Review article

Promising Role of CD200 Expression in Diagnosis and Prognosis of Chronic Lymphocytic Leukemia: A Review

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Abstract:

One of the most common leukemia in the world is chronic lymphocytic leukemia (CLL). CLL, as an incurable malignant disorder of B-lymphocytes. CD200, formerly known as OX-2, is a type I glycoprotein that is expressed on a variety of cell types. CD200 plays a vital role in the modulation of the immune system and is upregulated on the surface of numerous tumors, including chronic lymphocytic leukemia. In several studies, it is noted that CD200 was upregulated 1.6- to 5.4-fold in B cells from all patients with B-CLL and may suggest that CD200 upregulation is an early event in the B-CLL disease process. It might conclude that CD200 blocking therapy may be beneficial, and several studies have proven this. We can conclude that CD200 is an excellent prognostic factor that expresses in most CLL patients, and antiCD200 therapeutic interventions can be useful. This literature review article was conducted with the purpose of role of CD200 Expression in the Diagnosis of Chronic Lymphocytic Leukemia.

Keywords: Chronic Lymphocytic Leukemia, Prognosis, CD200, diagnosis.

Introduction:

Chronic lymphocytic leukemia (CLL), the most common form of leukemia in the United States, is a malignant disorder of lymphocytes, that affects lymph cells or lymphocytes that make lymphatic tissue (1). CLL is the same small B cell lymphoma in the blood, bone marrow, lymph nodes, or other lymphoid tissues (2). CLL, primarily a disorder of the older age group as the average age at initial diagnosis, is 65-70 years, male to female 2:1 ratio, is a generally slow-growing cancer which starts in the bone marrow's lymphocytes and progresses to the blood (3). CLL, as an incurable malignant disorder of B-lymphocytes (4), comprises the manifestations similar to other

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malignancies like non-Hodgkin lymphoma (5).

CD200 is a constitutive surface marker for hair bulge stem cells, which inhibits leukocyte activity when bound to the CD200 receptor (6). CD200 has a relatively wide range of tissue and cell types; it is mainly found in B cells, DCs, and activated T cells as well as vascular endothelial cells and many types of non-hematopoietic cells like cells (neurons) in the central nervous system and retina (7). This literature review article was conducted with the purpose of attempted to provide role of CD200 Expression in Diagnosis and prognosis of Chronic Lymphocytic Leukemia.

1) Diagnoses of CLL:

Clinical features:

People with CLL often being unaware of their disease because it is asymptomatic disorder, and they mostly become aware during rutin blood count. Some patients are fully active and asymptomatic. Fatigue, involuntary weight loss, excessive night sweats, abdominal fullness with early satiety, and increased frequency of infections, which might be associated with hypo gammaglobulinemia, are some symptoms in minority cases. Enlarged lymph nodes, splenomegaly, and hepatomegaly can be observed in physical examinations. Enlarged lymph nodes can easily be palpated in some regions such as cervical, axillary, and inguinofemoral regions (8, 9).

Laboratory assessment:

It includes complete blood cell count and flow cytometry. Lymphocytosis is the most common laboratory abnormality observed in these patients that mostly its count is above ~3,500 cells per µl, detected by a blood count (9). With flow cytometry or immunohistochemistry, we can distinguish CLL from different types of leukemia. CD5, CD19, and CD23 (low-affinity immunoglobulin-ε Fc receptor) expressed typically on CLL B cells, and these cells have low levels of CD20 (10).

2) CD200 and Chronic Lymphocytic Leukemia:

CD200, formerly known as OX-2, is a type I glycoprotein that is expressed on a variety of cell types. CD200 plays a vital role in the mo dulation of the immune system and is upregulated on the surface of numerous tumors, including CLL (11). CD200 is overexpressed in CLL (12). Recently, researchers discovered a soluble form of CD200 (sCD200) in human plasma and recognized that sCD200 was raised in the plasma of patients with CLL. CLL cells release CD200 at a constitutive stage, partly reduced by silencing ADAM28 (13). Most researches have focused on the role of CD200 to differentiate CLL and MCL, CD200 being almost consistently positive in CLL, and usually absent in MCL (14, 15). In this regard, the few MCL cases included in this series showed a lower expression of CD200 analyzed to CLL (16, 17). Concretely, CD200 has been reported to be extremely expressed in all CLL patients. Fouad E et al. studied 67 CLL patients retrospectively and found that all CLL patients showed positive CD200 expression, whereas all MCL patients were negative for CD 200 (18). One study reporting a

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sensitivity of 0.73 in CLL, and three studies were reporting positivity rates >25% in MCL. Similarly, positivity rates in splenic marginal zone lymphoma (SMZL) ranged from 0 to 100%, albeit in small studies (16, 19-22). Besides, we recognized different CD200 positive p rofiles, among other B-cell Chronic lymphoproliferative diseases non-MCL(23). Falay M et al. analyzed 339 patients and showed that CD200 expression was retained in the atypical morphological variant of CLL (24). CD200 expression in all other cytogenetic groups was similar (21, 22). However, Baraka H et al. studied 50 patients and reported CLL with trisomy 12 expresses CD200 lower than CLL with other cytogenetic abnormalities (19). There are a limited number of studies that have analyzed the expression of CD200 in other B cell neoplasms (20, 25). Together, our results have shown the concept that CD200 expression is common in CLL but also that CD200 can be variably expressed in B cell neoplasms, including MZL (26).There is only one study proposing to incorporate CD200 in a system called "CLL flow Score" calculated by the total percentage of positive cells(16). Some studies used a cutoff of 30% (14, 27, 28), but others used a cutoff of 20 %(15, 17, 23). Nevertheless, the accuracy of the CLL diagnosis did not change as a result of using a cutoff of either 20% or 30%. Extensive studies assessing the prevalence of each diagnostic option have several limitations, such as lacking peripheral blood samples and the heterogeneity of expression cutoffs, which limits the value of the results. Data on fluorescence intensity was rarely reported, and the descriptions were too heterogeneous. Most studies published on this aspect reported brighter intensity for CLL than most other disorders. Notwithstanding, one study that used a higher fluorescence cutoff reported a suboptimal sensitivity for CLL (29). Two additional studies reported the essential data to compare a standard threshold to a higher threshold both of them observed a predictable loss of sensitivity and an increase in specificity leading to a similar overall accuracy. Another potential limitation concerns the selection of the non-CLL, non-MCL group. Some of these disorders, particularly SMZL, can seldom express CD103, thus being closer to HCL-like disorders or HCL than to CLL or MCL (17). However, expression of CD103 in SMZL is uncommon and the distinction between CD103-positive disorders (including HCL, HCL-variant, and splenic diffuse red pulp lymphoma) and CD103-negative disorders (including MZL, LPL, and other unclassifiable leukemic LPD) is confirmed (17, 21, 30). In conclusion, CD200 is a sensitive and specific marker for discriminating between CLL and MCL in flow cytometry analysis., especially when the subtype of CLL is atypical, which morphologically can confuse with MCL.

3) Importance of prompt diagnosis of CLL at early stages:

CLL cases are asymptomatic at an early stage; abnormalities in whole blood count such as leukocytosis with lymphocytosis are solely findings (31). If CLL is not diagnosed at an early stage, it can show serious complications at advanced stages (16). CLL causes an alteration in both cell-mediated immunity (T-cell count and function abnormality, B-lymphocyte defects, natural killer defects) and humoral-mediated immunity (low gamma globulin levels) (27, 28). Predispose of second malignancy incidence due to impaired immune system, chemotherapy, or genomic instability makes

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CLL patients vulnerable (14, 27). In most cases, after several years of CLL development, the second malignancy occurs. Typically, it is the duration of sporadic CLL remission, which precedes the second occurrence of malignancy by months or years (in as many as 33% of CLL patients). The increased frequency (16%) of the second incidence of malignancy of CLL is well established, and more than two-thirds of these patients will suffer from this cause (15). The ability to diagnosis accurately and quickly and also initiating the appropriate treatment as soon as possible is one of the most important factors to physicians. Diagnosis of B-CLL in the peripheral blood specimen based on morphology and flow cytometry and differentiate it from other lymphoproliferative disorders is essential (17, 23).

Studies have been carried out on this topic, but no significant relationship has been identified yet. Further clinical studies are needed to obtain accurate conclusions on this topic (32, 33).

4) CD200 as a prognostic factor:

Prognostic factors can help us to categorize patients who need immediate therapy soon after diagnosis include certain clinical and laboratory features, genetic, molecular, and biochemical characteristics of the cell. In several studies, it is noted that CD200 was upregulated 1.6- to 5.4-fold in all patients with B-CLL and may suggest that CD200 upregulation is an early event in the B-CLL disease process (34). Several studies reported that blocked interaction between CD200: CD200R could attenuate innate immune reactions while enhancing the development of acquired immunity (35, 36).

Overexpression of CD200 is associated with advanced stage and earlier time to progression, it is also seen in a study that CD200 in high-risk patients compared to intermediate and low-risk patients had a higher expression which suggested that it can provide diagnostic and prognostic information (18, 19).Wang X et al. in a study to investigate the expression of CD200 in the bone marrow of CLL patients and its associations with clinical features, chromosome type, phenotype, and prognosis, analyzed 40 patients with CLL. They concluded that CD200 might be very important for the diagnosis, prognosis, individualized treatment, and the longer survival time of CLL patients (37). In a study by Miao Y et al. evaluated the mean fluorescence intensity (MFI) of CD200 in 307 consecutive, untreated patients with CLL. They recognized CD200 MFI as a possible prognostic factor in CLL (12). In another study by Challagundla et al. the relationship among CD200 MFI and cytogenetic abnormality was investigated, which described that +12 tended to show dimmer CD200 expression (38). On another hand, Mc Whriter et al. in their study showed that no associations were discovered among CD200 expression and other prognostic markers, including CD38 and ZAP70 (30). However, both studies only determined the association between CD200 expression and other prognostic factors, while the prognostic effect of CD200 expression alone was not examined. Bahaa et al. studied 43 patients with CLL and reported high CD200 expression had a relationship with older age, lymphocytosis, hepatomegaly, splenomegaly, and a higher

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Rai and Binet stage(18). Based on CD200 expression and its correlation with prognosis in patients with CLL, it appears that CD200 blocking therapy may be beneficial, however further studies are needed to prove this. The potential advantages of anti-CD200 blocking therapy suggest that evaluation in the clinic is warranted (34).

Conclusion:

CLL is the most frequent type of B cell lymphoproliferative disorder, and CD200 has become an essential marker for study low-grade lymphoproliferative disorders such as CLL. Several studies have reported that CD200 is expressed in CLL patients. We can conclude that CD200 is a useful marker in the evaluation of B cell-derived neoplasm and a potential prognostic factor in CLL patients and anti CD200 therapeutic interventions can be useful.

References:

1. Tausch E, Mertens D, Stilgenbauer S. Advances in treating chronic lymphocytic leukemia. F1000prime reports. 2014;6.
2. Zenz T, Mertens D, Küppers R, Döhner H, Stilgenbauer S. From pathogenesis to treatment of chronic lymphocytic leukaemia. Nature Reviews Cancer. 2010;10(1):37.
3. Rawstron AC, Kreuzer KA, Soosapilla A, Spacek M, Stehlikova O, Gambell P, et al. Reproducible diagnosis of chronic lymphocytic leukemia by flow cytometry: An European Research Initiative on CLL (ERIC) & European Society for Clinical Cell Analysis (ESCCA) Harmonisation project. Cytometry Part B: Clinical Cytometry. 2018;94(1):121-8.
4. Alsagaby SA, Alhumaydhi FA. Proteomics insights into the pathology and prognosis of chronic lymphocytic leukemia. Saudi medical journal. 2019;40(4):317.
5. Rai KR, Stilgenbauer S, Aster JC. Clinical features and diagnosis of chronic lymphocytic leukemia/small lymphocytic lymphoma. 2019.
6. Yang C-C, Chen C-C, Chen W-C. Aging and Anti-Aging in Hair and Hair Loss. Inflammation, Advancing Age and Nutrition: Elsevier; 2014. p. 231-46.
7. Parent RA. Comparative biology of the normal lung: Academic Press; 2015.
8. Kipps TJ, Stevenson FK, Wu CJ, Croce CM, Packham G, Wierda WG, et al. Chronic lymphocytic leukaemia. Nature reviews Disease primers. 2017;3:16096.
9. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines. Blood, The Journal of the American Society of Hematology. 2008;111(12):5446-56.
10. Alapat D, Coviello-Malle J, Owens R, Qu P, Barlogie B, Shaughnessy JD, et al. Diagnostic usefulness and prognostic impact of CD200 expression in lymphoid malignancies and plasma cell myeloma. American journal of clinical pathology. 2012;137(1):93-100.
11. Pallasch CP, Ulbrich S, Brinker R, Hallek M, Uger RA, Wendtner C-M. Disruption of T cell suppression in chronic lymphocytic leukemia by CD200 blockade. Leukemia research. 2009;33(3):460-4.

[DOR: 20.1001.1.23222913.2019.8.4.11.7]

12. Miao Y, Fan L, Wu Y-J, Xia Y, Qiao C, Wang Y, et al. Low expression of CD200 predicts shorter time-to-treatment in chronic lymphocytic leukemia. Oncotarget. 2016;7(12):13551.
13. Wong KK, Zhu F, Khatri I, Huo Q, Spaner DE, Gorczynski RM. Characterization of CD200 ectodomain shedding. PloS one. 2016;11(4):e0152073.
14. Gavrila G-A, Mihaila R-G, Manitiu I. Differential diagnosis problems in a patient with dysphonia and chronic lymphocytic leukemia. Pakistan journal of medical sciences. 2015;31(1):223.
15. Wiernik PH. Second neoplasms in patients with chronic lymphocytic leukemia. Current treatment options in oncology. 2004;5(3):215-23.
16. Eichhorst B, Hallek M. Guidelines for Diagnosis, Indications for Treatment, Response Assessment, and Supportive Management of Chronic Lymphocytic Leukemia: The 2018 Update. Chronic Lymphocytic Leukemia: Springer; 2019. p. 69-77.
17. Jakšić B, Pejša V, Ostojić-Kolonić S, Kardum-Skelin I, Bašić-Kinda S, Coha B, et al. Guidelines for Diagnosis and Treatment of Chronic Lymphocytic Leukemia. Krohem B-Cll 2017. Acta Clinica Croatica. 2018;57(1):190.
18. Fouad NBED, Ibrahim NY, Aziz RSA, Ibrahim SK. CD200 Expression in Diagnostic and Prognostic Assessment of Mature B Cell Lymphophoproliferative Neoplasms. Asian Pacific journal of cancer prevention: APJCP. 2018;19(12):3383.
19. Baraka A, Salem HM. Study of CD200 in chronic lymphocytic leukemia. The Egyptian Journal of Haematology. 2012;37(2):111.
20. D'Arena G, Vitale C, Rossi G, Coscia M, Omedè P, D'Auria F, et al. CD200 included in a 4-marker modified Matutes score provides optimal sensitivity and specificity for the diagnosis of chronic lymphocytic leukaemia. Hematological oncology. 2018;36(3):543-6.
21. Maitre E, Troussard X. Monoclonal B-cell lymphocytosis. Best Practice & Research Clinical Haematology. 2019.
22. Salem DA, Stetler-Stevenson M. Clinical Flow-Cytometric Testing in Chronic Lymphocytic Leukemia. Immunophenotyping: Springer; 2019. p. 311-21.
23. Salimi A, Roudkenar MH, Sadeghi L, Mohseni A, Seydi E, Pirahmadi N, et al. Ellagic acid, a polyphenolic compound, selectively induces ROS-mediated apoptosis in cancerous B-lymphocytes of CLL patients by directly targeting mitochondria. Redox Biology. 2015;6:461-71.
24. Falay M, Öztürk BA, Güneş K, Kalpakçı Y, Dağdaş S, Ceran F, et al. The role of CD200 and CD43 expression in differential diagnosis between chronic lymphocytic leukemia and mantle cell lymphoma. Turkish Journal of Hematology. 2018;35(2):94.
25. Rahman K, Kumar P, Gupta R, Singh M, Nityanand S. Role of CD 200 in differential diagnosis of mature B-cell neoplasm. International journal of laboratory hematology. 2017;39(4):384-91.
26. Cui B, Ghia EM, Chen L, Rassenti LZ, DeBoever C, Widhopf GF, et al. High-level ROR1 associates with accelerated

[DOR: 20.1001.1.23222913.2019.8.4.11.7]

disease progression in chronic lymphocytic leukemia. Blood. 2016;128(25):2931-40.
27. Morton LM, Curtis RE, Linet MS, Bluhm EC, Tucker MA, Caporaso N, et al. Second malignancy risks after non-Hodgkin's lymphoma and chronic lymphocytic leukemia: differences by lymphoma subtype. Journal of clinical oncology. 2010;28(33):4935.
28. Salimi A, Roudkenar MH, Seydi E, Sadeghi L, Mohseni A, Pirahmadi N, et al. Chrysin as an Anti-Cancer Agent Exerts Selective Toxicity by Directly Inhibiting Mitochondrial Complex II and V in CLL B-lymphocytes. Cancer Investigation. 2017;35(3):174-86.
29. Muñoz EC, Rodríguez PD, García AG, Palanca JM, del Toro Cervera J. Brain biopsy in the diagnosis of leptomeningeal involvement in stage I chronic lymphocytic leukemia. Clinical case reports. 2017;5(12):1919.
30. McWhirter JR, Kretz-Rommel A, Saven A, Maruyama T, Potter KN, Mockridge CI, et al. Antibodies selected from combinatorial libraries block a tumor antigen that plays a key role in immunomodulation. Proceedings of the National Academy of Sciences. 2006;103(4):1041-6.
31. Hus I, Roliński J. Current concepts in diagnosis and treatment of chronic lymphocytic leukemia. Contemporary Oncology. 2015;19(5):361.
32. Miao Y, Fan L, Wu Y-J, Xia Y, Qiao C, Wang Y, et al. Low expression of CD200 predicts shorter time-to-treatment in chronic lymphocytic leukemia. 2016;7(12):13551.
33. Rawstron AC, Kreuzer KA, Soosapilla A, Spacek M, Stehlikova O, Gambell P, et al. Reproducible diagnosis of chronic lymphocytic leukemia by flow cytometry: An European Research Initiative on CLL (ERIC) & European Society for Clinical Cell Analysis (ESCCA) Harmonisation project. 2018;94(1):121-8.
34. Kretz-Rommel A, Bowdish KS. Rationale for anti-CD200 immunotherapy in B-CLL and other hematologic malignancies: new concepts in blocking immune suppression. Expert opinion on biological therapy. 2008;8(1):5-15.
35. Gorczynski RM, Chen Z, Lee L, Yu K, Hu J. Anti-CD200R ameliorates collagen-induced arthritis in mice. Clinical Immunology. 2002;104(3):256-64.
36. Gorczynski RM. CD200 and its receptors as targets for immunoregulation. Current opinion in investigational drugs (London, England: 2000). 2005;6(5):483-8.
37. Wang X, Zhang Z, Liu Y, Wang L, Yuan H, Xie P, et al. Expression of CD200 in the bone marrow of chronic lymphocytic leukemia patients and its correlations with clinical prognosis. Xi bao yu fen zi mian yi xue za zhi= Chinese journal of cellular and molecular immunology. 2014;30(1):75-8.
38. Challagundla P, Medeiros LJ, Kanagal-Shamanna R, Miranda RN, Jorgensen JL. Differential expression of CD200 in B-cell neoplasms by flow cytometry can assist in diagnosis, subclassification, and bone marrow staging. American journal of clinical pathology. 2014;142(6):837-44.

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