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Epidemiology, Diagnosis and Treatment of Chronic Lymphocytic Leukemia

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Abstract Chronic lymphocytic leukemia is the most common type of leukemia. Although the cause of CLL is unknown, a family history has been reported in some cases. CLL is rare in Japan and China. In chronic lymphocytic leukemia, CD5-positive B cells undergo malignant transformation. B cells are continuously activated by acquiring mutations, resulting in monoclonal B-cell lymphocytosis (MBL). Further accumulation of genetic abnormalities and subsequent oncogenic transformation of monoclonal B cells leads to the development of CLL. Lymphocytes first accumulate in the bone marrow and then disseminate to the lymph nodes and other lymphoid tissues, eventually causing splenomegaly, hepatomegaly, and systemic manifestations such as fatigue, fever, night sweats, early satiety, and unexplained weight loss. Diagnosis is based on flow cytometry and peripheral blood immunophenotyping. Treatment is delayed until symptoms develop and typically involves chemotherapy and immunotherapy. However, treatment modalities are progressing and first-line regimens may include targeted agents such as Bruton tyrosine kinase (Btk) inhibitors and Bcl-2 regulators of apoptosis, with or without chemotherapy.

Keywords Chronic lymphocytic leukemia, Immunophenotyping, Chemotherapy

1. Introduction

Chronic lymphocytic leukemia is a clonal lymphoproliferative neoplastic disease characterized by proliferation and an increase in the number of mature lymphocytes in the peripheral blood against the background of lymphocytic infiltration of the bone marrow, lymph nodes, spleen and other organs.

In the latest update of the SEER database, the age-adjusted incidence of chronic lymphocytic leukemia (CLL) was 4.6 per 100,000 inhabitants per year, making CLL the most common type of leukemia. The median age at diagnosis is 70 years [1,2].

In European countries and the USA, CLL occurs significantly more often than in Asian countries. SEER estimates that there will be 20,700 new cases of CLL in the United States in 2024, representing 1% of all new cancer cases. The CLL-related mortality rate was 1.1 per 100,000 men and women per year. The 5-year relative survival rate for patients with CLL was 65,1% in 1975 and has steadily increased over the past decades, with the rate estimated to be 88,5% in 2024 [1,2].

The cellular substrate of chronic lymphocytic leukemia is represented by morphologically mature lymphocytes, mainly the B-population (about 95%) and much less frequently by T-lymphocytes (about 5%). The ability to generate clonal B cells is acquired at the hematopoietic stem cell (HSC) stage [4], suggesting that the primary leukemogenic event in CLL may involve multipotent, self-renewing HSCs. The process of stepwise leukemogenic transformation is becoming increasingly understood. CLL is often initiated by the loss or gain of large chromosomal material (e.g., deletion 13q, deletion 11q, trisomy 12), followed by additional mutations that make the leukemia increasingly aggressive [5].

The significance of genetic abnormalities. Approximately 50% of patients with CLL have chromosomal abnormalities, most frequently in the region of chromosomes 12, 13, and 14. Del(13q) is the most common chromosomal abnormality, occurring in approximately 55% of all cases. Isolated del(13q14) usually indicates a less aggressive form of the disease. MicroRNAs miR-15a and 16–1, located in the critical del(13q14) region [6], regulate the expression of proteins that inhibit apoptosis or control cell cycle progression [7]. Deletions of the short arm of chromosome 17 (del(17p)) are found in 5%–8% of patients who have not received chemotherapy. These deletions almost always include band 17p13, where the TP53 tumor suppressor gene is located. Patients with CLL carrying the del(17p) clone demonstrate marked resistance to genotoxic chemotherapies [8].

Among cases with confirmed del(17p), the majority show mutations in the remaining TP53 allele (>80%). In cases without del(17p), TP53 mutations are much less common but have a similar detrimental effect on chemotherapy response and overall survival [9]. Deletions of the long arm of chromosome 11 (del(11q)) can be found in approximately

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25% of chemotherapy patients with advanced disease and in 10% of patients with early disease [10,11]. These deletions often span band 11q23, containing the ATM gene, which encodes the proximal DNA damage response kinase ATM. Furthermore, patients carrying the del(11q) clone typically exhibit bulky lymphadenopathy, rapid progression, and decreased overall survival [12]. Interestingly, some of the poor prognostic features of del(11q) have been overcome by chemoimmunotherapy [8]. Trisomy 12 is observed in 10%–20% of patients with CLL and is associated with an intermediate prognosis [13]. The genes involved in the pathogenesis of CLL carrying trisomy 12 are largely unknown.

Genomic landscape CLL. In addition to the chromosomal aberrations described above, a total of 44 recurrent mutated genes and 11 recurrent somatic copy number variations have been identified [5]. These include the genes NOTCH1, MYD88, TP53, ATM, SF3B1, FBXW7, POT1, CHD2, RPS15, IKZF3, F292, ZMYM3, ARID1A, and PTPN11 [2,5]. These analyses have identified RNA processing and export, MYC activity, and MAPK signaling as central pathways involved in CLL [5]. Additionally, proteins involved in DNA damage signaling and DNA repair have been frequently implicated [16]. Interestingly, both del(17p) and del(11q), as well as inactivating somatic mutations in TP53 and ATM, are enriched in patients with secondary resistance to DNA damaging chemotherapy [11,14]. Mutations in an enhancer located on chromosome 9p13 can reduce the expression of the B-cell -specific transcription factor PAX5 [15]. Robbe et al. confirmed the significance of genomic alterations, including structural variants, copy number changes, and global genomic features including telomere length, mutational signatures, and genomic complexity, for clinical outcome [17].

Epigenome CLL has emerged as an additional disease-defining characteristic [18,19]. The expanding CLL cell population is diversified by stochastic changes in DNA methylation, termed epimutations [20]. Single-cell multiplex bisulfite down-regulation sequencing of B cells from healthy donors and CLL patients has provided new insights into DNA methylation changes, known as epimutations [21,22]. The results demonstrate that integrating genetic, epigenetic, and transcriptional information at the single-cell level enables mapping the origin history of individual CLL cases and their evolution with therapy.

Diagnostics. In most cases, the diagnosis of CLL is established by blood count, differential analysis, blood smear, and immunophenotyping. The 5th edition of the World Health Organization classification of hematolymphoid tumors classifies CLL as a mature B-cell neoplasm. Within this category, CLL is placed in the "preneoplastic and neoplastic small lymphocytic proliferations categories: MBL and CLL" [23]. This family includes monoclonal B-cell lymphocytosis (MBL) and CLL/SLL. CLL is described as a leukemic lymphocytic lymphoma, which differs from SLL in its leukemic appearance [23]. CLL is always a disease of neoplastic B cells, while the disease previously described as T-CLL is called T-cell prolymphocytic leukemia (T-PLL) [23,24]. B-cell prolymphocytic leukemia is no longer recognized as a distinct disease.

The diagnosis of CLL requires the presence of ≥ 5000 B lymphocytes/μl in the peripheral blood for at least 3 months. The clonality of circulating B lymphocytes should be confirmed by flow cytometry. Lymphocytes may be found mixed with larger or atypical cells, cleaved cells or prolymphocytes, which may constitute up to 55% of blood lymphocytes [25]. Detection of prolymphocytes above this percentage would support the diagnosis of prolymphocytic leukemia (B-cell PLL). Gumprecht's nuclear ghosts or speckled cells found as cellular debris are other characteristic morphologic features found in CLL.

Monoclonal B-lymphocytosis. In the absence of lymphadenopathy or organomegaly (detected by physical examination or CT scanning), cytopenia, or disease-related symptoms, the presence of fewer than 5000 B cells per μL of blood is defined as "monoclonal B lymphocytosis" (MBL) [26]. The presence of cytopenia due to a typical bone marrow infiltrate establishes the diagnosis of CLL, regardless of the peripheral blood B cell count or lymph node involvement. MBL appears to progress to overt CLL at a rate of 1–2% per year [26].

The definition of SLL requires the presence of lymphadenopathy and the absence of cytopenias caused by a clonal bone marrow infiltrate. Furthermore, the B-lymphocyte count in the peripheral blood should not exceed 5000/μL. In SLL, the diagnosis should be confirmed by histopathologic evaluation of a lymph node biopsy when possible.

Immunophenotyping. CLL cells co-express the CD5 surface antigen along with the B cell antigens CD19, CD20, and CD23. Surface immunoglobulin, CD20, and CD79b levels are characteristically low compared to those found in normal B cells [27,28]. Each leukemic cell clone is restricted to expressing either kappa or lambda immunoglobulin light chains [27]. CD5 expression can also be seen in other lymphoid malignancies such as mantle cell lymphoma [29]. Recent major harmonization efforts have confirmed that the CD19, CD5, CD20, CD23, kappa, and lambda panels are usually sufficient to establish the diagnosis [30]. In borderline cases, markers such as CD43, CD79b, CD81, CD200, CD10 or ROR1 may help clarify the diagnosis [30].

Risk stratification, staging and indications for treatment. There are two widely accepted clinical staging systems [31,32]. The Rai classification was later modified to reduce the number of prognostic groups from five to three [33]. Both systems describe three main prognostic groups with discrete clinical outcomes. These two staging systems are simple, inexpensive, and based on physical examination and standard laboratory tests. They do not require ultrasound, CT, or MRI.

The Rai staging system defines low-risk disease as patients who have lymphocytosis with leukemic cells in the blood and/or bone marrow (lymphoid cells > 30%) (formerly Rai stage 0). Patients with lymphocytosis, enlarged nodes in any area, and splenomegaly and/or hepatomegaly (lymph nodes palpable or not) are defined as having intermediate-risk disease (formerly considered Rai stage I or stage II).

High-risk disease includes patients with disease-related anemia (defined as a hemoglobin (Hb) level less than 11g/dl) (formerly stage III) or thrombocytopenia (defined as a platelet count less than 100×10^9/l) (formerly stage IV).

The Binet staging system is based on the number of sites involved, defined by the presence of enlarged lymph nodes >1 cm in diameter or organomegaly and the presence of anemia or thrombocytopenia. Sites of involvement considered are: head and neck including Waldeyer's ring (this is considered one site even if more than one group of nodes is enlarged), axillae (involvement of both axillae is considered one site), groin including superficial femur (involvement of both inguinal cavities is considered one site), palpable spleen, palpable liver (clinically enlarged). The Binet staging system defines stage A as Hb ≥ 10 g/dl and platelets ≥ 100×10^9/l and up to two of the above sites involved; Stage B - Hb level ≥ 10 g/dL, platelet count ≥ 100×10^9/l, and organomegaly exceeding that of stage A (i.e., three or more areas of node or organ enlargement); and stage C - Hb level less than 10 g/dl and/or platelet count less than 100×10^9/l.

International Prognostic Index for chronic lymphocytic leukemia (CLL) is a risk-assessment system that helps doctors predict how the disease will progress in a particular patient. The index is based on several factors, including age, stage of the disease, and the results of certain lab tests, and allows patients to be divided into groups with low, moderate, high, or very high risk of progression.

Treatment of CLL. Not all patients with chronic lymphocytic leukemia need to rush to chemotherapy and start treatment immediately. This disease can remain in a compensated state for years and not bother the patient in any way or threaten his life (the overall life expectancy of such people is comparable to the general population). Therapy is prescribed according to strict indications, since the treatment itself is quite difficult, its early start does not affect the patient's life expectancy and can lead to the tumor cells becoming insensitive to the drugs used ahead of time.

When patients have progressive or symptomatic/active disease, treatment should be initiated [2].

Alkylating agent monotherapy has served as first-line therapy for CLL, and chlorambucil has been the therapeutic "gold standard" for several decades [34]. Three purine analogues have been investigated in CLL: fludarabine, pentostatin, and cladribine (2-CdA). Fludarabine remains the most studied compound of the three in CLL. Fludarabine monotherapy produced more overall responses (OR) and complete remissions (CR) than other chemotherapies such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), CAP (cyclophosphamide, doxorubicin, prednisone), or chlorambucil, but did not improve overall survival [35,36]. Similarly, cladribine monotherapy yields a higher CR rate than chlorambucil plus prednisone without improving survival [37].

Bendamustine was compared with chlorambucil and showed improved response rates but showed greater toxicity and no survival benefit. Bendamustine was also compared with fludarabine in 96 patients with relapsed CLL who required treatment after one previous systemic regimen [2]. Overall and complete response rates were higher for bendamustine than for fludarabine, with no improvement in overall survival. Collectively, these results established bendamustine as a potent single agent for the treatment of CLL.

Monoclonal antibodies. Antibodies to CD20. CD20 is an activated glycosylated phosphoprotein expressed on the surface of mature B cells. This protein has no known natural ligand and its function is unclear. It is thought to act as a calcium channel in the cell membrane. CD20 is expressed in most B-cell malignancies, and the introduction of the anti-CD20 antibody rituximab in 1998 improved the treatment of most CD20-positive non-Hodgkin lymphomas, including CLL [2]. Several newer anti-CD20 antibodies are challenging rituximab [38].

Rituximab. In CLL, rituximab is less active as monotherapy than in follicular lymphoma unless very high doses are used [39]. In contrast, combinations of rituximab with chemotherapy have proven to be very effective treatments for CLL.

Ofatumumab is a fully humanized antibody targeting a unique epitope on the CD20 molecule. It is no longer marketed for the treatment of B-cell malignancies despite interesting biological and clinical properties [40].

It is important to note that a complete cure for CLL is currently not possible and treatment is aimed at controlling the disease, relieving symptoms and improving quality of life. The choice of treatment method is individual and depends on many factors. New treatments such as targeted therapy are increasingly used as first-line therapy, while chemotherapy may be used in patients with certain characteristics. The introduction of new drugs and treatment regimens is constantly evolving, expanding the possibilities of CLL therapy.

The introduction of new drugs into clinical practice is associated with many difficulties, among which clinical (adverse events) make up a smaller part than administrative and financial ones. To solve these problems, it is necessary to solve such tasks as creating and improving a registry of lymphoproliferative diseases; monitoring the availability and frequency of use of modern diagnostic and treatment methods; determining the real need for medical technologies and drugs; strengthening the interaction of the professional medical community and healthcare organizers at the regional level on the availability of treatment; expanding the interaction of federal centers and regional clinics in order to provide expert support for the introduction of new treatment technologies into practice; introducing modern diagnostic methods; introducing treatment and rehabilitation of diseases based on advanced technologies; expanding the types of high-tech medical care based on the procedures for providing medical care.

It is quite simple for a doctor to justify the treatment tactics: the nature of the disease (clinical manifestations, prognostic factors); the patient's condition (comorbidities, somatic status of the patient); factors associated with treatment (restrictions and contraindications to therapy, previous treatment, quality

and response to treatment, toxicity). When justifying the observation tactics, the quality of remission is necessarily assessed - by analyzing the presence or absence of minimal residual disease (MRD), since MRD is a predictor of the response to treatment and the depth of the response.

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