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Unmet needs in the treatment of chronic lymphocytic leukemia and prospects for patients in the Republic of Moldova

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Abstract

Background: Chronic lymphocytic leukemia (CLL) is a malignant lymphoproliferative, monoclonal, indolent hemopathy characterized by pathologically increased synthesis of mature but immunologically dysfunctional B lymphocytes. CLL is considered the pathology of the adult with comorbidities, whose average age is 55 years, who is integrated into the work field. Despite advances in the field of medicine, CLL remains an incurable disease, but the use of targeted, personalized therapy with new agents' conditions not only increases the life span, but also improves the of quality life of these patients, ensuring social, family and professional integration. This fact presents a favourable socioeconomic impact, a valuable indicator especially in countries with a low and medium socio-demographic index. The identification of biomarkers and the advent of personalized therapies have transformed the way the disease is treated and changed the lives and quality of life of CLL patients.

Conclusions: CLL remains a current medical and socioeconomic problem, and the behaviour of patients with CLL remains a challenge for the health system in the Republic of Moldova. The implementation of cyto-genetic and molecular-biological diagnosis is important for the stratification of patients, the selection of optimal targeted therapy. CLL comorbidity is an independent indicator of treatment response, predisposes to adverse drug effects and reduces the quality of life of CLL patients. The individual approach to the patient with CLL, the administration of therapy according to international guidelines will give patients better chances of survival and a longer plateau of stabilization.

Key words: chronic lymphocytic leukemia, personalized therapy.

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Introduction

Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) is a malignant lymphoproliferative, monoclonal, indolent hemopathy characterized by increased pathological synthesis of mature but immunologically dysfunctional B-lymphocytes [1]. Every year, 191000 patients are diagnosed *de novo* worldwide [2]. The incidence in the Republic of Moldova is 2.2 per 100000 inhabitants, according to the National Cancer Registry.

CLL is considered the pathology of the adult, with an increase in the incidence of *de novo* cases with age. Worldwide, the average age of a patient with CLL is 55 years. CLL develops extremely rarely in children [3]. Population-based studies have shown that CLL presents epidemiologic, geographic, and ethnic variations [4]. It is most frequently diagnosed in the Western population, Caucasians, the United States of America. Lymphoproliferative pathology is rarely estimated in Asian countries (China and Japan) and India [5]. According to the data of the Hematology Department of the Republic of Moldova at the Oncological Institute, there are 508 patients with CLL (+144 patients with SLL), which is alarming, considering the decreasing number of the general population.

In the last 10 years, a number of new agents have been added to the therapeutic approach of CLL, including Bruton's tyrosine kinase (BTK) or Phosphatidylinositol-3-kinase delta (PI3Kδ), an antagonist of the antiapoptotic protein BCL-2, and novel anti-CD20 monoclonal antibodies, providing a period of varied survival of 2-20 years, with a median survival of 10 years [6]. In recent years, the identification of biomarkers and the advent of personalized therapies have transformed the way the disease is treated, which changed the lives of CLL patients, optimally integrating these new agents into the traditional treatment algorithm without overlooking or compromising the benefits of established treatments, especially chemoimmu-

notherapy. It is even more relevant in the era when most countries with universal health coverage are switching to chemotherapy-free regimens. Although chlorambucil monotherapy is considered palliative in these countries [7] it is often the only therapy available to most patients in low to medium socio-demographic index countries [8]. According to the same sources, the Republic of Moldova is placed among the countries with a medium-high socio-demographic index, as well as the neighbouring countries: Ukraine and Romania. Despite advances in medicine, CLL is still an incurable disease, but the targeted use of newer biological agents increases the duration and quality of life of these patients.

The literature search was performed using the search terms "chronic lymphocytic leukemia", "individualized treatment", "biological profile" and they were selected from databases, such as PubMed, Google Scholar, Scopus and Elsevier. The material was selected based on the studies published until 01/ 2023, which aimed to elucidate the new challenges of lymphoproliferative diseases. The articles which do not correspond to this article goal were excluded.

Analysis and discussion

Knowledge about CLL has undergone radical changes over the past decades and remains in constant evolution [6]. The stages of the development of CLL treatment options denote the close connection between the progress of the deeper study of the pathogenesis of this malignant hemopathy and the development of targeted treatment methods, which allows an individualization of the therapeutic behaviour of a patient with CLL (fig. 1).

Newer molecular techniques, clinical trials with new agents have led to a change in the natural history of this disease. Ongoing preclinical and clinical studies will reveal newer therapeutic targets and continue to improve patient medication outcomes, which will have a positive impact on their quality of life [9]. Current treatment options cannot cure CLL, except for allergenic hematopoietic stem cell transplantation [10].

The clinical progression of CLL is heterogeneous and ranges from patients who require treatment immediately after diagnosis to others who do not require active therapy for many years, if at all [11]. The selection of first-line therapy in patients with CLL depends on the patient, patient preferences, the biological profile of the tumour, and the goals of the proposed therapy. Elderly patients, who constitute the representative group, often have one or more comorbidities (Charlson score ≥2), a fact that does not allow them to follow and tolerate chemotherapy [12]. According to the static data of the National Cancer Registry of the Republic of Moldova of 508 CLL patients and 144 patients diagnosed with small lymphocytic lymphoma, 345 (68%) are elderly people over 65 years old, and in 93 (27%) patients with CLL, 2 or more comorbidities were found. According to the National Bureau of Statistics, in 2021, the Republic of Moldova saw a decrease in the average life expectancy, which was 69.1 years, decreasing by 0.7 years compared to 2020 and by 11.3 years less compared to the average level of life expectancy at birth in the 27 EU countries in 2020 (80.4 years) [13]. According to the NCCN guidelines (Version 1.2023), the treatment strategy for elderly patients with comorbidities includes the administration of obinutuzumab in the first line of treatment [14], but to which patients from the Republic of Moldova still do not have access (tab. 1).

Obinutuzumab is a humanized type II anti-CD20 monoclonal antibody of the IgG1 subclass, in combination with chlorambucil is indicated for the treatment of adult patients with previously untreated CLL and comorbidities [15]. Clinical studies have confirmed the ability of obinutuzumab:

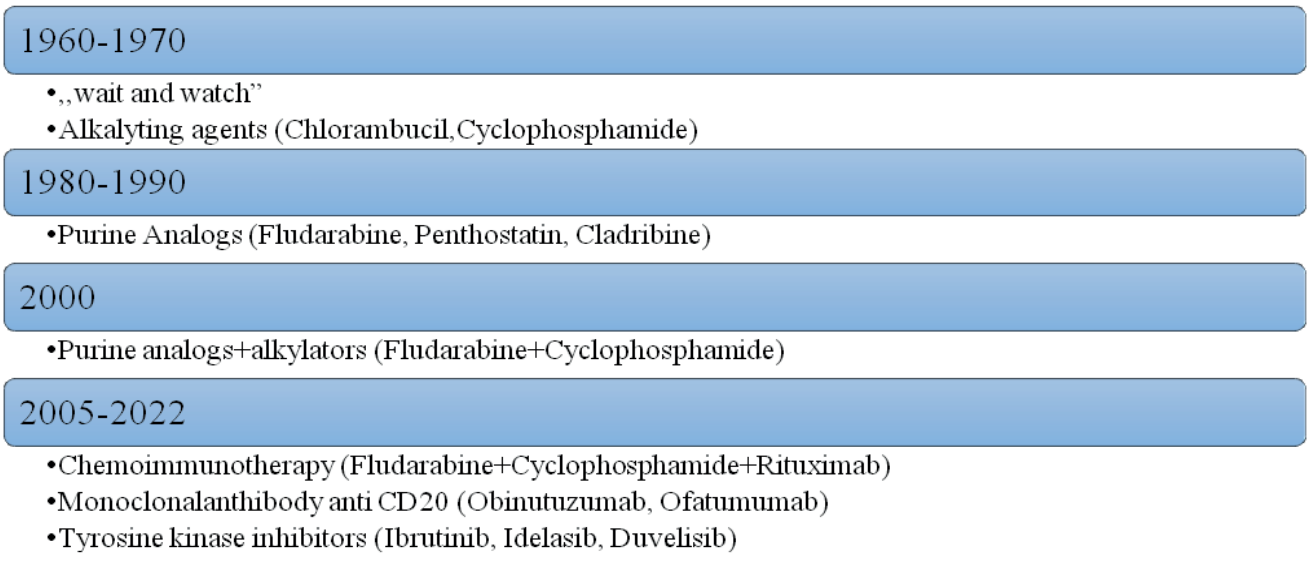

Fig. 1. Historical progress of CLL therapy [6]

Table 1. Suggested treatment regimens CLL/SLLl without del (17p)/*tp53* mutation. First line therapy, NCCN [15]

Preferred regimens	Other recommended regimens	Useful in certain circumstances
Acalabrutinib±obinutuzumab (category 1). Venetoclax+obinutuzumab (category 1). Zanubrutinib (category 1).	– Ibrutinib (category 1). – Bendamustine+anti-CD20 mAb. – Chlorambucil+Obinutuzumab – Obinutuzumab. – High-dose methylprednisolone (HDMP)+rituximab or obinutuzumab (category 2B; category 3 for patients <65 y without significant comorbidities). – Ibrutinib+obinutuzumab (category 2B). – Ibrutinib+ rituximab (category 2B). – Ibrutinib+venetoclax (category 2B).	(Consider for IGHV-mutated CLL in patients age <65 y without significant comorbidities) – FCR (fludarabine, cyclophosphamide, rituximab).

– To induce cell death and increases direct cytotoxicity [16, 17],
– To increase cytotoxicity of antibody-dependent lymphocytes and phagocytosis [16, 18],
– To reduce complement-dependent cytotoxicity [16],
– To initiate malignant B cell apoptosis.

The mechanism by which obinutuzumab induces cell death is explained by the fact that it binds to another part of the CD20 chain, unlike rituximab. In this way, an increase in antibody-dependent lymphocyte cytotoxicity and cell death is induced [19].

CLL11 is a phase III study comparing obinutuzumab with the standard treatment for patients with CLL (rituximab + chlorambucil), demonstrating that compared to the combination of rituximab + chlorambucil, the combination of obinutuzumab + chlorambucil, in patients with comorbidities in the first line of CLL therapy, is 3 times more likely to achieve complete remission [18, 20].

Chemotherapy being non-specific is associated with significant toxic effects, which is why the duration of treatment and its level are limited to older patients with a more deteriorated physical condition.

Research into the biology of CLL has profoundly improved our ability to identify patients at higher risk for disease progression and our ability to treat patients with drugs that selectively target distinct phenotypic or physiologic features of CLL. According to the recommendations of the ESMO Clinical Practice Guidelines, the therapeutic approach is mainly focused on the biological profile of the leukemic clone [21]. Thus, to guide the choice between chemoimmunotherapy or targeted treatments, testing for del(17p), TP53 mutations and immunoglobulin heavy chain variable status (IGHV) is a priority [22]. These researches, aimed at evaluating the biological profile, are listed in the national clinical protocol PCN-65, however they are not yet accessible to CLL patients in the Republic of Moldova [23].

Chemoimmunotherapy using anti-CD20 monoclonal antibodies, such as the fludarabine, cyclophosphamide, and rituximab regimen, remains the standard of care for CLL patients aged <65 years, in good health, and with low-risk prognostic factors [24]. Recent advances in the understanding of the pathogenesis of CLL have significantly improved the range of therapeutic approaches of the treatment of CLL. Therapeutic strategies targeting BCR signalling have been developed due to the pivotal role of BCR signalling in the pathogenesis of CLL. In addition, venetoclax, a BCL2 inhibitor, has significantly changed the therapeutic strategy for the treatment of CLL.

Regarding surface molecules, CD19, CD20 and CD52 have been extensively investigated as therapeutic target molecules in CLL. CD19 is a B-lymphocyte lineage-specific surface molecule (LB) involved in BCR signal transduction [25]. CD19 expression is restricted to the LB and hematopoietic stem cell lineage. T lymphocytes bearing a chimeric antigen receptor (CAR T cells) have been developed as a new cell therapy [26]. The efficacy of CAR T cells against CLL was first reported in 2011 [27-32].

CD20 is a surface glycoprotein expressed on mature LBs and its expression is restricted to the B-cell lineage. Most hematopoietic cells do not show this expression, therefore anti-CD20 monoclonal antibodies, such as rituximab, ofatumumab and obinutuzumab have been developed and used in the treatment of malignant tumours with mature LB [33]. Rituximab has revolutionized therapeutic strategies for mature B-cell malignancies, including CLL. Rituximab has been shown to be as effective and tolerable as monotherapy for non-Hodgkin's lymphoma [34]. Still, rituximab monotherapy was less effective against CLL [35]. In contrast to rituximab monoregimen, immunochemotherapy using riruximab, such as fludarabine, cyclophosphamide, and rituximab, is significantly more effective against CLL [36].

Ofatumumab monotherapy, a human monoclonal anti-CD20 antibody, is an effective, well-tolerated treatment for patients with fludarabine-refractory CLL [37]. The safety and efficacy of combination therapies and maintenance therapy using ofatumumab have been investigated in several studies [38-40].

A phase 1/2 clinical trial showed that obinutuzumab monotherapy is effective for patients with heavily pretreated refractory/relapsed CLL [41]. A randomized phase 3 trial demonstrated that the addition of obinutuzumab to chlorambucil significantly prolonged overall survival compared with chlorambucil monotherapy in patients with untreated CLL ineligible for intensive chemotherapy [42].

Alemtuzumab is a humanized anti-human CD52 IgG1 monoclonal antibody. The efficacy of alemtuzumab has been investigated in previously treated [43] and untreated CLL patients [44], and the FDA approved it for the treatment of fludarabine-refractory CLL in 2001.

In addition to surface molecules, therapeutic strategies targeting BCR signalling have been developed to treat CLL. Ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, is an orally bioavailable small molecule that covalently binds to the cysteine-481 residue of BTK. Ibrutinib has shown potent activity against previously treated CLL or CLL with TP53 aberrations [45-48].

New BTK inhibitors, such as acalabrutinib, tirabrutinib and zanubrutinib have been developed and their efficacy and safety profiles have been clarified in clinical trials [49-52]. Recent studies investigating acalabrutinib, a second-generation BTK inhibitor, confirmed the efficacy of combination therapy consisting of acalabrutinib and obinutuzumab in patients with *de novo* and relapsed/ refractory CLL [53].

Idelalisib is a potent and selective PI3Kδ inhibitor [54, 55]. Oral idelalisib therapy showed a favourable safety profile and rapidly induced stable disease control in the majority of heavily pre-treated CLL patients [56]. Combination therapy with idelalisib and rituximab resulted in a higher overall response rate than rituximab monotherapy in patients with relapsed CLL [57, 58]. Duvelisib, a dual inhibitor of PI3Kδ and PI3Kγ, was approved by the FDA for relapsed or refractory CLL/small lymphocyte lymphoma in 2018 based on the results of the phase 3 DUO trial [59].

In addition to new drugs targeting BCR signalling pathways, such as BTK and PI3K inhibitors, the BCL2 inhibitor venetoclax has significantly changed the treatment of CLL. This BH3 domain sign prevents the interaction between BCL2 and BH3 and inhibits the anti-apoptotic effects of BCL2. The efficacy and safety of daily oral venetoclax for relapsed or refractory CLL was reported in a phase 1 dose-escalation trial [60]. A phase 2 trial of venetoclax monotherapy in patients with del17p relapsed or refractory CLL reported an overall response rate of 79.4% at a median follow-up of 12.1 months [61]. The recent phase 2 CLARITY trial investigating the combination of ibrutinib and venetoclax for relapsed or refractory CLL reported a high minimal residual disease (MRD) eradication rate [62]. Based on these trials, a MRD-guided treatment strategy may be the standard of care for CLL in the near future. Further studies will be useful to establish therapeutic strategies using such novel drugs and to improve clinical outcomes in CLL.

On December 2, 2022, in Chisinau, the Republic of Moldova, the advisory council of experts in the field of haematology oncology was held, entitled "Unsolved problems in the therapy of chronic lymphocytic leukemia and the prospects for patients from the Republic of Moldova".

It is important to note that the discussions at the end of this meeting involved all the participants who unanimously advocated a renewed approach to patients with CLL and the adaptation of treatment strategy according to international standards. The presence of authorities, representatives of the MoH and CNAM speaks of everyone's interest in solving patients' problems and improving their quality of life, by increasing funding for oncological diseases in general and CLL in particular.

Conclusions

1. CLL remains a current medical and socioeconomic problem in the Republic of Moldova, and the behaviour of patients with CLL remains a challenge for the health system in the country.

2. Implementation of cyto-genetic and molecular-biological diagnosis is important for the stratification of patients and the choice of the optimal therapeutic regimen, including target therapy.

3. CLL comorbidity is an independent indicator of treatment response, predisposes to adverse drug effects and reduces the quality of life of CLL patients.

4. The individual approach to the patients with CLL and the administration of therapy according to international guidelines will give patients better chances of survival and longer remission.

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IV designed the research, did statistics and interpreted the data, drafted the first version of the manuscript; TP conceptualized the project and designed the research, revised the manuscript critically; OK, IS interpreted the data, revised the manuscript critically; SB revised the manuscript critically. All the authors revised and approved the final version of the manuscript.

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