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COMPARATIVE EFFECTIVENESS OF CHRONIC LYMPHOCYTIC LEUKEMIA THERAPY: THE EXPERIENCE OF THE ALMATY CLINIC

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ABSTRACT

Relevance: *Clinical and genetic heterogeneity of chronic lymphocytic leukemia (CLL) influences therapy choices and outcomes. Cytogenetic and biological markers are crucial for disease staging, therapeutic decision-making, and prognosis. Real-world data comparing chemo-, immunotherapy, and targeted regimens are essential for refining patient management strategies.*

The study aimed to *evaluate the comparative effectiveness of chemotherapy, immunotherapy, and targeted therapy in patients with chronic lymphocytic leukemia, taking into account cytogenetic parameters, age, and stage of the disease.*

Methods: *This retrospective cross-sectional study included 114 CLL patients treated at the City Clinical Hospital No. 7 (Almaty, Kazakhstan) between 2001 and 2024. Patients received either chemoimmunotherapy (FC, FCR, CR, COP, chlorambucil) or targeted regimens (BTK/PI3K inhibitors, anti-CD20 antibodies). Primary endpoints were progression-free survival (PFS) and overall response rate (ORR).*

Results: *Distribution of patients with CLL by disease stage: stage B – 59.6% (n = 68), stage A – 25.4% (n = 29), stage C – 9.6% (n = 11), stage not established – 5.4% of cases (n = 6). According to cytogenetic testing (n = 63), the most frequent abnormality was del(13q14) (33%, n = 21), either isolated or combined with other aberrations. Del(11q22.3) was detected in 17.5% (n = 11), trisomy 12 in 11% (n = 7), and TP53 mutations in 6.3% (n = 4). Among treatment regimens, the highest median PFS was observed with FC (46.6 months), CR (45 months), and ibrutinib (32.1 months). In patients receiving ibrutinib in later therapy lines (n=10), comparable complete response rates and disease stabilization were achieved.*

Conclusion: *In real clinical practice, targeted therapy demonstrates superior PFS and better tolerability in high-risk patients and in those pretreated with one or more prior lines of therapy, whereas chemotherapy remains a viable option for selected subgroups (younger patients, IGHV-mutated, favorable cytogenetics). Treatment personalization based on genetic profiling improves outcomes in CLL. Expanding access to comprehensive genetic testing is critical to further enhance prognosis and survival.*

Keywords: *chronic lymphocytic leukemia; comparative effectiveness; targeted therapy; chemoimmunotherapy; cytogenetics.*

Introduction: Chronic lymphocytic leukemia (CLL) is one of the most common types of leukemia in adults and represents a major public health problem [1]. The global age-standardized incidence rate (ASIR) is 4.7 cases per 100,000 people, resulting in more than 103,400 cases annually. By the end of 2025, 23,690 new cases of CLL are expected, with a projected increasing trend until 2030 [2, 3]. CLL incidence varies significantly by geographic location, gender, age, and ethnicity, with a higher prevalence in men and older adults. In East Asians, Asian Indians, and Native Americans, age-adjusted CLL incidence is 5-10 times lower than in people of predominantly European descent [4]. However, gender differences persist regardless of ethnicity [3]. Several studies have reported a growing incidence of CLL in developing countries. At that, overall survival (OS), treatment strategies, and effectiveness largely depend on socioeconomic conditions and access to quality medical care, including diagnostic methods and new medications [4].

The clinical course of CLL can be quite heterogeneous, ranging from an indolent disease requiring no treatment to an aggressive disease refractory to several lines of therapy. The vast majority of patients may be asymptomatic at the time of diagnosis [2, 3, 5]. However, in some patients, the disease progresses aggressively, with multiple relapses, and requires aggressive treatment.

The prognosis of CLL varies greatly depending on the stage of the disease, age, functional status of comorbidities, and many other factors, and remains serious for the majority of patients. Currently, risk group stratification is performed using the International Prognostic Index (CLL-IPI), which includes, in addition to age (>65 years), Rai staging (I-IV), determination of the level of ?-2 microglobulin (>3.5 mg/l), also genetic markers: the presence or absence of mutations in the genes of immunoglobulin heavy chains (*IGHV), TP53* and the del17p deletion determined by fluorescence in situ hybridization (FISH) [6]. These changes, independently of each other, can affect overall survival. Thus, patients with CLL and *TP53 dysfunction* or a complex karyotype belong to a very high-risk group and have a shorter survival [7]. Deletion of the short arm of chromosome 17 (del(17p)), which in-

cludes the *TP53* tumor suppressor gene locus, can often be mutated and is associated with both an unfavorable course of CLL and refractoriness to chemoimmunotherapy [8]. Based on the *IGHV mutation status,* a distinction is made between more mature, genetically stable CLL and more immature, genetically unstable CLL. Patients with unmutated *IGHV genes* have a more aggressive course of the disease and are more likely to develop adverse genetic events than patients with mutated *IGHV* [9].

Historically, CLL therapy has undergone significant changes. Beginning with the use of the alkylating agent chlorambucil or its combination with glucocorticoids in the 1970s, later combination regimens (CHOP, CVP), and the combined use of fludarabine and cyclophosphamide (FC regimen) in first-line therapy, to the recent use of targeted immunotherapy with the chimeric monoclonal antibody to CD20, rituximab, including in combination with fludarabine, cyclophosphamide (FCR), and other targeted and immunotherapeutic agents.

The introduction of new targeted and immune drugs into practice, such as Bruton kinase inhibitors, venetoclax (a selective inhibitor of the anti-apoptotic B-cell lymphoma (BCL-2) protein), ofatumumab, obinutuzumab, idelalisib, and duvelisib, among others, has significantly increased the survival of patients with CLL. However, in some cases, treatment remains ineffective, requiring multiple lines of therapy and a personalized approach with multiparametric risk assessment.

Due to the importance of molecular genetic markers of CLL in stratifying risk groups, and also considering the variability of data on disease course and the use of various treatment approaches and regimens, the authors assessed the effectiveness of CLL therapy in patients in Almaty.

The study aimed to evaluate the comparative effectiveness of chemotherapy, immunotherapy, and targeted therapy in patients with chronic lymphocytic leukemia, taking into account cytogenetic parameters, age, and the disease stage.

Materials and methods: A retrospective analysis of data from 114 patients diagnosed with CLL who received treatment at the City Clinical Hospital No. 7 (Almaty, Kazakhstan) from 2001 to 2023 inclusive was conducted.

Diagnosis and monitoring of CLL were performed in accordance with the recommendations of the 2018 International Workshop on Chronic Lymphocytic Leukemia (IWCLL).

The research methods for prognosis and monitoring of CLL included: complete blood count at the time of diagnosis and during the disease dynamics; morphological and cytological examination of bone marrow at diagnosis; immunophenotyping of atypical B cells of peripheral blood to confirm the diagnosis (n = 112 patients, normal B lymphocytes were not taken into account in the analysis, the panel included CD19, CD5, CD20, CD23, κ and λ to confirm the diagnosis); standard cytogenetic study and FISH on interphase nuclei of peripheral blood lymphocytes n = 63 (55.2%) using locus-specific probes for CLL from Abbot (Chicago, IL, USA).

Statistical processing of data was carried out using MS Excel tables.

The distribution of quantitative variables was analyzed using the Shapiro-Wilk test. After assessing compliance with the normal distribution law, the statistical analysis method was selected. In the normal distribution of quantitative variables, the central tendency and dispersion of features were described using the mean (M) and the standard deviation (SD). When the distribution of quantitative characteristics differed from normal, the description was carried out using the median (Me). Confidence intervals were calculated for a probability of p = 95%. Differences between compared parameters were considered statistically significant at $p < 0.005$.

When comparing patient groups by categorical characteristics, the $\chi 2$ test with Yates' correction was used. The statistical significance of differences between two related groups was calculated using Student's t-test. For two unrelated groups, the Student's t-test or the nonparametric Mann-Whitney test was used. At $p < 0.005$, the alternative hypothesis of group differences was accepted, and paired comparisons were performed using the Mann-Whitney test.

Results: The structure of a cohort of patients with CLL (the total number of those registered for dispensary care, newly diagnosed cases, and the number of deaths) was studied for the period from 2001 to 2023 in Almaty. The study included 114 patients with CLL; staging was established based on the 1981 Binet classification [10]. The age of patients ranged from 38 to 92 years, with a median of 68 years, which is consistent with the data from the world literature. The proportion of patients over 65 years was 62% (n = 71). Women predominated among the patients (57%, n = 65); men accounted for 43% (n = 49).

Distribution of patients by stages. Patients were divided according to CLL stages. as follows: stage B was the most frequently diagnosed stage in 59.6% (n = 68), stage A occurred in 25.4% (n = 29), stage C – in 9.6% of patients (n = 11), and some had no data on the stage of the disease (Table 1). It should be noted that most cases of CLL were asymptomatic at the time of diagnosis.

Cytogenetic testing was performed on 63 patients. Analysis of cytogenetic changes revealed that the most common alteration (33%, n = 21) was deletion of 13q14, either isolated or in combination with other abnormalities. Del 11q22.3 was detected in 18% of cases (n = 11), trisomy 12 in 11% (n = 7), and *TP53* mutations in 6.3% of cases (n = 4) (Figure 1).

The limitations of cytogenetic research data are primarily due to the lack of access to FISH research for adult patients in the Republic of Kazakhstan until 2017-2018.

Table 1 – Distribution of patients by CLL stages (Binet J, 1981) [10]

Stage	Number of patients, n	Percentage of patients, %
Stage A	29	25.4
Stage B	68	59.6
Stage C	11	9.6
No data	6	5.4

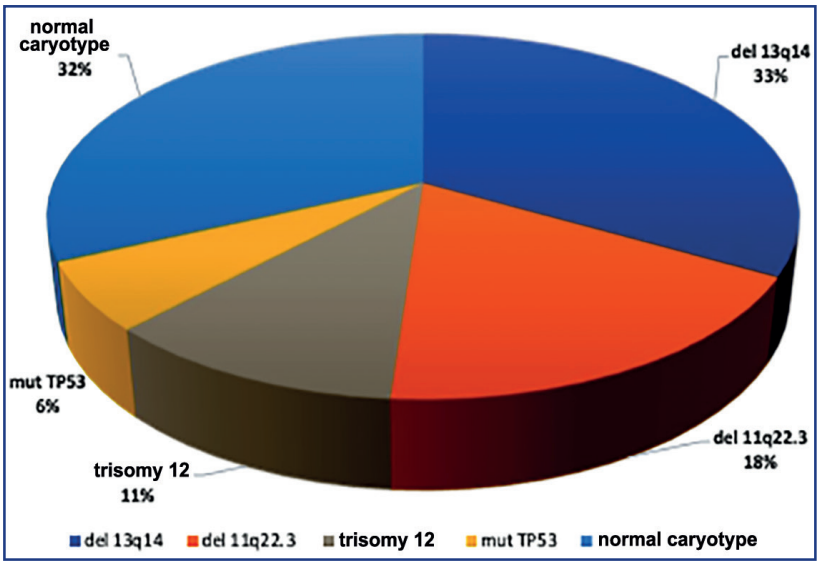

Figure 1 – Structure of cytogenetic aberrations in patients with CLL (n = 63)

Therapy. When choosing treatment tactics, in 32 cases (41.2%), patients did not receive initial active treatment due to a lack of indications for therapy initiation according to the protocols for managing patients with CLL. Chemo- and chemoimmunotherapy (FC, FCR, CR, COP, chlorambucil) was used in the majority of patients. Targeted therapy with the Bruton tyrosine kinase inhibitor ibrutinib was received by 14 patients (12.8%), including 4 patients with the *TP53* mutation. In 10 patients without the *TP53* mutation, ibrutinib was used after one or more previous lines of chemotherapy. As a previous therapy, patients received treatment in the form of combination regimens using fludarabine, chlorambucil, cyclophosphamide, and rituximab (FC, FCR, CR, COP) (Table 3).

Table 3 – Treatment of patients with CLL (n=114)

Treatment (with treatment regimen)	Number of patients, n	Percentage of patients, %
FC	17	14.9
Ibrutinib	14	12.8
With R	13	11.4
FCR	12	10,5
Chlorambucil	10	8.7
COP	2	1.75
No therapy at the time of diagnosis	47	41.2

Notes to Tables 3 and 4: FC – fludarabine, cyclophosphamide; CR – cyclophosphamide, rituximab; FCR – fludarabine, cyclophosphamide, rituximab; COP – cyclophosphamide, vincristine + prednisolone.

Response to therapy was recorded in all groups. Complete and partial response rates, as well as median progression-free survival (PFS), are presented in Table 4.

When comparing the treatment regimens, the highest median PFS was observed with the FC regimen (46.6 months), with sustained remission achieved in 55.5% of patients in this group. The CR rate was higher in the group of patients treated with the SOR regimen (the difference was not significant), with a PFS of 31.6 months. Patients receiving ibrutinib in subsequent lines of therapy achieved comparable rates of complete responses and disease stabilization.

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Table 4 – Response to therapy depending on the treatment regimen for CLL

Treatment regimen	Number of patients, n	Full answer, % patients	Partial response, % of patients	Disease progression, % of pa-tients	Medana progression-free survival (months)
FCR	12	78.2	15.1	14.4	31.4
FC	17	89.1	9	0.5	46.6
COP	2	91	6	0.0	31.6
CP	13	89	8	1.8	45.2
Ibrutinib	14	88	7	0.0	32.1

Discussion: The obtained results demonstrate that the structure of the Almaty cohort of patients with CLL is comparable with international data. The median age, stage distribution, and frequency of major cytogenetic changes are generally consistent with published epidemiological data [1-4].

The 13q14 deletion, being the most common anomaly, was associated with a favorable prognosis, consistent with the literature. Meanwhile, *TP53 mutations* and 17p deletion, not fully identified due to diagnostic limitations, remain key prognostic markers guiding treatment decisions.

Ibrutinib treatment has demonstrated efficacy even in patients with poor prognoses and multiple prior treatment lines. This confirms the high clinical value of targeted therapy in high-risk groups.

The use of traditional chemotherapy regimens has also shown an effect, especially in young people, which allows the use of traditional treatment regimens and careful stratification of patients.

Limitations of the study include its retrospective design, incomplete coverage of cytogenetic testing (due to limited availability of FISH and modern molecular technologies), and a small sample size of patients receiving targeted therapy.

Take-aways:

The structure of the cohort of patients with CLL in Almaty corresponds to international data on age and distribution of disease stages.

Cytogenetic alterations, especially del (13q14), del (11q22.3), TP53 mutations, and trisomy 12, play a key role in prognosticating the course of CLL.

Ibrutinib demonstrated efficacy in a cohort of patients with a poor prognosis and late lines of therapy, confirming its important role in modern CLL treatment strategies.

Expanded access to genetic research and the introduction of next-generation sequencing technologies are needed to stratify risk and optimally select treatments.

Further research in the field of CLL, including multicenter studies, particularly in asymptomatic, progressing, or relapsing patients as our own data accumulate, shall improve the quality of treatment and optimize approaches to patient management, including in conditions of limited access to modern treatment methods.

Conclusion: Modern tactics for managing patients with CLL involve a comprehensive assessment of the patient's condition and biological markers to stratify risk groups, determine treatment strategies, and assess prognosis. An important role is played by independent indicators, such as the patient's age, general physical condition, comorbidities, the presence of *TP53* and *IGHV* mutations, and the level of ?-2 microglobulin. Cytogenetic changes play a key role in prognosticating the course of CLL. Deletion of 13q14, the most common aberration, is associated with a relatively favorable prognosis. The presence of *TP53* mutations and the deletion of 17p (del17p) indicates an unfavorable prognosis and resistance to standard immune chemotherapy [7-9]. In these cases, the effectiveness of chemotherapy and CD20 monoclonal antibodies is reduced. The presence of isolated trisomy 12 is considered an "intermediate" prognosis, while the combination of trisomy 12 with deletion 11q22.3 is associated with a more aggressive course of the disease [7]. The data obtained by the authors correlate with data from the world literature regarding the age structure; discrepancies in the sex distribution may depend on the overall life expectancy in our country. The diagnostic capabilities, availability of necessary reagents, method resolution, and accessibility of genetic and biological diagnostics limit the spectrum of cytogenetic changes outlined in the study. Widespread implementation of genetic diagnostic methods is necessary for the purpose of stratification and the selection of treatment tactics, as well as the introduction of new drugs to expand therapeutic options, improve survival, and reduce the side effects of therapy.

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АҢДАТПА

СОЗЫЛМАЛЫ ЛИМФОЛЕЙКОЗДЫ ЕМДЕУДІҢ САЛЫСТЫРМАЛЫ ТИІМДІЛІГІ: АЛМАТЫ КЛИНИКАСЫНЫҢ ТӘЖІРИБЕСІ

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Өзектілігі: *Созылмалы лимфоцитарлық лейкоздың (CLL) клиникалық және генетикалық гетерогенділігі терапия таңдауы мен нәтижелеріне әсер етеді. Цитогенетикалық және биологиялық маркерлер аурудың сатылануында, емдеу тактикасын айқындауда және болжам жасауда маңызды рөл атқарады. Нақты клиникалық тәжірибе деректерін талдау, химио-, иммунотерапия және нысаналы терапия режимдерінің нәтижелерін салыстыру СЛЛ бар науқастарды емдеудің оңтайлы алгоритмдерін қалыптастыруға мүмкіндік береді.*

Зерттеудің мақсаты *– цитогенетикалық параметрлерді, аурудың жасын және сатысын ескере отырып, созылмалы лимфолейкозбен ауыратын науқастарда химиотерапияның, иммунотерапияның және мақсатты терапияның салыстырмалы тиімділігін бағалау болды.*

Әдістері: *Зерттеуге 2001-2024 жылдар аралығында №7 қалалық клиникалық ауруханада (Алматы, Қазақстан) емделген 114 CLL пациентінің медициналық деректеріне ретроспективті талдау енгізілді. Науқастар екі топқа бөлінді: химио-иммунотерапия тобы (FC, FCR, CR, COP, хлорамбуцил режимдері), нысаналы терапия тобы (BTK/PI3K тежегіштері, анти-CD20 препараттары). Негізгі нүктелер: удемесіз өмір сүру ұзақтығы (ҮӨҰ) және жалпы жауап жиілігі (ЖЖЖ).*

Нәтижелері: *СЛЛ-мен ауыратын науқастарды ауру сатысы бойынша бөлу: В сатысы – 59,6% (n=68), А сатысы – 25,4% (n=29), С сатысы – 9,6% (n=11), анықталмаған сатысы – 5,4% жағдайлар (n=6). Цитогенетикалық зерттеуге сәйкес (n=63), ең жиі аберрация del13q14 (33%, n=21), оқшауланған немесе басқа ауытқулармен біріктірілген. Del11q22.3 – 17,5% (n=11), 12-хромосоманың трисомиясы – 11% (n=7), TP53 мутациялары – 6,3% (n=4) науқастарда анықталды. Ем нәтижелері бойынша ең жоғары медианалық ҮӨҰ FC (46,6 ай), CR (45 ай) және ибрутиниб (32,1 ай) режимдерінде байқалды. Кейінгі емдеу желілерінде ибрутиниб қабылдаған науқастарда (n=10) толық жауап жиілігі мен аурудың тұрақтану көрсеткіштері салыстырмалы деңгейде болды.*

Қорытынды: *Нақты клиникалық тәжірибеде нысаналы терапия жоғары қауіп тобындағы науқастарда және бұрын бір немесе бірнеше ем желілерін алған топта ҮӨҰ бойынша артықшылық береді әрі жақсырақ көтерімділікпен ерекшеленеді. Ал химиотерапия жекелеген кіші топтарда (жас науқастар, IGHV-мутациясы бар, қолайлы цитогенетика) қолданылатын опция болып қала береді. Генетикалық профильге негізделген емді жекелендіру СЛЛ бар науқастардағы нәтижелерді жақсартады. Болжамды арттыру үшін генетикалық зерттеулердің қолжетімділігін және спектрін кеңейту қажет.*

Түйінді сөздер: *созылмалы лимфолейкоз; салыстырмалы тиімділік; нысаналы терапия; химиоиммунотерапия; цитогенетика.*

АННОТАЦИЯ

СРАВНИТЕЛЬНАЯ ЭФФЕКТИВНОСТЬ ТЕРАПИИ ХРОНИЧЕСКОГО ЛИМФОЛЕЙКОЗА: ОПЫТ КЛИНИКИ Г. АЛМАТЫ

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Актуальность: *Клинико-генетическая гетерогенность хронического лимфолейкоза (ХЛЛ) влияет на выбор терапии и исходы. Большое значение в стадировании, выборе тактики лечения и прогнозе заболевания имеют цитогенетические и биологические маркеры. Изучение данных реальных клинической практики, сравнение результатов химио-, иммунотерапии и таргетных режимов помогает определить алгоритмы ведения пациентов с ХЛЛ.*

Цель исследования *– оценить сравнительную эффективность химио, иммунотерапии и таргетной терапии у пациентов с хроническим лимфолейкозом с учётом данных цитогенетики, возраста и стадии.*

Методы: *Проведен ретроспективный анализ данных 114 пациентов с ХЛЛ, получавших лечение в ГКП на ПХВ «Городская клиническая больница №7» (Алматы, Казахстан) в 2001-2024 гг. Группы: химио-иммунотерапии (FC, FCR, CR, COP, хлорамбуцил) и таргетные режимы (ингибиторы BTK/PI3K, анти-CD20). Конечные точки: выживаемость без прогрессирования (ВБП), частота общего ответа (ЧО).*

Результаты: *Распределение пациентов с ХЛЛ по стадиям заболевания: стадия В – 59,6% (n=68), стадия А – 25,4% (n=29), стадия С – 9,6% (n=11), стадия не установлена – 5,4% случаев (n=6). Согласно цитогенетическому исследованию (n=63), наиболее распространённой аберрацией являлась del13q14 (33%, n=21), изолированная или в сочетании с другими нарушениями. Del11q22.3 выявлена у 17,5% (n=11), трисомия 12 хромосомы – у 11% (n=7), мутации TP53 – у 6,3% (n=4). По результатам лечения наибольшая медиана ВБП наблюдалась при применении схемы FC (46,6 мес), CR (45 мес), ибрутиниб (32,1). У пациентов, получавших ибрутиниб в последующих линиях терапии (n=10), удалось достичь сопоставимой частоты полных ответов и стабилизации заболевания.*

Заключение: *В реальной клинической практике таргетная терапия обеспечивает преимущество по ВБП и лучшую переносимость у пациентов высокого риска и в группе пациентов, получивших одну или несколько линий предшествующей терапии, тогда как химиотерапия остаётся опцией для выбранных подгрупп (молодые, IGHV-мутация, благоприятная цитогенетика). Персонализация лечения на основе генетического профиля улучшает исходы у пациентов с ХЛЛ. С целью улучшения прогноза, выживаемость необходимо расширение доступа и спектра генетических исследований.*

Ключевые слова: *хронический лимфолейкоз; сравнительная эффективность; таргетная терапия; химиоиммунотерапия; цитогенетика; TP53.*

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