

CD39 Expression on T Lymphocytes Correlates With Severity of Disease in Patients With Chronic

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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 immunohistochemistry .

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- 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

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**) increased in patients with β 2-microglobulin levels of >3 g/L compared to patients with β 2-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 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

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

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?

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

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 immunohistochemistry

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	54.2
			Stage 1-2	60.53
			Stage 3-4	72.31
2	Nashwa Khairat Abousamra, etal	2015	Stage 0-2	18.13
			Stage 3-4	31.18
3	Dianne Pulte and Richard, etal	2011	Stage-0	11.2
			Stage 1-2	21.3
			Stage 3-4	31.1
4	Dianne Pulte and Olson, etal	2007	Stage 0-2	88.2
			Stage 3-4	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 ($\leq 10\%$), 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 $\beta 2$ -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.

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