Incidence of lymphoid malignancies in patients with lymphocytosis identified by general practitioners

Marika Kasahara, Kajetan Karaszewski, Maria Król, Mateusz Ziarkiewicz, Wiesław Wiktor Jędrzejczak

Medical University of Warsaw, Warsaw, Poland

Address for correspondence:
Marika Kasahara
Medical University of Warsaw
Zwirki i Wigury 61
02–091 Warsaw, Poland
e-mail: marikakasahara@gmail.com

Hematology in Clinical Practice
2023, vol. 14, 52–54
DOI: 10.5603/hicp.91605

ISSN: 2720–1015
e-ISSN: 2720–2690

Received: August 28, 2022
Accepted: September 29, 2023

ABSTRACT

General practitioners are currently instructed to refer patients with lymphocyte counts exceeding 5.0×10^9/L to hematologists due to the possibility of chronic lymphocytic leukemia (CLL). This study assessed the usefulness of this procedure through the analysis and evaluation of referrals made to a hematologist over a period of 12 years (2010–2022).

During the 12 years, there were 256 patients whose absolute lymphocyte count (ALC) at least once exceeded 5.0×10^9/L and who were referred to the hospital. There were 145 males and 111 females in this group, and the median age was 66. The mean ALC at the time of referral was 30.0×10^9/L

It was found that among the 256 patients, a diagnosis was established for 249 (97.3%) of the patients. There were 224 CLL cases, 2 small lymphocytic leukemia cases, and 5 monoclonal B-cell lymphocytosis cases, making 231 cases with CLL phenotype (92.8%). There were 9 cases of other B-cell lymphomas (3.6%), including 4 mantle cell lymphoma cases, 4 marginal zone lymphoma cases, and 1 splenic lymphoma with villous lymphocytes case. Furthermore, there were 6 cases of T-cell lymphomas (2.4%), including 5 T-cell large granular lymphocyte cases and 1 T-cell prolymphocytic leukemia case. The cohort also had 1 acute myeloid leukemia (AML) case (0.4%) and 3 reactive lymphocytosis cases (1.2%), including 1 with infectious mononucleosis (0.4%). In the group, 16/224 patients (7.1%) with CLL and 1 with AML required immediate treatment.

The ALC has demonstrated its reliability as a possible dependable diagnostic tool in a specific cohort of patients with suspected lymphoid malignancy.

Keywords: absolute lymphocyte count, chronic lymphocytic leukemia, lymphoid malignancy

INTRODUCTION

Peripheral blood lymphocytosis is a hallmark of chronic lymphocytic leukemia (CLL) and is commonly used for the early diagnosis of this disease [1]. However, it is not always appreciated that this may also be the first sign of other lymphoid malignancies. The patients included in this study were specifically referred to a hematologist in order to undergo assessment due to suspected hematopoietic system malignancy. In Poland, general practitioners are advised [2] to refer patients with lymphocytosis over 50.0×10^9/L to a hematologist. Some of these patients would not have monoclonal B-cell counts $\geq 50.0 \times 10^9$/L and would fall into the category of monoclonal B-cell lymphocytosis (MBL) [3]. Moreover, lymphocytosis over 5.0×10^9/L may also be reactive [4] and, as mentioned, could be produced by other related malignancies.

The purpose of this study is to evaluate the efficacy of the absolute lymphocyte count (ALC) as a dependable diagnostic tool for detecting lymphoid malignancy in patients referred to a hematologist based on suspicion of lymphoid malignancy.

MATERIAL AND METHODS

There was a cohort of 256 patients in the study (145 males and 111 females) aged between 27 and 80, with a median of 66.

Complete blood counts with differential (both automatic and manual) were performed using standard methods. In addition, flow cytometry was performed to characterize lymphoid cells in the peripheral blood. The following markers were used for analysis: CD5, CD19, CD20, CD10, CD22, CD23, CD38, CD200, CD43, CD3, CD8, CD4, CD5,

Table 1. Patients' comprehensive characteristics

Diagnosis	Cases	Average age at diagnosis	Males /females ratio	Lymphocytes at diagnosis [× 10^9/L]	Leukemic cells at diagnosis [× 10^9/L]	Requiring treatment in total (at the time and after diagnosis)
Total	256	66	145/111	30.0	19.8	81
CLL	224	66	129/95	32.3	21.8	77
MBL	5	52.7	3/2	10.9	3.9	0
SLL	2	44	0/2	18	10.3	0
MZL	4	70	1/3	10.9	5.0	2
MCL	4	66.5	2/2	30.8	20.4	1
T-LGL	5	68.6	3/2	7.6	5.5	0
T-PLL	1	49	1/0	–	25	0
AML	1	–	0/1	–	–	1
SLVL	1	–	0/1	14.7	–	0
Reactive	3	28	2/1	8	–	0

AML — acute myeloid leukemia; CLL — chronic lymphocytic leukemia; MBL — monoclonal B-cell lymphocytosis; MCL — mantle cell lymphoma; MZL — marginal zone lymphoma; SLL — small lymphocytic leukemia; SLVL — splenic lymphoma with villous lymphocytes; T-LGL — T-cell large granular lymphocyte; T-PLL — T-cell prolymphocytic leukemia

CD7, CD2, CD45RA, CD45RO, TcRαβ, TcRγδ, CD71, CD14, CD45, and immunoglobulins κ and λ in order to determine the immunophenotype of lymphoid cells and to establish a diagnosis.

The following variables were analyzed and compared: age, sex, lymphocyte count, lymphocyte percentage, white blood cell count, percentage of B cells of CD19+ phenotype, neoplastic cell count, neoplastic cell percentage, final diagnosis, date of diagnosis, date of treatment, and vital status of patients.

RESULTS

The level of ALC, which has prompted general practitioners to refer patients to a hematologist with suspicion of CLL, was between 5.0×10^9/L to 221.9×10^9/L; the mean was 30.0×10^9/L. The percentage of lymphocytes in the differential leukocyte count was 75.3% [95% confidence interval (CI): 73.1–77.5%]. White blood cell count was averaged at 36.5×10^9/L (95% CI: 31.1–42.0 × 10^9/L).

The frequency of leukemic cells, as defined by flow cytometry, was 59.3% (95% CI: 55.9–62.8%). The mean absolute number of neoplastic cells was 19.8 × 10^9/L (95% CI: 14.0–25.5 × 10^9/L). In the evaluated cohort of 249 diagnosed patients, there were 224 CLL cases, 2 small lymphocytic leukemia (SLL) cases, and 5 MBL cases, making 231 cases with a CLL phenotype (92.8%). Additionally, there were 9 cases of other B cell lymphomas (3.6%), including 4 mantle cell lymphoma (MCL) cases, 4 marginal zone lymphoma (MZL) cases, and 1 splenic lymphoma with villous lymphocytes (SLVL) case. There were 6 cases of T-cell lymphomas (2.4%), including 5 T-cell large granular lymphocyte (T-LGL) cases and 1 T-cell prolymphocytic leukemia (T-PLL) case. This cohort also had 1 acute myeloid leukemia (AML) case and 3 cases of reactive lymphocytosis; among them, there was 1 case of infectious mononucleosis. The mean value of lymphoid cells with a typical phenotype of CD19+ was 70.6% (95% CI: 63.8–77.3%). The positive predictive value (PPV) for CLL was 87.5%, meanwhile for the other malignancies it was 7%. More precise characteristics of the patients are shown in Table 1.

Of the 224 CLL patients for whom there was information available, 16 (7.1%) met the International Workshop of Chronic Lymphocytic Leukemia (iwCLL) criteria to start treatment at the time of diagnosis; there was also 1 AML patient who required immediate initiation of the treatment. The remaining patients were managed according to "watch and wait" strategies. The number of CLL patients that have been confirmed to require treatment at any time from the diagnosis was 77 (data available for 76). On the other hand, 67 patients did not require treatment until the end of their follow-up in this study.

The follow-up period ranged from 6 to 170 months, and the median follow-up duration was 27 months.

DISCUSSION

Unexpectedly, in a search of the PubMed database for the subject: "absolute lymphocyte count in lymphoid malignancy", there were only 107 entries, none of which provided similar information related to this study. Similarly, a search of the subject "absolute lymphocyte count in lymphoid leukemia" revealed 274 entries and only one individual entry relevant to the subject. Based on a study with histologically confirmed patients with CLL, Hayran et al. [5] suggested the ALC of 6.65×10^9/L as a threshold to initiate the diagnostic procedure for CLL. In another study, Thalhammer-Scherrer et al. [6] investigated four hundred peripheral blood samples with flow cytometry for lymphoid malignancies. They found that 78% of samples with ALC ≥ 4.0×10^9/L and 2% of samples with ≤ 4.0×10^9/L exhibited a specific lymphoma phenotype. In the study of te Raa et al. [7] involving 520 patients with lymphocytosis above 3.5 × 10^9/L, 207 were found to have CD19+ cells indicating the presence of lymphoid malignancy. The present study's threshold of 5.0×10^9/L was chosen based on Polish guidelines for general practitioners. It was found that adopting this value resulted in a diagnosis of blood

malignancy in 97.3% of cases; therefore, it is highly effective in practice. It was found that 7.1% of these patients required immediate treatment, while the remaining patients were put on active surveillance in order to start treatment after meeting specific criteria. The proportion of MBL in the present cohort was significantly lower than in the study conducted by Shanafelt et al. [8], who reclassified 42% of former CLL patients into MBL after a change of the criteria to diagnose CLL from 5.0×10^9/L lymphocytes threshold to 5.0×10^9/L B-monoclonal cells. It might be due to a different policy or referral process, i.e., referral of patients with any lymphocytosis and not with lymphocytosis exceeding 5.0×10^9/L. In the present cohort, only 7.1% of CLL patients met the criteria to start therapy at diagnosis. Simultaneously, this suggests that the vast majority of patients were diagnosed incidentally, and only a few because of symptoms of leukemia such as lymphadenopathy, anemia, or B symptoms. The number of 7.1% may seem low, but it is rather a measure of the health care system. In better healthcare systems this number may even be lower, and in poorly organized systems it may be significantly higher.

It is unknown, how the present cohort reflects the situation in the population from which it was sampled. However, it is unlikely that Polish general practitioners were reluctant to refer patients with lymphocytosis to a hematologist. In Poland, general practitioners have no access to additional laboratory tests to evaluate lymphocytosis. They may postpone referral for one or two months in the case of moderate lymphocytosis hoping that it may disappear with time. Potential causes of such lymphocytosis include viral infections (such as influenza, mononucleosis, hepatitis, cytomegalovirus), rarely bacterial infections (such as pertussis, tuberculosis, brucellosis, rickettsial infections, and syphilis) [9], drug-induced lymphocytosis as a part of hypersensitivity syndrome [10, 11] or congenital lymphocytosis [12]. Finally, they refer patients with persistent lymphocytosis. The exact proportion of patients who followed this approach is unknown. On the other hand, all symptomatic patients, such as those demonstrating lymphadenopathy, fever, frequent infections, night sweats, weight loss, fatigue, and abdominal discomfort (organomegaly) [3] were most likely referred immediately. Additional information, such as files from general practitioners and data from other institutions, is necessary to obtain the conclusive value of peripheral blood lymphocytosis as a screening test for lymphoid malignancy.

CONCLUSION

ALC was confirmed as a potential dependable diagnostic tool in patients with a suspicion of chronic lymphocytic leukemia or other lymphoid malignancies.

Article Information and Declarations

Acknowledgments: None.

Conflict od interest: The authors declare no conflict of interest.

Funding: None.

Supplementary material: None.

REFERENCES

1. Müller-Hermelink HK, Montserrat E, Catovsky D, Campo E, Harris NL. Chronic lymphocytic leukaemia/small lymphocytic lymphoma. In: Swerdlow SH, Campo E, Harris NL. ed. WHO classification of tumours of the haematopoietic and lymphoid tissues. IARC Press, Lyon 2008.
2. Jędrzejczak WW. Wczesna diagnostyka chorób krwi — wskazania do skierowania chorego do hematologa. In: Jędrzejczak WW, Robak T, Podolak-Dawidziak M ed. Praktyka hematologiczna. Termedia, Poznań 2017: 109–114.
3. Hallek M, Cheson BD, Catovsky D, et al. International Workshop on Chronic Lymphocytic Leukemia. 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. 2008; 111(12): 5446–5456, doi: 10.1182/blood-2007-06-093906, indexed in Pubmed: 18216293.
4. Eichhorst B, Robak T, Montserrat E, et al. ESMO Guidelines Committee. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021; 32(1): 23–33, doi: 10.1016/j.annonc.2020.09.019, indexed in Pubmed: 33091559.
5. Hayran M, Koca E, Haznedaroglu IC, et al. Predicting chronic leukaemias from assessment of complete peripheral blood counts. J Int Med Res. 2006; 34(6): 640–647, doi: 10.1177/147323000603400609, indexed in Pubmed: 17294996.
6. Thalhammer-Scherrer R, Veitl M, Exner M, et al. Role of immunological lymphocyte subset typing as a screening method for lymphoid malignancies in daily routine practice. Cytometry. 2000; 42(1): 5–10, indexed in Pubmed: 10679737.
7. te Raa GD, Fischer K, Verweij W, et al. Use of the CD19 count in a primary care laboratory as a screening method for B-cell chronic lymphoproliferative disorders in asymptomatic patients with lymphocytosis. Clin Chem Lab Med. 2011; 49(1): 115–120, doi: 10.1515/CCLM.2011.018, indexed in Pubmed: 21054188.
8. Shanafelt TD, Kay NE, Call TG, et al. MBL or CLL: which classification best categorizes the clinical course of patients with an absolute lymphocyte count >or= $5\times10^9L^{-1}$ but a B-cell lymphocyte count $<5\times10^9L^{-1}$? Leuk Res. 2008; 32(9): 1458–1461, doi: 10.1016/j.leukres.2007.11.030, indexed in Pubmed: 18179821.
9. Stock W, Hoffman R. White blood cells 1: non-malignant disorders. Lancet. 2000; 355(9212): 1351–1357, doi: 10.1016/S0140-6736(00)02125-5, indexed in Pubmed: 10776761.
10. Teraki Y, Shibuya M, Izaki S. Stevens-Johnson syndrome and toxic epidermal necrolysis due to anticonvulsants share certain clinical and laboratory features with drug-induced hypersensitivity syndrome, despite differences in cutaneous presentations. Clin Exp Dermatol. 2010; 35(7): 723–728, doi: 10.1111/j.1365-2230.2009.03718.x, indexed in Pubmed: 19874350.
11. Akcam FZ, Aygun FO, Akkaya VB. DRESS like severe drug rash with eosinophilia, atypic lymphocytosis and fever secondary to ceftriaxone. J Infect. 2006; 53(2): e51–e53, doi: 10.1016/j.jinf.2005.10.028, indexed in Pubmed: 16352341.
12. Snow AL, Xiao W, Stinson JR, et al. Congenital B cell lymphocytosis explained by novel germline CARD11 mutations. J Exp Med. 2012; 209(12): 2247–2261, doi: 10.1084/jem.20120831, indexed in Pubmed: 23129749.