH level, ECOG status, stage bone marrow involvement, and expression of Ki-67. According to the methodology of these studies, the statistically significant data in our study was the high expression level of Ki-67 ($p = 0.017$).

To sum up, the studies in patients with PTCL remain difficult to perform, mainly due to the rarity of this disease. Almost all recently completed large PTCL therapeutic trials were designed to support drug approval and conducted in patients with relapsed and refractory disease who were eligible for clinical trials.

The results of the treatment of T-cell lymphomas obtained in a Ukrainian population study

are similar to the results of many other European studies, which remain unsatisfactory. Therefore, further research is required to develop a new strategy for examination and therapy to improve treatment outcomes. An emphasis should be placed on the pragmatic clinical trials comparing the efficacy of the first-line treatment in PTCL patients with both favorable and unfavorable clinical factors. This approach can improve the treatment outcomes.

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ПЕРИФЕРИЧНА Т-КЛІТИННА ЛІМФОМА НЕУТОЧНЕНА:
РЕЗУЛЬТАТИ ДОСЛІДЖЕННЯ В ОДНОМУ ЦЕНТРІ

Стан питання. Найпоширенішим підтипом периферичної Т-клітинної лімфоми (ПТКЛ), який охоплює принаймні 25% ПТКЛ, є неуточнена Т-клітинна лімфома (ПТКЛ-NOS), на яку припадає понад 15% усіх лімфом. У статті наведено результати першого в Україні проспективного дослідження пацієнтів із ПТКЛ-NOS. **Мета:** у Національному інституті раку було проведено проспективне когортне дослідження пацієнтів з нещодавно діагностованою ПТКЛ. Метою дослідження було проаналізувати захворюваність пацієнтів цієї категорії та проведене лікування, оцінити загальну виживаність (ЗВ) та безрецидивну виживаність (ВБП) і визначити фактори, які прогнозують відповідь на лікування. **Пацієнти та методи.** З лютого 2018 року до теперішнього часу проаналізовано дані 31 пацієнта з ПТКЛ-NOS. Т-клітинні лімфоїдні новоутворення діагностовано згідно з класифікацією ВООЗ 2016 року. Схеми лікування відповідали рекомендаціям ESMO та NCCN, і понад 90% з них були на основі антрациклінів (CHOP; CHOEP — циклофосфамід, доксорубіцин, етопозид, вінкристин, преднізон). Початкове лікування було схемою на основі CHOP у 38,70% (n = 12) пацієнтів, із включенням етопозиду до 58,06% пацієнтів (n = 18). **Результати.** Відповідь оцінювали за критеріями відповіді для злоякісної лімфоми (Cheson, 2008, 2014). Загальна відповідь на терапію становила 58,06 % (n = 18), повна відповідь зафіксована у 29,03% пацієнтів і часткова відповідь у 29,03% пацієнтів. Стабілізація захворювання була зафіксована у 3,44% пацієнтів, прогресування захворювання у 41,37% пацієнтів. Показники 12-місячної та 24-місячної ЗВ становили відповідно 75,44 та 50,81%. 12-місячна і 24-місячна ВБП становили 47,68% і 33,1%. Фактором несприятливого прогнозу був рівень експресії Ki-67 > 65 %. **Висновки.** Результати лікування Т-клітинних лімфом, отримані в даному українському популяційному дослідженні, досі залишаються незадовільними. Про це ж свідчать і результати низки інших європейських досліджень. Тому необхідні подальші дослідження для розробки нової стратегії обстеження та терапії для покращення результатів лікування. Наголос слід зробити на прагматичних клінічних випробуваннях для порівняння ефективності лікування першої лінії у пацієнтів із ПТКЛ як зі сприятливими, так і з несприятливими клінічними факторами. Такий підхід може покращити результати лікування.

Ключові слова: Т-клітинна лімфома, Т-клітинна лімфома неуточнена, захворюваність, прогностичний фактор, відповідь на лікування, виживаність.