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Review

The Role of LEF1 Protein in Chronic Lymphocytic Leukemia and Different Treatment Methods

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ABSTRACT

A subtype of white blood cells called lymphocytes is the source of chronic lymphocytic leukemia (CLL), a malignancy of the bone marrow and blood. A single lymphocyte can transform into a cancer cell, proliferate over time, and finally displace normal lymphocytes in the lymph nodes and bone marrow. These cells can no longer fight infection, in contrast to normal lymphocytes. It has been demonstrated that lymphoid enhancer-binding factor-1 (LEF1), a member of the LEF/TCF transcription factor family, plays an essential role in regulating Wnt-pathway target genes. LEF1 plays a crucial role in many cancers. Recent studies have shown that LEF1 is overexpressed in CLL. LEF1 is specifically expressed at early stages of B-cell differentiation and is essential for survival and proliferation. In this review, the general course of the disease in CLL, the applied treatment strategies and the role of the LEF1 protein are analyzed in the light of current studies.

INTRODUCTION

Adult patients with chronic lymphocytic leukemia (CLL) are typically older. CLL is the most prevalent adult leukemia in Western Countries due to its high incidence rate and extended survival rate, which generally starts as a relatively indolent illness. A single CD5+ B cell overgrowth that also expresses low levels of CD79b, CD20, and CD23, as well as surface membrane immunoglobulin (smIg) of a single IG light (L) chain type, causes the disorder. Clinical results for this clonal overgrowth vary greatly; some patients pass just 2-4 years after diagnosis, while others continue to survive for decades. This heterogeneity is caused by both extrinsic (such as inputs provided by different signaling pathways in the tissue microenvironment; TME) and intrinsic (such as genetic and epigenetic changes in coding and noncoding genes) factors in leukemic B cells.[1] Following the introduction of targeted therapies, they have been shown to significantly improve overall survival in CLL patients.[2]

Lymphoid enhancer binding factor (LEF1) functions through the wingless-type mouse mammary tumor virus integration site (Wnt) signaling pathway and is an essential transcription factor for the survival and proliferation of B and T cells.[3] Recent studies have shown that high LEF1 expression is a predictive marker for CLL diagnosis and prognosis.[4-6] This review addresses the role of the LEF1 protein in

the development of CLL, as well as the environmental, genetic, and epidemiologic factors that influence the disease, starting with clinical presentation, diagnosis and prognostic markers. Finally, it concludes with factors that contribute to disease progression or resistance to treatment, identifying both current and novel treatment options.

Chronic Lymphocytic Leukemia Process Distribution by Age, Race and Gender

When we look at it, the average age of diagnosis of the disease is stated as 70. However, it is revealed that the number of cases is highest between the ages of 65-74.[2] In addition, since the incidence of this disease varies according to races or ethnicity, the rates may also vary. When we look at the ratios, the order is as follows: White>Black->Hispanic>Asian>Pacific Islands. The incidence also varies according to gender. It is twice more common in men than in women.[7]

Environmental Factors

When we look at environmental factors, it has been seen that various poisons are associated with the development of CLL.[8] It was revealed that substances used in wars in the past years also triggered the disease. However, it cannot be said that these substances are a serious factor in the disease.[9] More research is needed for this. In addition, some diseases that weaken the immune system (respiratory tract infections, herpes zoster, etc.) may be a precursor to CLL. In addition, hypogammaglobulinemia is common in most CLL patients. This problem is thought to be helpful in the diagnosis of the disease.[10,11]

Genetic Factors

When we look at genetic factors in CLL, it has the highest incidence of familial association. Disease development rates of first-degree relatives increase approximately 8-9 times. But in the Asian region, on the contrary, the incidence of CLL remains low.[7] The nine most probable genes that are transcriptionally active in CLL cells and control human B-cell development, signaling, or immunological function were selected from this group.[12,13] GWASs of myeloma and CLL patients verified this by identifying common risk loci impacted by variants in B-cell regulatory elements that impact genes involved in B-cell development. In accordance with this, mutations in B-cell regulatory elements that impact genes involved in B-cell development found to affect common risk loci in GWASs of CLL and myeloma patients.[13]

Chromosome anomalies in leukemic cells from patients with CLL were observed in another part. Additionally, leukemic clones of normal cells from CLL patients in the early phases of hematopoiesis include mutations. These mutations result in a pre-leukemic condition that is similar to monoclonal B lymphocytosis, but they are insufficient to cause the disease.[14] The somatic abnormalities del13q, tri12, del11q, and del17p are the most frequently observed in mature CLL cells, in that order of frequency. At diagnosis, 13q and tri12 deletions are revealed. Typically, del11q and del17p are identified later in the disease.[15]

Lymphoid Enhancer-binding Factor 1

LEF1/TCF transcription factor family, which includes lymphoid enhancer-binding factor-1 (LEF1), has been demonstrated to be important in controlling Wnt-pathway target genes.[16] The expression of LEF1 is restricted to the initial phases of B-cell differentiation and is essential for the survival and growth of these cells. Studies have shown that LEF1 is overexpressed in CLL. In addition, it has been shown that highly malignant acute leukemias express more LEF1 compared to low-grade chronic leukemias.[17]

Howe et al.[18] found that patients with CLL showed higher expression of LEF1. They discovered that CLL cells showed higher amounts of LEF1, which were almost absent in non-Hodgkin lymphoma cells, when they compared LEF1 expression in the two types of cancer. They concluded that with the exception of CLL, LEF1 is not consistently expressed in all lymphoproliferative malignancies with mature B-cell properties. Further studies into gene expression verified that CLL cells exhibited a substantial overexpression of LEF1 in contrast to typical B lymphocytes.[19,20]

Menter et al.[4] demonstrated the diagnostic utility of LEF1 in CLL. LEF1 was expressed in 77 out of 80 CLL patients. The specificity and sensitivity of LEF1 for the diagnosis of CLL were 0.93 and 0.96, respectively. Walther et al.[21] observed that LEF1 is absent from mantle cell and marginal zone lymphomas but expressed and transcriptionally active in the majority of Burkitt lymphoma patients and 3% of DLBCL. According to Tandon et al.,[22] immunohistochemistry revealed that LEF1 was expressed 100% in CLL; a small subset of high-grade Follicular Lymphoma and several Diffuse Large B Cell Lymphoma (38%) also displayed LEF1 expression, although to a lower extent.

In a study of 197 CLL and 6 Monoclonal B-cell Lymphocytosis patients, the duration of treatment-free survival (TFS) and overall survival (OS) was much longer in CLL patients with low LEF1 expression than in those with high LEF1 levels.[6] Erdfelder et al.[23] showed that high LEF1 expression was associated with poor prognosis and disease progression in patients with CLL. Additionally, the mean LEF1 RER for patients in need of treatment was 85.61, while the mean for patients in the newly diagnosed Binet A stage was just 22.01 ($p<0.001$).

Clinical and Laboratory Parameters

In most Western Countries with developed healthcare systems, CLL is diagnosed by finding a high number of lymphocytes in a complete blood count obtained during standard medical screenings. The diagnosis is established by flow cytometric measurement of the quantity of CD5+CD19+ B cells if the lymphocyte count increases further. Physical examination alone is adequate because most of CLL patients are asymptomatic, since they lack symptoms like fever, sweats at night, weight loss.[24]

Prognostic Markers

Once CLL is diagnosed, a number of prognostic indications identify the disease's stage and indicate the clinical path the disease will take in each individual. This is done by examining the physical examination and whole blood results together. These two conditions are still important in the diagnosis of CLL. Two risk classifications, Modified Rai and Binet, are used in CLL staging.[25,26] Together with these two laboratory-based and clinical categories, a new classification method incorporating genetic data has been introduced. The Chronic Lymphocytic Leukemia-International Prognostic Index (CLL-IPI) is a novel classification method that uses five independent prognostic criteria.[27] Table 1 displays the risk groups and survival percentages assessed in four distinct categories based on this system. Estimates of the clinical progression and result are determined by the analysis of several laboratory data. One of the most reliable methods among these analyzes is IGVH (immunoglobulin variable heavy-chain) mutation status. In other words, the number of somatic mutations in the IGVH gene or the absence of mutations are examined.[28,29]

Therapeutic Methods Applied in CLL

Taking a look back, we are making significant progress on understanding the nature of CLL. There is hope for a cure in the future due to the increased understanding of the disease and the development of new prognostic and treatment alternatives. Comprehensive treatment involves the use of multiple modalities such as immunotherapeutic methods monoclonal antibodies, chemotherapy, and other small molecule therapies.[29]

Treatment of CLL US Food and Drug Administration (FDA) Approved

The frontline settings of CLL include alkylating agents (such as bendamustine, chlorambucil, and cyclophosphamide), purine analogs (such as fludarabine and pentostatin), anti-CD20 monoclonal antibodies (such as obinutuzumab, ofatumumab, and rituximab), and Bruton Tyrosine kinase inhibitors (such as ibrutinib). The US FDA approved cellular therapies (allogenic hematopoetic stem cell transplantation as a relapsed setting of CLL), ibrutinib, phosphatidylinositol-3-kinase inhibitor idelalisib + rituximab, duvelisib, BCL-2 inhibitor (venetoclax) +/− rituximab, and anti-CD20 monoclonal antibodies (Obinutuzumab, Ofatumumab, Rituximab).[30]

Table 1. CLL-International Prognostic Index (CLL-IPI)

Age	≤65: 0 point	
	>65: 1 point	
Clinical stage	Binet A/Rai 0: 0 point	
	Binet B, C/Rai I-IV: 1 point	
B2 mikroglobulin	≤3.5: 0 point	
level (mg/L)	>3.5: 2 point	
IGVH mutation	Yes: 0 point	
	None: 2 point	
Del (17p) and/or p53	None: 0 point	
mutation	Yes: 4 point	
CLL-IPI score	**Risk category**	**5-year OS (%)**
0-1	Low risk	93.2
2-3	Intermediate risk	79.3
4-6	High risk	63.3
7-10	Very high risk	23.3

IGHV: Immunoglobulin variable heavy-chain, OS: Overall survival

Patients with advanced CLL are not cured with conventional therapy. Treatment aims to improve overall quality of life and, particularly, to prolong overall survival by reversing cytopenias and relieving associated symptoms. Predicting overall survival with current treatments including novel agents has proved difficult due of the short follow-up of studies analyzing these combinations. Expected overall survival with new treatments varies from a few years to decades, dependent on the severity of the disease, the patient, and the selected strategy of treatment.[30]

When Del 17p or TP53 mutation positive; there are different options for targetted therapies. Ibrutinib, ibrutinib plus obinituzumab, acalabrutinib, venetoclax plus obinutuzumab, venetoclax are options for del 17p or TP53 positivity. When IGVH unmutated; ibrutinib, ibrutinib plus obinutuzumab, acalabrutinib, venetoclax plus obinutuzumab are treatment options. If IGVH mutated and the patient is fit; ibrutinib, ibrutinib plus obinutuzumab, acalabrutinib with or without obinutuzumab, venetoclax plus obinutuzumab, FCR, BR are treatment options. If IGVH mutated and the patient is unfit; ibrutinib, acalabrutinib with or without obinutuzumab, venetoclax plus obinutuzumab, BR, chlorambucil plus obinutuzumab are treatment options.[30]

Anti-CD 20 Monoclonal Antibodies

For the past ten years, patients with chronic lymphocytic leukemia (CLL), chemoimmunotherapy has been the accepted course of treatment. The development of a new generation of anti-CD20 antibodies with improved therapeutic efficacy is a result of advances in monoclonal antibody technology.[31]

Rituximab, ofatumumab, and obinutuzumab are the three monoclonal antibodies that have been approved for the treatment of CLL Survival rates of patients with CLL have been found to be significantly higher when anti-CD20 monoclonal antibodies (mAbs) and chemotherapy are used together. In patients with CLL who have not received prior treatment, adding rituximab to ibrutinib does not increase PFS because of ibrutinib's antagonistic effect on anti-CD20 antibodies. In patients with CLL who have not received prior treatment, adding rituximab to ibrutinib does not increase PFS because of ibrutinib's antagonistic effect on anti-CD20 antibodies. On the other hand, PFS might be increased by combining a more selective BTKi, acalabrutinib, with a glycoengineered anti-CD20 mAbs, obinutuzumab. For patients with autoimmune cytopenia or rapidly progressive diseases, the combination of an an-

ti-CD20 mAb and a BTKi is recommended. Unlike BTKi, anti-CD20 mAbs combined with fixed-duration venetoclax can result in an elevated rate of undetectable minimal residual disease and profound remission; this combination has been linked to better survival rates for CLL patients in both first line and relapse/resistant.[32]

Purine Analogs

Some of the purine analogs that we're looking at are: Fludarabine, pentostatin, and cladribine. In most reported CLL studies, patient survival was associated with response to chemotherapy and disease onset. Fludarabine can elicit a major cytoreductive response in a proportion of patients with previously untreated CLL.[33] Fludarabine is by far the most extensively studied analogue.[34] It provides complete remission. Specifically, older patients with advanced disease and those who have previously received treatment respond better to single agent fludarabine.

Fludarabine is the most comprehensive and widely evaluated of these nucleoside analogues and is typically the leading and widely used major drug in the FCR (fludarabine, cyclophosphamide, and rituximab) regimen. Because prolonged remissions have been reported in this setting, FCR remains the recommended first-line therapy for eligible young patients (<60 years) with IGVH.[35,36]

Pentostatin has also been shown to have clinical activity in CLL and is less toxic than its fludarabine counterpart, which may provide some important advantages. Pentostatin is used together with cyclophosphamide and rituximab. When administered previously, it did not respond as fully as the more commonly used FCR regimen.[37]

In studies on cladribine, it was noted that it showed remission similar to fludarabine as a single agent or in combination treatments.[38]

Bruton Tyrosine Kinase Inhibitors

There are two types of BTKi. First generation BTKi is İbrutibib. FDA approved ibrutinib who had received at least one previous thereapy or with del 17p, mantle cell lymphoma with ≥ 1 prior therapy Waldenstrom's macroglobulinemia. This indication supported with RESONATE Phase III clinical trial for CLL, Pivotal Phase II trial for mantle cell, Pivotal phase II for Waldenstrom's Macroglobulinemia.[39,40]

Second generation BTK inhibitor is Acalabrutinib FDA approved in year 2019 for treatment of CLL. This indication supported with ELEVATE-TN and ASCEND trials. Obinituzumab plus chlorambucil versus monotherapy acalabrutinib or obinituzumab plus acalabrutinib compared about progression free survival (PFS) therapy of untreated CLL patients in ELEVATE-TN trial PFS was sinificantly longer on the monotherapy acalabrutinib and combination with obinituzumab.[41]

Phosphoinositide 3-kinase (PI3K) inhibitors

There are different types of PI3K inhibitors named İdelalisib, Copanlisib, Alpelisib, Umbralisib, and Duvelisib. İdelalisib approved at 2014 and duvelisib aproved 2018 in FDA. In 2019 umbralisib was approved for fast tract status for CLL. This tree agent was used for relapsed refractory CLL. It is well known that although many CLL patients show disease responsive to treatment with kinase inhibitors, they often discontinue treatment because of side effects.[42]

Chemoimmunotherapy

Immunochemotherapy is another form of treatment. Immunotoxins and monoclonal antibodies are becoming significant agents in this therapeutic modality and are being investigated in clinical studies with patients with CLL. A chimeric human mouse monoclonal antibody that targets the CD20 antigen is called rituximab.[33,34] At every stage of B cell development, with the exception of stem cells and plasma cells, CD20 is expressed.[43] The antileukemia effects of rituximab include lysis that is dependent on complement, cytotoxicity that is mediated by antibodies on cells, and the direct activation of apoptosis. Nevertheless, studies showed that compared to other forms of lymphoma, higher doses of rituximab are successful for CLL.[44,45]

Alemtuzumab is another drug. It is a monoclonal antibody to the CD52 antigen that is recombinant and completely human.[38] Alemtuzumab significantly improves overall response rates and survival rates in individuals with relapsing CLL, according to several studies. Additionally, alemtuzumab has been shown to help CLL as well as other diseases with poor prognosis. Also, the combination of Rituximab with Fludarabine has been found to improve overall response rates in CLL.[46]

Allogeneic Hematopoietic Stem Cell Transplant

Upon reviewing the literature and publications, we find that the European Bone Marrow Transplantation Group has released a study. It is emphasized in this work that the required criteria for allogeneic hematopoietic stem cell transplantation for CLL are given.[47] The scientists who published the study emphasize that this method works well in patients with various abnormalities who are unresponsive to chemotherapy or who relapse after achieving complete remission using a purine analogue. In addition to this study, it is stated that the mortality rate is high in most studies.[48]

Other Treatment Methods

In addition to immunotherapy and other treatments, additional CLL treatment approaches are also reviewed. Oblimersen, an antisense phosphothioate oligonucleotide, is one of them. Oblimersen targets BCL-2, an anti-apoptotic molecule's messenger RNA.[43] This drug has a moderate effect in patients with recurrent CLL in a single use. However, when combined with Fludarabine-Cyclophosphamide, the effect level increases.[45]

How I treat CLL?

As we mentioned, chronic lymphocytic leukemia (CLL) is a type of cancer that is usually seen in middle-aged and

older people and has a slow course in the bone marrow and blood. It occurs when lymphocytes, one of our white blood cells, increase in an uncontrolled and abnormal number in the bone marrow, blood and lymph nodes. The purpose of lymphocytes in the immune system of our body is to create a defense against the diseases that occur. When CLL occurs, lymphocytes become unable to function. As a result, the body's defense system weakens and becomes weak against diseases. When it comes to adult cancer, CLL is often the second most frequent kind. There are several components involved in this disease. One of these is overexpression of the LEF1 protein. Recently studies supported this situation. In addition, various mutations play a role in the emergence of the disease. In addition, the cause of the disease varies in gender, race and different ethnic origins. Looking at the studies, different parameters of the disease were examined and revealed. As a result of these parameters, different treatment methods have emerged.

General chemotherapy applications and specialized biological agents are used in the first and later advanced treatment stages in the treatment of CLL. Generalized non-chemotherapy regimens currently recommended for CLL include monotherapy and combination therapies with BTK inhibitors, monoclonal antibodies, PI3K inhibitors, lenalidomide and B-cell lymphoma inhibitors. Clinical developments focusing on individual CAR T cell monotherapy have been slowed by poor response levels and short periods of remission. Apart from various analogue and drug trials, it was concluded that bone marrow transplantation also gave successful results in some studies, but the mortality rate was high in most studies. It is emphasized that studies on bone marrow transplantation should still be continued. In addition, these treatment variations give the hematologists some great options, to choice the best treatment model.

Conclusion

CLL is still a disease that is challenging to cure and has a significant recurrence rate even with current treatment plans. Consequently, it is still essential to look for new drugs and make a thorough effort to comprehend the molecular processes underlying the disease's pathogenesis. The LEF1 protein, which has a critical role in this disease, needs to be investigated in detail. New drug studies for this protein should be started.

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

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Conflict of Interest

None declared.

REFERENCES

1. Chiorazzi N, Chen SS, Rai KR. Chronic lymphocytic leukemia. Cold Spring Harb Perspect Med 2021;11:a035220. [CrossRef]
2. Alrawashdh N, Sweasy J, Erstad B, McBride A, Persky DO, Abraham I. Survival trends in chronic lymphocytic leukemia across treatment eras: US SEER database analysis (1985-2017). Ann Hematol 2021;100:2501–12. [CrossRef]
3. Staal FJ, Clevers HC. WNT signalling and haematopoiesis: A WNT-WNT situation. Nat Rev Immunol 2005;5:21–30. [CrossRef]
4. Menter T, Trivedi P, Ahmad R, Flora R, Dirnhofer S, Tzankov A, et al. Diagnostic utility of lymphoid enhancer binding factor 1 immunohistochemistry in small b-cell lymphomas. Am J Clin Pathol 2017;147:292–300. [CrossRef]
5. Menter T, Dirnhofer S, Tzankov A. LEF1: A highly specific marker for the diagnosis of chronic lymphocytic B cell leukaemia/small lymphocytic B cell lymphoma. J Clin Pathol 2015;68:473–8. [CrossRef]
6. Wu W, Zhu H, Fu Y, Shen W, Miao K, Hong M, et al. High LEF1 expression predicts adverse prognosis in chronic lymphocytic leukemia and may be targeted by ethacrynic acid. Oncotarget 2016;7:21631–43. [CrossRef]
7. Gale RP, Cozen W, Goodman MT, Wang FF, Bernstein L. Decreased chronic lymphocytic leukemia incidence in Asians in Los Angeles County. Leuk Res 2000;24:665–9. [CrossRef]
8. Leon ME, Schinasi LH, Lebailly P, Beane Freeman LE, Nordby KC, Ferro G, et al. Pesticide use and risk of non-Hodgkin lymphoid malignancies in agricultural cohorts from France, Norway and the USA: A pooled analysis from the AGRICOH consortium. Int J Epidemiol 2019;48:1519–35. [CrossRef]
9. Baumann Kreuziger LM, Tarchand G, Morrison VA. The impact of Agent Orange exposure on presentation and prognosis of patients with chronic lymphocytic leukemia. Leuk Lymphoma 2014;55:63–6. [CrossRef]
10. Landgren O, Rapkin JS, Caporaso NE, Mellemkjaer L, Gridley G, Goldin LR, et al. Respiratory tract infections and subsequent risk of chronic lymphocytic leukemia. Blood 2007;109:2198–201. [CrossRef]
11. Landgren O, Gridley G, Check D, Caporaso NE, Morris Brown L. Acquired immune-related and inflammatory conditions and subsequent chronic lymphocytic leukaemia. Br J Haematol 2007;139:791–8. [CrossRef]
12. Di Bernardo MC, Crowther-Swanepoel D, Broderick P, Webb E, Sellick G, Wild R, et al. A genome-wide association study identifies six susceptibility loci for chronic lymphocytic leukemia. Nat Genet 2008;40:1204–10. [CrossRef]
13. Crowther-Swanepoel D, Broderick P, Di Bernardo MC, Dobbins SE, Torres M, Mansouri M, et al. Common variants at 2q37.3, 8q24.21, 15q21.3 and 16q24.1 influence chronic lymphocytic leukemia risk. Nat Genet 2010;42:132–6. [CrossRef]
14. Damm F, Mylonas E, Cosson A, Yoshida K, Della Valle V, Mouly E, et al. Acquired initiating mutations in early hematopoietic cells of CLL patients. Cancer Discov 2014;4:1088–101. [CrossRef]
15. Marsilio S, Khiabanian H, Fabbri G, Vergani S, Scuoppo C, Montserrat E, et al. Somatic CLL mutations occur at multiple distinct hematopoietic maturation stages: Documentation and cautionary note regarding cell fraction purity. Leukemia 2018;32:1041–4. [CrossRef]
16. Travis A, Amsterdam A, Belanger C, Grosschedl R. LEF-1, a gene encoding a lymphoid-specific protein with an HMG domain, regulates T-cell receptor alpha enhancer function [corrected]. Genes Dev 1991;5:880–94. Erratum in: Genes Dev 1991;5:1113. [CrossRef]

17. Reya T, O'Riordan M, Okamura R, Devaney E, Willert K, Nusse R, et al. Wnt signaling regulates B lymphocyte proliferation through a LEF-1 dependent mechanism. Immunity 2000;13:15–24. [CrossRef]
18. Howe D, Bromidge T. Variation of LEF-1 mRNA expression in low-grade B-cell non-Hodgkin's lymphoma. Leuk Res 2006;30:29–32. [CrossRef]
19. Gutiérrez NC, Ocio EM, de Las Rivas J, Maiso P, Delgado M, Fermiñán E, et al. Gene expression profiling of B lymphocytes and plasma cells from Waldenström's macroglobulinemia: Comparison with expression patterns of the same cell counterparts from chronic lymphocytic leukemia, multiple myeloma and normal individuals. Leukemia 2007;21:541–9. [CrossRef]
20. Jelinek DF, Tschumper RC, Stolovitzky GA, Iturria SJ, Tu Y, Lepre J, et al. Identification of a global gene expression signature of B-chronic lymphocytic leukemia. Mol Cancer Res 2003;1:346–61.
21. Walther N, Ulrich A, Vockerodt M, von Bonin F, Klapper W, Meyer K, et al. Aberrant lymphocyte enhancer-binding factor 1 expression is characteristic for sporadic Burkitt's lymphoma. Am J Pathol 2013;182:1092–8. [CrossRef]
22. Tandon B, Peterson L, Gao J, Nelson B, Ma S, Rosen S, et al. Nuclear overexpression of lymphoid-enhancer-binding factor 1 identifies chronic lymphocytic leukemia/small lymphocytic lymphoma in small B-cell lymphomas. Mod Pathol 2011;24:1433–43. [CrossRef]
23. Erdfelder F, Hertweck M, Filipovich A, Uhrmacher S, Kreuzer KA. High lymphoid enhancer-binding factor-1 expression is associated with disease progression and poor prognosis in chronic lymphocytic leukemia. Hematol Rep 2010;2:e3. [CrossRef]
24. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. IwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood 2018;131:2745–60. [CrossRef]
25. Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN, Pasternack BS. Clinical staging of chronic lymphocytic leukemia. Blood 1975;46:219–34. [CrossRef]
26. Binet JL, Auquier A, Dighiero G, Chastang C, Piguet H, Goasguen J, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer 1981;48:198–206. [CrossRef]
27. Fidan K. Chronic lymphocytic leukemia. J Curr Hematol Oncol Res 2023;1:59–67. [CrossRef]
28. Schroeder HW Jr, Dighiero G. The pathogenesis of chronic lymphocytic leukemia: Analysis of the antibody repertoire. Immunol Today 1994;15:288–94. [CrossRef]
29. Hashimoto S, Dono M, Wakai M, Allen SL, Lichtman SM, Schulman P, et al. Somatic diversification and selection of immunoglobulin heavy and light chain variable region genes in IgG+ CD5+ chronic lymphocytic leukemia B cells. J Exp Med 1995;181:1507–17. [CrossRef]
30. Ahn IE, Brown JR. Selecting initial therapy in CLL. Hematology Am Soc Hematol Educ Program 2022;2022:323–8. [CrossRef]
31. Yosifov DY, Wolf C, Stilgenbauer S, Mertens D. From biology to therapy: The CLL success story. Hemasphere 2019;3:e175. [CrossRef]
32. Shah HR, Stephens DM. Is there a role for anti-CD20 antibodies in CLL? Hematology Am Soc Hematol Educ Program 2021;2021:68–75. [CrossRef]
33. Del Poeta G, Del Principe MI, Buccisano F, Maurillo L, Capelli G, Luciano F, et al. Consolidation and maintenance immunotherapy with rituximab improve clinical outcome in patients with B-cell chronic lymphocytic leukemia. Cancer 2008;112:119–28. [CrossRef]
34. Robak T, Smolewski P, Cebula B, Szmigielska-Kaplon A, Chojnowski K, Blonski JZ. Rituximab combined with cladribine or with cladribine and cyclophosphamide in heavily pretreated patients with indolent lymphoproliferative disorders and mantle cell lymphoma. Cancer 2006;107:1542–50. [CrossRef]
35. Klepfish A, Gilles L, Ioannis K, Eliezer R, Ami S. Enhancing the action of rituximab in chronic lymphocytic leukemia by adding fresh frozen plasma: Complement/rituximab interactions & clinical results in refractory CLL. Ann N Y Acad Sci 2009;1173:865–73. [CrossRef]
36. Badoux XC, Keating MJ, Wang X, O'Brien SM, Ferrajoli A, Faderl S, et al. Fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy is highly effective treatment for relapsed patients with CLL. Blood 2011;117:3016–24. [CrossRef]
37. Zent CS, Taylor RP, Lindorfer MA, Beum PV, LaPlant B, Wu W, et al. Chemoimmunotherapy for relapsed/refractory and progressive 17p13-deleted chronic lymphocytic leukemia (CLL) combining pentostatin, alemtuzumab, and low-dose rituximab is effective and tolerable and limits loss of CD20 expression by circulating CLL cells. Am J Hematol 2014;89:757–65. [CrossRef]
38. Osterborg A, Mellstedt H, Keating M. Clinical effects of alemtuzumab (Campath-1H) in B-cell chronic lymphocytic leukemia. Med Oncol 2002;19:S21–6. [CrossRef]
39. Smith MR. Ibrutinib in B lymphoid malignancies. Expert Opin Pharmacother 2015;16:1879–87. [CrossRef]
40. Byrd JC, Brown JR, O'Brien S, Barrientos JC, Kay NE, Reddy NM, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med 2014;371:213–23. [CrossRef]
41. Sharman JP, Egyed M, Jurczak W, Skarbnik A, Pagel JM, Flinn IW, et al. Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naïve chronic lymphocytic leukemia. Leukemia 2022;36:1171–5. Erratum in: Leukemia 2025;39:529. [CrossRef]
42. Vanhaesebroeck B, Perry MWD, Brown JR, André F, Okkenhaug K. PI3K inhibitors are finally coming of age. Nat Rev Drug Discov 2021;20:741–69. Erratum in: Nat Rev Drug Discov 2021;20:798. [CrossRef]
43. O'Brien SM, Cunningham CC, Golenkov AK, Turkina AG, Novick SC, Rai KR. Phase I to II multicenter study of oblimersen sodium, a Bcl-2 antisense oligonucleotide, in patients with advanced chronic lymphocytic leukemia. J Clin Oncol 2005;23:7697–702. [CrossRef]
44. O'Connor OA, Czuczman MS, Lacasce AS, Gerecitano J, Leonard JP, Dunleavy K, et al. A phase 1 study evaluating the safety, PK & efficacy of ABT-263 in subjects with refractory or relapsed lymphoid malignancies. Ann Oncol 2008;19:115–6.
45. O'Brien S, Moore JO, Boyd TE, Larratt LM, Skotnicki A, Koziner B, et al. Randomized phase III trial of fludarabine plus cyclophosphamide with or without oblimersen sodium (Bcl-2 antisense) in patients with relapsed or refractory chronic lymphocytic leukemia. J Clin Oncol 2007;25:1114–20. Erratum in: J Clin Oncol 2008;26:820. [CrossRef]
46. Lozanski G, Heerema NA, Flinn IW, Smith L, Harbison J, Webb J, et al. Alemtuzumab is an effective therapy for chronic lymphocytic leukemia with p53 mutations and deletions. Blood 2004;103:3278–81. [CrossRef]
47. Dreger P, Corradini P, Kimby E, Michallet M, Milligan D, Schetelig J, et al. Indications for allogeneic stem cell transplantation in chronic lymphocytic leukemia: The EBMT transplant consensus. Leukemia 2007;21:12–7. [CrossRef]
48. Jabbour E, Keating MJ, Champlin RE, Khouri IF. Stem cell transplantation for chronic lymphocytic leukemia: Should not more patients get a transplant? Bone Marrow Transplant 2004;3:289–97. [CrossRef]

Kronik Lenfositik Lösemide LEF1 Proteininin Rolü ve Farklı Tedavi Yöntemleri

Kemik iliği ve lenf düğümlerinin bir malignitesi olan kronik lenfositik löseminin (KLL) kaynağı, beyaz kan hücrelerinin bir alt türü olan lenfositlerdir. Tek bir lenfosit kanser hücresine dönüşebilir, zamanla çoğalabilir ve sonunda lenf düğümlerinde ve kemik iliğinde normal lenfositlerin yerini alabilir. Bu hücreler artık normal lenfositlerin aksine enfeksiyonla savaşamaz. Lenfoid güçlendirici bağlama faktörü-1 (LEF1), Wnt yolu hedef genlerinin düzenlenmesinde önemli bir rol oynadığı gösterilen LEF/TCF transkripsiyon faktörü ailesinin bir parçasıdır. LEF1 birçok kanserde çok önemli bir rol oynar. Son yıllarda yapılan çalışmalar LEF1'in CLL'de aşırı eksprese edildiğini göstermiştir. LEF1, özellikle B hücresi farklılaşmasının erken aşamalarında eksprese edilir ve hayatta kalma ve çoğalma için gereklidir. Bu derlemede, KLL'de hastalığın genel seyri, uygulanan tedavi stratejileri ve LEF1 proteininin rolü güncel çalışmalar ışığında analiz edilmiştir.

Anahtar Sözcükler: İlaçlar; KLL; LEF-1; tedavi.