

UKRAINIAN PROSPECTIVE STUDY IN PATIENTS WITH T-CELL NON-HODGKIN LYMPHOMAS

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Background: T-cell lymphoma (TCL) is a heterogeneous group of lymphoproliferative diseases that account for 10–15% of all non-Hodgkin lymphomas. The *aim* of the study was to analyze the incidence of TCL in Ukraine, distribution according to subtypes and to assess the results of treatment of patients with TCL depending on lymphoma subtype and clinical-and-laboratory risk factors. **Patients and Methods:** Data from 70 patients with TCL were analyzed from February 2018 to May 2021. T-cell lymphoid neoplasms were diagnosed according to the 2016 WHO classification. The patients were divided into 4 groups: 1st (A) — leukemic forms (n = 13) (received SMILE or HyperCVAD +/- auto/alloSCT); 2nd (B) — nodal T-cell lymphomas (n = 43) (CHOP-like regimens); 3rd (C) — cutaneous T-cell lymphomas (n = 9) (PUVA therapy, interferon, and methotrexate); 4th (D) — extranodal T-cell lymphomas (n = 5) (CHOP-like regimens). The response was determined according to the Lugano 2014 criteria. **Results:** According to the study results, 5–6% of all non-Hodgkin lymphoma registered in Ukraine in 2018–2020 were T-cell lymphomas. The most common subtype was peripheral TCL (61%). In the studied groups of TCL patients, the overall response rate was 50% (n = 35). 2-years event-free survival rate was 62.27%. 2-years overall survival rate was 65.76%. 18-month progression-free and overall survival in group B was higher *versus* groups A, C and D. The factors of unfavorable prognosis were bone marrow involvement and the expression of Ki67 > 65% ($p = 0.03$ and $p = 0.006$, respectively). **Conclusions:** Histologic subtype of T-cell non-Hodgkin lymphoma influence the treatment outcome. The best overall response rate, overall survival rate, progression-free survival were in group of patients with nodal T-cell non-Hodgkin lymphomas, the worst — in patients from leukemic group. Poor prognostic factors are bone marrow involvement, and Ki-67 expression > 65%.

Key Words: T-cell lymphoma, incidence, prognostic factor, response to treatment, overall survival, progression-free survival.

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T-cell lymphoma (TCL) is a heterogeneous group of lymphoproliferative diseases that account for 10–15% of all non-Hodgkin lymphomas (NHLs). About 2,400 new cases of NHLs are registered annually in Ukraine, the incidence is 6.6 per 100 thousand of the population and the TCLs accounts for 124 cases per year (5.54% of all cases of NHL) [1].

Patients with TCLs have a poor outcome (5-year overall survival rate (OS) is about 25–30%), in contrast to the progress that has recently been made in Hodgkin lymphoma and B-cell lymphoma. The mortality rates in patients with T-cell lymphomas are higher compared to aggressive B-cell lymphomas.

The revision of the classification of lymphoid neoplasms by the World Health Organization in 2016 is a modern classification of T-cell lymphomas, which includes 27 different subtypes [2]. There are two broad categories of T-cell lymphomas according to their clinical course: aggressive and indolent. The most common T-cell lymphomas are peripheral T-cell lymphoma (PTCL), unspecified, angioimmunoblastic T-cell lymphoma, and anaplastic lymphoma kinase (ALK)nega-

tive anaplastic large cell lymphoma, which account for about 60% of all cases of T-cell lymphomas. Patients with anaplastic large cell lymphomas have better clinical outcome in comparison with other subtypes of TCL. The risk factors for patients with TCLs are still being studied. There are a few large retrospective and prospective studies organized by the International T-cell Project, British Columbia Cancer Agency and “Intergruppo Italiano Linfomi” [3, 4]. Nevertheless, there are still a lot of debates regarding their clinical implementation.

The results of Ukrainian retrospective study of PTCLs confirmed the influence to the survival of the International Prognostic indices (IPI, modified Prognostic Index for T-cell lymphoma — modified PIT, International T-cell Lymphoma Project) [5].

Taking into account poor results with conventional chemotherapy, hematopoietic cell transplantation was suggested to TCLs patients. Worldwide retrospective studies showed that autologous hematopoietic stem cell transplantation (autoSCT) as consolidation can provide long-term improvement in survival in high-risk patients in a first complete or partial response, and allogeneic SCT (alloSCT) can lead to long-term disease control for relapses and refractory patients [6]. The results of the treatment could be also improved today due to chemoimmunotherapy, which is the most important therapy breakthrough for other lymphoma types in the past decade [7].

The aim of the study was to analyze the incidence of TCL in Ukraine, distribution according to subtypes and to assess the results of treatment of patients with

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Abbreviators used: ALK — anaplastic lymphoma kinase; auto-SCT — autologous hematopoietic stem cell transplantation; allo-SCT — allogeneic hematopoietic stem cell transplantation; ECOG — Eastern Cooperative Oncology Group; IPI — International Prognostic Index; LDH — lactate dehydrogenase; PFS — progression-free survival; PIT — Prognostic Index for T-cell lymphoma; PTCL — peripheral T-cell lymphoma; ORR — overall response rate; OS — overall survival rate; TCL — T-cell non-Hodgkin lymphoma.

TCL depending on lymphoma subtype and clinical laboratory risk factors.

MATERIALS AND METHODS

Patients with primary diagnosed TCLs who underwent treatment at the Department of Oncohematology, National Cancer Institute of Ukraine from February 2018 until May 2021 were included in the study. The pathology diagnosis was made according to the revision of the WHO classification of lymphoid neoplasms (2016) [2]. The treatment response was assessed using computed tomography or positron emission tomography/computed tomography and was evaluated using Lugano 2014 criteria [8].

The patients were divided into 4 groups depending on the subtype of TCL:

1st group (A) — leukemic forms (n = 13):

- T-cell lymphoblastic lymphoma 20% (n = 13, 18.57%);

2nd group (B) — nodal T-cell lymphomas (n = 43):

- anaplastic large-cell lymphoma, ALK⁺ (n = 8, 11.42%),
- anaplastic large-cell lymphoma, ALK⁻ (n = 8, 11.42%),
- PTCL, NOS (n = 14, 20%),
- angioimmunoblastic T-cell lymphoma 19% (n = 13, 18.57%)

3^d group (C) — cutaneous T-cell lymphomas (n = 9):

- primary cutaneous anaplastic large cell lymphoma (n = 1, 1.4%),
- primary cutaneous CD4⁺ small/medium T-cell lymphoproliferative disorder 1% (n = 1, 1.4%),
- mycosis fungoides/Sézary syndrome (n = 6, 8.57%),
- primary cutaneous $\gamma\delta$ T-cell lymphoma 1% (n = 1, 1.4%).

4th group (D) — extranodal T-cells lymphoma (n = 5):

- enteropathy-associated T-cell lymphoma (n = 1, 1.4%);
- hepatosplenic T-cell lymphoma (n = 1, 1.4%);
- extranodal NK/T-cell lymphoma, nasal type (n = 3, 4.28%).

Factors such as age, Ann Arbor disease stage, lactate dehydrogenase (LDH) level, Eastern Cooperative Oncology Group Performance status (ECOG), extranodal involvements, bone marrow involvement, albumin level, platelets, hemoglobin, total protein levels, Ki67 expression, and B-symptoms were evaluated as prognostic factors.

All patients received standard treatment of TCLs according to histologic subtype: CHOP-like regimens (group-B and D), SMILE or HyperCVAD with or without auto/alloSCT (group-A), metotrexat, interferon, PUVA therapy (group-C). 8% (n = 6) of patients from group A received SCT as a consolidation of the first line treatment: 2 patients received autoSCT and 4 patients received alloSCT [6, 9–11]/

Progression-free survival (PFS) was defined as the time from the diagnosis to disease progression or relapse, or to death (from any cause). OS was defined

as the time from the diagnosis to death from any cause. Survival curves were calculated by the method of Kaplan and Meier. The difference was considered statistically significant at $p < 0.05$. Statistica software version 10.0 was used for data analysis.

RESULTS

The clinico-pathological data of 70 patients with primary diagnosed TCLs are summarized in the Table.

Overall response rate (ORR) was 50% (35 patients achieved complete or partial remission). 32.85% (n = 23) of patients had relapse/refractory disease. 22.85% (n = 16) of patients had an early relapse and 10% (n = 7) — late relapse (follow-up 39 months). 2-years OS rate was 65.76% (Fig. 1). 74.28% of patients are under follow-up now. 27.14% (n = 19) of patients died. 18-month OS of group B (74.81%) was higher compared to groups A, C and D (27.32%, 47.23% and 30.0%, respectively, $p < 0.05$) (Fig. 2). It also appeared that 2-years OS rate depended on treatment response (achievement of CR/PR) to the 1st line treatment. This rate was 71.51% in patients who responded to the first line treatment compared to 51.56% ($p = 0.05$) in patients with stable or progressive disease (Fig. 3). 2-years PFS was 62.27% (Fig. 4). The highest 18-month PFS rate was also observed in patients from group B with nodal TCLs (74.81%) compared to patients from groups A, C and D (Fig. 5).

We found that bone marrow involvement and Ki67 expression $> 65\%$ were risk factors for all groups of patients. The ORR in patients with bone marrow involvement was worse compared to patients without bone marrow involvement ($p = 0.03$). Similarly, the ORR was worse in patients with expression of Ki67 $> 65\%$ in comparison with patients with lower level expres-

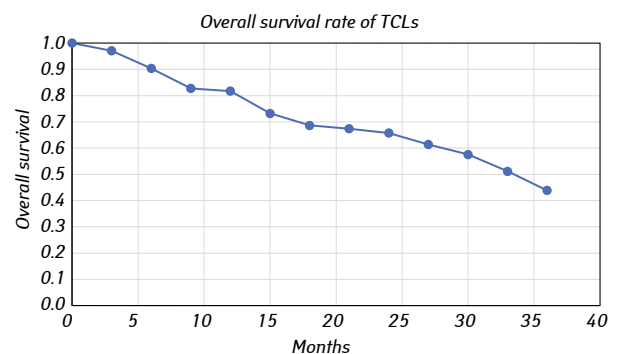


Fig. 1. OS of TCLs patients

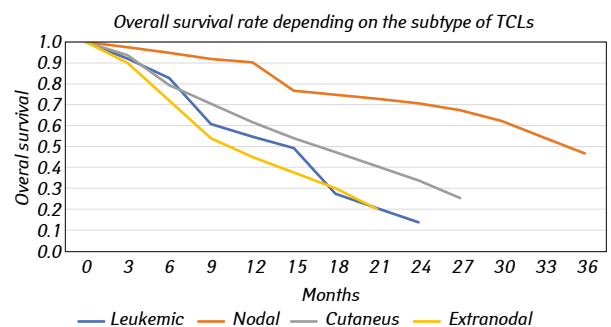


Fig. 2. OS depending on the subtype of TCLs

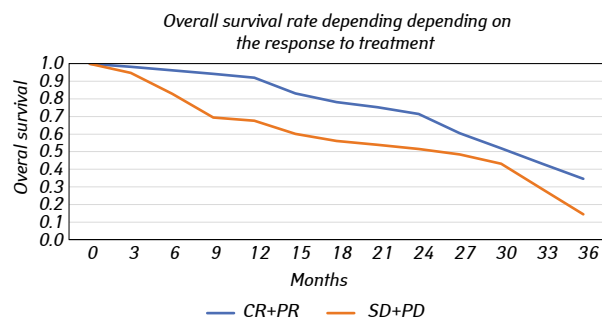


Fig. 3. OS depending on the response to treatment

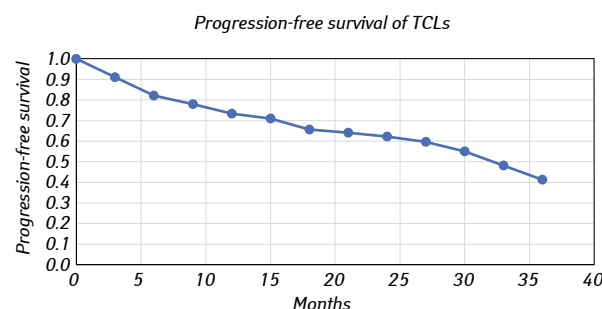


Fig. 4. PFS of TCLs patients

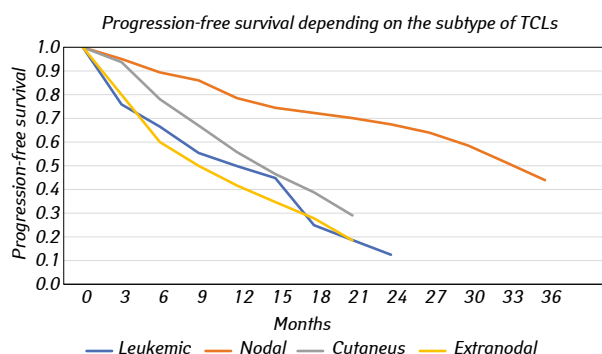


Fig. 5. PFS depending on the subtype of TCLs

sion in the tumor cells ($p = 0.006$). Levels of albumin < 35 g/l ($p = 0.08$), total protein level < 65 g/l ($p = 0.06$) and presence of extranodal lesion ($p = 0.06$) showed trend toward poor response rate. The levels of hemoglobin, white blood cells, thrombocytes, granulocytes, lymphocytes, monocytes, erythrocyte sedimentation rate and beta-2 microglobulin have not demonstrated any significant influence.

DISCUSSION

TCLs comprise a heterogeneous group of neoplasms, which accounts for 10–15% of lymphoid malignancies in Western countries, while this proportion is higher in Eastern countries for epidemiological and genetic reasons. TCLs have been long time an orphan pathology due to their relatively low frequency, difficulty in analyzing them, and gloomy prognosis. About 2,400 new cases of NHL are registered annually in Ukraine, 124 cases of TCLs per year. Thus, T-cell lymphomas account 5.54% of NHLs in Ukraine that is less than in other counties possibly due to difficulties in diagnostic and/or imperfect functioning of National Cancer Register.

Table. Clinical and laboratory characteristics of patients ($n = 71$)

Characteristics	n (%)
Median age at diagnosis	47.5 (range, 20–72)
Male	45 (63.38%)
Female	25 (35.72%)
Early stages (I–II)	23 (32.86%)
Advanced stages (III–IV)	47 (67.14%)
ECOG < 2	37 (52.86%)
ECOG ≥ 2	33 (47.14%)
Presence of B-symptoms	26 (37.14%)
Absence of B-symptoms	44 (62.86%)
Bone marrow involvement	15 (21%)
Extranodal lesion	32 (45.71%)
Evaluated serum LDH	11 (15.71%)
Ki-67 $> 65\%$	21 (30%)
Ki-67 $< 65\%$	49 (70%)
Hemoglobin < 12 g/dL	14 (20%)
Platelets $< 150 \cdot 10^3/\text{ml}$	7 (10%)
Absolute neutrophil count $> 6.5 \cdot 10^3/\text{ml}$	18 (25%)
Albumin < 35 g/l	8 (11.42%)
Total protein < 65 g/l	7 (10%)
Complete remission	25 (35%)
Partial remission	10 (14%)
Stable disease	5 (7%)
Progressive disease	24 (34%)
Auto-SCT	2 (3%)
Allo-SCT	4 (5.6%)

This study is the first prospective study in Ukraine based on the analysis of patients with all variants of T-cell lymphomas that were observed and treated at the National Cancer Institute since 2018 to May 2021. Previously in Ukraine, only one retrospective study of PTCLs was conducted in which prognostic factors were assessed [5].

In the world, TCLs tend to affect people aged 60 and over and is slightly more common in men than in women. Our study also follows this trend, but the average age range was younger (median age was 47.5 years) compared with data from International T-cell lymphoma project (2008). This could be due to the heterogeneity of our study group.

The analysis of the cohort showed that the 2-year OS was 65.76% (Fig. 1). Currently, 74.28% ($n = 52$) of patients are alive and are under observation. 27.14% ($n = 19$) of patients died from disease progression.

According to the analyzed data, the 18-months OS for group patients with nodal T-cell lymphomas was higher than in other groups and achieved 74.81%, comparing to disseminated/leukemic TCL — 27.32%, cutaneous (CTCL) — 47.23% and primarily extranodal types of TCL — 30.0%, respectively ($p < 0.09$).

According to the analyzed data, the 18-months OS for group patients with nodal T-cell lymphomas in our cohort was significantly higher than in other groups and achieved 74.81%. In published data of Horwitz *et al.* [12] and Savage *et al.* [13], 5-year OS rates in T-cell lymphoma entities which contains nodal category ranged from 32% in patients with AITL and PTCL-NOS, 49% in ALCL, ALC- to 23–68% in patients with ALCL, ALC+ depending on IPI score. Discordance of our results may be due to different times of survival assessment in relation to the end of therapy.

In our study, the 18-months OS in other group of disseminated/leukemic TCL reaches 27.32%. Taken into account a quite early assessment of OS in our study and the evolutionary improvement of OS in study [14] — the data are comparable. Ac-

cording to the data based on population based Osaka Cancer Registry, Fuji *et al.* [14] reported the following 3-year OS rates in T-cell leukemia-lymphoma patients: 12.0% in 1977–1999, 12.4% in 2000–2008, and 17.5% in 2009–2014.

According to the review by Rubio-Gonzalez *et al.* [15], 5-year survival rates of different subtypes of cutaneous TCL varied from less than 20% in Sezary syndrome to more than 90% in primary cutaneous CD30⁺ lymphoproliferative disorders, such as lymphomatoid papulosis or primary cutaneous anaplastic large cell lymphoma. Our analysis showed 47.2% and 38.7% OS and PFS rates, respectively, for this category of patients. The lack of observed cases of cutaneous TCL in our study makes it difficult to stratify them into groups for a reasonable comparison with the existing literature data. Similarly, a small number of primarily extranodal lymphomas were included in our study.

The IPI was first introduced in 1993 to identify patients with aggressive NHL who are at increased risk of treatment failure, relapse, and death. It was mostly based on B-NHL rather than T-NHL, especially diffuse large B-cell lymphomas, but its ability to stratify PTCL patients emerged in later years. In particular, the International Lymphoma Study Group showed that overall and disease-free survival varied significantly between patients with low and high IPI. Unfortunately, our analysis did not reveal reliable risk factors on the IPI scale in contrast to the PTCL. In 2004, an Italian group (Intergruppo Italiano Linfomi) proposed a new predictive model based on a retrospective multicenter clinical analysis of 385 PTCL patients. The new model included bone marrow damage, age, performance, LDH and expression of Ki 67% for modified-PIT. When these four variables were combined into four groups, PIT was able to identify subgroups of patients with different outcomes. According to this group's methodology, the statistically significant data we found in our study were bone marrow involvement and Ki-67 expression ($p = 0.03$ and $p = 0.006$, respectively).

The treatment strategy of analyzed patients corresponded to European Society for Medical Oncology and National Comprehensive Cancer Network recommendations. Autologous and allo-SCT as a consolidation of the 1st line treatment has been done only for 6 patients. There are several explanations for this — lack of hematological centers where transplant could be performed, lack of financial support and mixed data about superiority of transplant in the 1st line setting.

Due to the limitations mentioned above, there may be some bias in the selection of patients.

This study is a first prospective study based on real-life data of TCLs incidence, subtype distribution, analysis of clinical and laboratory factors. The most common subtypes in study group were PTCL (61%). Incidence of cutaneous TCLs and leukemic TCLs was the same (30%). The histologic subtype of TCLs influence the treatment outcome. The best ORR, OS, PFS were in group of patients with nodal TCLs,

the worst — in patients from leukemic group. Poor prognostic factors such as bone marrow involvement, Ki-67 expression > 65% were identified.

Overall, the obtained results are promising and could reveal geographical distribution of this rare lymphoma subtype. Therefore, we need more new data and patients with longer follow up to be included in further prospective studies.

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УКРАЇНСЬКЕ ПРОСПЕКТИВНЕ ДОСЛІДЖЕННЯ У ПАЦІЄНТІВ З Т-КЛІТИННИМИ НЕХОДЖКІНСЬКИМИ ЛІМФОМАМИ

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Стан питання: Т-клітинні неходжкінські лімфоми (ТКЛ) є рідкісним підтипом неходжкінських лімфом (НХЛ), який становить 10–15% від усіх НХЛ та уявляє собою гетерогенну групу. **Мета:** Проаналізувати частоту випадків ТКЛ в Україні, розподіл за підтипами та оцінити результати лікування залежно від підтипу лімфоми та клініко-лабораторних факторів ризику. **Хворі та методи:** З лютого 2018 р. до травня 2021 р. проаналізовано дані 70 пацієнтів з первинними ТКЛ. Т-клітинні лімфоїдні новоутворення діагностували згідно з класифікацією ВООЗ 2016 р. Пацієнтів було розді-

лено на 4 групи: 1-ша (А) — лейкоемічні форми (n=13) (отримали SMILE або HyperCVAD +/- auto/alloSCT); 2-га (В) — нодальні Т-клітинні лімфоми (n=43) (СНОР-подібні схеми); 3-тя (С) — шкірні Т-клітинні лімфоми (n=9) (ПУВА-терапія, інтерферон та метотрексат); 4-та (D) — екстранодальні Т-клітинні лімфоми (n=5) (СНОР-подібні схеми). Відповідь визначалася відповідно до критеріїв Лугано 2014 р.

Результати: Загальна відповідь на терапію становила 50% (n = 35). 2-річна виживаність без прогресування становила 62,27%. Загальна 2-річна виживаність — 65,76%. 18-місячна виживаність без прогресування і загальна виживаність пацієнтів у групі В були вищими в порівнянні з групами А, С і D. Факторами несприятливого прогнозу були ураження кісткового мозку та експресія Ki-67 > 65% (p = 0,03 і p = 0,006 відповідно). **Висновки:** Це дослідження є першим проспективним дослідженням, заснованим на реальних даних. За результатами дослідження 5–6% усіх неходжкінських лімфом, зареєстрованих в Україні у 2018–2020 рр., становили ТКЛ. Найпоширенішим підтипом була периферична ТКЛ (61%). Найкращими показниками загальної відповіді, загальна виживаність та виживаність без прогресування були у групі пацієнтів з нодальною ТКЛ, найгіршими — у групі з лейкоемічними формами. Факторами несприятливого прогнозу були ураження кісткового мозку, експресія Ki-67 > 65 г/л. Потрібні більш перспективні дослідження, щоб поглибити знання про ТКЛ та покращити результат лікування пацієнтів.

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