**CD39 Expression on T Lymphocytes Correlates With Severity**

**of Disease in Patients With Chronic**

**Hasnaa. A. Abo- Elwafa , Ahmed. N. Mohammed , Eman .H. Ali, Tamer. M.Abdellatef , Marwa. A. Mahmoud**

**Abstract:**

Chronic lymphoid leukemia (CLL), is the most common type of leukemia (a type of cancer of the white blood cells) in adults representing 25%-30% of all leukemias, CLL is a disease of adults. Most (>75%) people newly diagnosed with CLL are over the age of 50, and the majority are men, The leukemia is characterized by a clonal expansion of long-lived mature-appearing B lymphocytes that co-express the CD5, CD19, and CD23 surface antigens.CD39 (ectonucleotidase, NTDPase1) is an ADPase found on the surface of endothelial cells, normal lymphocytes and other leukocytes, Its principal function on the endothelial cell surface is to decrease platelet activation and recruitment by metabolizing platelet-released adenosine diphosphate (ADP). In leukocytes the enzyme has a variety of other direct or indirect effects as well, including modulation of cytokine expression and the inflammatory response. The aim of this study to review the role CD39 in patients with chronic lymphocytic leukemia and correlate it with the severity of the disease. A total of 5 papers were obtained using the mentioned keywords in the research of all internet-based databases. The total number of cases in all of the studies was 716 cases.The mean age was recorded in 5 papers was 64.7 years. There are different method of detection of CD39 in different studies such as flow cytometry and immunohistochimistry .

**Introduction**

Chronic lymphoid leukemia (CLL), is the most common type of leukemia (a type of cancer of the white blood cells) in adults representing 25%-30% of all leukemias, CLL is a disease of adults **( 1).** The leukemia is characterized by a clonal expansion of long-lived mature-appearing B- lymphocytes that co-express the CD5, CD19, and CD23 surface antigens **(2).** CD39 (ectonucleotidase, NTDPase1) is an ADPase found on the surface of endothelial cells, normal lymphocytes and other leukocytes **( 3).** Its principal function on the endothelial cell surface is to decrease platelet activation and recruitment by metabolizing platelet-released adenosine diphosphate (ADP). In leukocytes the enzyme has a variety of other direct or indirect effects as well, including modulation of cytokine expression and the inflammatory response **( 4).** The absolute number of T lymphocytes is often increased in CLL, largely caused by increases in the CD8\_population, although the relative number is usually reduced because of the large number of malignant B lymphocytes that accumulate **(5 ).** T-lymphocyte CD39 expression was lower in patients with stage 0 disease compared with patients with either stage 1-2 or stage 3-4 disease and in patients who did not require chemotherapy**(6)**

The percentage of CD4+CD39+ lymphocytes was also significantly higher in ZAP-70+ve patients compared to ZAP-70–ve patients CD4+ve,CD39+ve lymphocytes were increased in patients with β2-microglobulin levels of >3 g/L compared to patients with β2-microglobulin levels of <3 g/L **( 6)** .Patients were diagnosed as having progressive disease on the basis of the presence of one or more of the following criteria ; lymphocyte count doubling time of less than 6 months; progression to a more advanced stage; massive (i.e. 6 cm below the left costal margin) or progressive or symptomatic splenomegaly ; massive nodes (i.e. 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy ; development of systemic symptoms; autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroids or other standard therapy**( 7).**

**Objectives:**

This study is designed to review the role CD39 in patients with chronic lymphocytic leukemia and correlate it with the severity of the disease

**Strategy and methods**

The strategy of this systematic review will be based upon raising some research questions addressing the different techniques of role of CD39 in CLL and put a plan to find the best available answers for each. This will be done by looking in the literature and critically appraising the available researches in this field. Good quality researches will be selected to reach a conclusive answer for each question.

**The research questions are:**

Is there an evidence-based value of CD39 in CLL?

How can we detect the level of CD39 ?

Is there any significant correlation between CD39 and other markers?

**Selection criteria of the available researches:**

a) **Type of study:** systematic review.

b) **Time of studies:** studies had been published during the last five years from first of 2007 to 2015

C) **Sites visited:** Cochrane library, PubMed, Medline, Science direct, any other site containing useful information

b) **Key words used:** CD39, Chronic lymphocytic leukemia

e) **The topic of interest:** role of CD39 in chronic lymphocytic leukemia

**Results of the study**

A total of 5 papers were obtained using the mentioned keywords in the research of all internet-based databases.

**Table-1;** Mean age of the study population

The mean age was recorded in 4 papers, and the mean age of each of them was as follows:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Serial** | **Author** | **Year** | **Number of cases** | **Mean age(years)** |
| 1 | **Chava Perry, et al** | 2012 | 62 | 66 |
| 2 | **Nashwa Khairat Abousamra, et al** | 2015 | 68 | 55 |
| 3 | **Dianne Pulte and Richard, et al** | 2011 | 65 | 67 |
| 4 | **Dianne Pulte and** **Olson, et al** | 2007 | 21 | 71 |

**Table-2; The method of detection in different studies**

|  |  |  |  |
| --- | --- | --- | --- |
| **Serial** | **Author** | **year** | **Method** |
| **1** | **Chava Perry, et al** | **2012** | **Flowcytometry** |
| **2** | **Nashwa Khairat Abousamra , et al** | **2015** | **Flowcytometry** |
| **3** | **Dianne Pulte and Richard, et al** | **2011** | **Flowcytometry** |
| **4** | **Dianne Pulte and Olson, et al** | **2007** | **Flowcytometry** |
| **5** | **Jeremy Bastid, et al** | **2014** | **Flowcytometry and immunohistochimistry** |

**Table-3 ; Comparison between stage of the disease and level of CD39**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Serial** | **Author** | **Year** | **Stage** | **Level of CD39 expresseion(%)** |
| **1** | **Chava Perry, etal** | **2012** | **Stage-0**  **Stage 1-2**  **Stage 3-4** | **54.2**  **60.53**  **72.31** |
| **2** | **Nashwa Khairat Abousamra, etal** | **2015** | **Stage 0-2**  **Stage 3-4** | **18.13**  **31.18** |
| **3** | **Dianne Pulte and Richard, etal** | **2011** | **Stage-0**  **Stage 1-2**  **Stage 3-4** | **11.2**  **21.3**  **31.1** |
| **4** | **Dianne Pulte and Olson, etal** | **2007** | **Stage 0-2**  **Stage 3-4** | **88.2**  **44.7** |

**Table-4 ; Important comments and conclusions of different studies**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Serial** | **Author** | **Year** | **Number of cases** | **Conclusion** |
| **1** | **Chava Perry,**  **et al** | **2012** | **62** | **The expression of CD39 on the CD4+**  **lymphocyte pool in patients with CLL and found an association between increased levels of the CD4+CD39+ lymphocyte population and progressive disease. Patients with CLL had higher levels of CD4+CD39+lymphocytes than healthy controls, which correlated with the clinical stage of disease. The highest levels were present in patients with more advanced stages and in those who eventually needed therapy for their disease. Expansion of the CD4+CD39+ cell population was found to correlate with classical clinical prognostic factors such as Rai and Binet stage** |
| **2** | **Nashwa Khairat Abousamra, et al** | **2015** | **68** | **T-cell CD39 expression was significantly increased in patient's peripheral blood compared to healthy controls. The higher levels were associated with advanced stages of disease and negatively interacted with time to first treatment** |
| **3** | **Dianne Pulte and Richard, et al** | **2011** | **65** | **T-lymphocytes CD39 expression is higher in pt with CLL and associated with later stage disease** |
| **4** | **Dianne Pulte and Olson,**  **et al** | **2007** | **21** | **Majority of lymphocytes from CLL patients express active CD39 and amuch higher levels than normal lymphocytes** |
| **5** | **Jeremy Bastid,**  **et al** | **2014** | **500** | **The vascular endothelial always stained positive for CD39 in both normal and tumor cells,interestingly,CD39 expression was higher in tumor tissue more in normal specimens** |

**Discussion**

Chronic lymphocytic leukemia (CLL) is one of the most commonly diagnosed lymphoid malignancies in the western countries, and although it generally has an indolent clinical course, at least 50% of patients are still at risk for disease Progression **(8)**. B cell-type chronic lymphocytic leukemia (B-CLL) cells can be divided into two broad subtypes based on morphology—typical and atypical, typical morphology is defined as small mature-appearing lymphocytes with a large nuclear to cytoplasmic ratio ,condensed chromatin with rare nucleoli ,and few accompanying atypical cells (≤10%), cases with atypical morphology have greater than 10% atypical cells, defined in various way, e.g., prolymphocytes “cleaved,” or “large” lymphocytes ,lymphoplasmacytoid cells, **(9).** Expansion of the CD4+CD39+ cell population was found to correlate with classical clinical prognostic factors such as Rai and Binet stage as well as with the expression of other surrogate markers including ZAP70 positivity and increased levels of β2-microglobulin and LDH**(10).** T-lymphocyte CD39 expression was lower in patients with stage 0 disease compared with patients with either stage 1-2 or stage 3-4

disease and in patients who did not require chemotherapy **(11)**. Unlike CD39−Tregs, CD39+Tregs are resistant to ATP-induced cell death and able to invade the tumor environment , survive, and subsequently suppress antitumor immunity, as increased levels of Tregs have been previously reported to correlate with progressive disease in patients with CLL **(12).** Nashwa et al **,**suggested that T-cell CD39 expression may provide a useful insight into the complex interrelationship of prognostic variables to predict the clinical course of patients with CLL, suggesting its use as a part of panel of molecules (CD38 and ZAP-70) as a new prognostic model, however, the additional clinical value of CD39 indicated in the present study should be validated in larger datasets of well-characterized patients with CLL**(13).** Pulte D et al, proved that CD39 expression is increased in the nonmalignant T-lymphocyte population in patients with CLL , there is a greater increase in patients with later stage disease , in contrast CD73 expression is decreased in patients with CLL compared with controls, but the level of CD73 expression is not strongly associated with stage or the requirement for chemotherapy**(11).** By immunohistochemistry Jeremy bastid et al, found that vascular endothelia always stained positive for CD39 in both normal and tumor tissues, furthermore some lymphocytes in lymph node tissues stained positive for CD39 interestingly, CD39 expression was higher in many tumor tissue than in normal specimens**(14).**

**Conclusion**

In conclusion, the results of our research suggest that the levels CD39 on T Lymphocytes correlates with severity of CLL.

**References:**

1. **Byrd and John;** "Chronic Lymphocytic Leukemia". Leukemia & Lymphoma Society, Retrieved 24 March 2014
2. .**Chiorazzi N, Rai KR, Ferrarini M; (2005).** "Chronic lymphocytic leukemia". N. Engl. J. Med. 352 (8): 804–15. doi:10.1056/NEJMra041720
3. **Deaglio S, Dwyer KM, Gao W and Friedman D, et al**. Adenosine generation catalyzed by CD39 and CD73 expressed on regulatory T cells mediates immune suppression. J. Exp. Med. 2007;204:1257–1265.
4. .**Hyman MC, Petrovic-Djergovic D and Visovatti SH et al** ; Self-regulation of inﬂammatory cell trafﬁcking in mice by the leukocyte surface apyrase CD39.JClinInvest 2009; 119:1136-49. 13.

**5 -Patten PE, Buggins AG, Richards J, et al.** CD38 expression in chronic lymphocytic leukemia is regulated by the tumor microenvironment. Blood 2008;111(10):5173-5181.

**6- Chava Perry and Aaron Polliack,2012** ;Regulatory T cells in chronic lymphocytic leukemia: Leukemia & Lymphoma, May 2013; 54(5): 903–904, 2013 Informa UK, Ltd.ISSN:1042-8194print / 1029-2403 onlineDOI: 10.3109/10428194.2012.747681

**7-Hallek M;** Chronic lymphocytic leukemia: 2017 update on diagnosis, risk stratification, and treatment. Am J Hematol. 2017;92:946–965. [https://doi.org/10.1002/ajh. 24826](https://doi.org/10.1002/ajh.%2024826)

**8-John C. Byrd, Stephan Stilgenbauer and Ian W. Flinn** Chronic Lymphocytic Leukemia doi: 10.1182/asheducation-2004.1.163 ASH Education Book January 1, 2004 vol. 2004 no. 1 163-183

**9-Matutes E, and Polliack A,2000 ;** Morphological and immunophenotypic features of chronic lymphocytic leukemia. First published: March 2000 DOI: 10.1046/j.1468-0734.2000.00002.

**10-Quiroga MP1, Balakrishnan K, Kurtova AV ,et al;**. B-cell antigen receptor signaling enhances chronic lymphocytic leukemia cell migration and survival: Blood. 2009 Jul 30; 114(5): 1029–1037. Prepublished online 2009 Jun 2. doi:  10.1182/blood-2009-03-212837PMCID: PMC4916941,Lymphoid Neoplasia.

**11-Pulte D, Furman RR, Broekman MJ, et al ;** CD39 expression on T lymphocytes correlates with severity of disease in patients with chronic lymphocytic leukemia. Clin Lymphoma Myeloma Leuk 2011;11

**12-D'Arena G, Laurenti L, Minervini MM et al (2011)** Regulatory Tcell number is increased in chronic lymphocytic leukemia patients and correlates with progressive disease. Leuk Res 35:363–368

**13-Nashwa Khairat, Abousamra Manal Salah El-Din, Eman Hamza Elzahaf ,**2015 Ectonucleoside triphosphate diphosphohydrolase-1 (E-NTPDase1/CD39) as a new prognostic marker in chronic lymphocytic leukemiaPages 113-119 | Received 28 Oct 2013, Accepted 18 Mar 2014, Accepted author version posted online: 31 Mar 2014, Published online: 05 Jun 2014

**14-Bastid J, Regairaz A, Bonnefoy N, et al** **;** Inhibition of CD39 enzymatic function at the surface of tumor cells alleviates their immunosuppressive activity. Cancer Immunol Res. 2015;3:254–65.

**الملخص العربي**

يعد سرطان الدم الليمفاوي المزمن واحدا من اللوكيميا الأكثر شيوعا في أمريكا الشمالية، وهو ما يمثل ۲٥٪ -٣٠٪ من جميع سرطانات الدم.

كما يتميز سرطان الدم بزياده في الخلايا الليمفاوية طويلة العمر التي تظهر نضجا في النوع - ب والتي تحمل مجموعة التمايز سي دي- ٥ وسي دي-١٩وسي دي-۲٣.

وقد وجد في سرطان الدم الليمفاوي المزمن ارتفاعا في العدد المطلق للخلايا اللمفياوية - ت والتي سببها الزيادة في عدد الخلايا الحامله لسي دي- ٨ على الرغم من أن العدد النسبي يكون منخفضا بسبب وجود عدد كبير من الخلايا الليمفاوية -ب الخبيثة المتراكمه.

كما إن الخلايا الليمفاوية التائيه تكون اقل انتشارا ونشاطا وبذلك تكون غير قادرة علي تحفيزالخلايا الليمفاوية – ب لانتاج الاجسام المضاده.

جزيء سي دي-٣٩هو جزيء يوجد علي سطح الخلايا البطانية، الخلايا الليمفاوية الطبيعية، وكريات الدم البيضاء الأخرى

وظيفة سي دي-٣٩ الرئيسية على سطح الخلية البطانية هو تقليل تنشيط الصفائح الدمويه عن طريق تكسير أدينوسين ثنائي الفوسفات في كرات الدم البيضاء الانزيم الذي لديه العديد من الآثار المباشرة و الغير مباشرة ، بما في ذلك تعديل التعبير الخلوى والاستجابة الالتهابية .

يوجد سي دي-٣٩ في الاشخاص الذين لا يعانون من هذا المرض بنسبة ٦- ٨ %علي الخلايا التائية بينما يوجد علي اغلب الخلايا الليمفاوية – ب.

جزيء سي دي-٣٩ يوجد بنسبة اعلي علي الخلايا التائية النشطه والخلايا الزاكرة عن الخلايا الليمفاوية الساذجة, كما وجد ارتفاع في نسبة سي دي-٣٩في العديد من امراض الدم من ضمنها سرطان الدم وسرطان الغدد الليمفاوية.

**الخاتمه:**

سي دي-٣٩ يساعد في تشخيص مرض سرطان الخلايا الليمفاويه المزمن ومدي شدة المرض .