Article published online: 2023-10-13

Analysis of Treatment Outcome in Large Granular Lymphocytic Leukemia: A Retrospective Study from India

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South Asian J Cancer

Abstract

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Large granular lymphocytic (LGL) leukemia is a rare and indolent lymphoproliferative disorder that belongs to mature T and natural killer (NK) cell neoplasms, as per the World Health Organization classification. This article assesses the response to immunosuppressive therapy. In this retrospective study, various cases of chronic lymphoproliferative disorders (CLPDs) evaluated and treated in two tertiary care settings were screened and taken for subanalyses. After fulfilling the criteria for LGL leukemia, cases were further assessed for presenting features and response to treatment. Statistical analysis was performed using the Statistical Package for the Social Sciences, version 23. Out of 384 cases of CLPDs analyzed, 14 cases of LGL leukemia were identified (3.64%) and subjected to further analysis. There were six males (42.85%) and eight females (57.14%) (M: F = 1:1.33) with an age group ranging from 42 to 82 years. Thirteen cases (92.85%) were T-LGL type, and one case belonged to NK-LGL type (7.14%). Anemia was the most common presentation (92.85% of cases), followed by lymphocytosis (85.71% of cases) and neutropenia (78.57% of cases). Four patients (28.57%) presented with thrombocytopenia, and two patients presented with pancytopenia (14.28%). Splenomegaly was seen in two patients (14.28%), and lymphadenopathy in one patient (7.14%). One patient (7.14%) had rheumatoid arthritis, and one (7.14%) had recurrent chest infections. Out of the 14 cases, 5 (35.71%) attained complete remission, 5 (35.71%) attained partial remission, 2 patients were resistant to first-line treatment, and 2 patients were closely followed with observation only. The overall treatment response rate was 83.33%. This study highlights the excellent response rates with immunosuppressive therapy in a rare lymphoproliferative disorder.

Keywords

- large granular lymphocytic leukemia
- chronic lymphoproliferative disorder
- remission

DOI https://doi.org/10.1055/s-0043-1773806 ISSN 2278-330X

How to cite this article: Zafar MSH, Geelaani SA, Bhat JR. Analysis of Treatment Outcome in Large Granular Lymphocytic Leukemia: A Retrospective Study from India. South Asian J Cancer 2023;00 (00):00–00

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Large granular lymphocytic (LGL) leukemia is a low-grade and rare lymphoproliferative disorder that is recognized as cytotoxic T and natural killer (NK) cell lymphomas and leukemia in the 2016 World Health Organization classification. It involves lymphocytic infiltration of several organs including the bone marrow (BM), liver, and spleen.[1,2] LGL leukemia constitutes 2 to 5% of all chronic lymphoproliferative disorders (CLPDs) in the United States and Europe and 5 to 6% of all cases in the Asian population. Recent demographic studies of European and North American cohorts place the average incidence of LGL leukemia at 0.2 to 0.72 per million persons per year.[3]

T-LGL leukemia and NK-LGL leukemia subtypes form more than 85 and 10% of cases, respectively, while aggressive NK-LGL leukemia is rare and represents 5% of LGL proliferations. LGL leukemia is associated with a median overall survival of 9 to 10 years. Mortality is mainly due to severe infections that occur in about 10% of the patients.[4,5]

Clinical presentation involves neutropenia (85%), recurrent infections (15–56%), anemia (5–35%), splenomegaly (20–50%), thrombocytopenia (20%), rheumatoid arthritis (RA) (11–35%), and B symptoms (20–30%); however, lymphadenopathy is very rare. Recommendations regarding treatment are similar for the main two subtypes of LGL leukemia.[6,7]

With this background and deficiency of data regarding treatment outcomes of this unusual disorder in Indian literature, the present study was conducted in two tertiary care hospitals of North India, with the hope that it will form baseline data for future reference.

Materials and Methods

Various cases of CLPDs evaluated and treated in the departments of clinical hematology of two tertiary care hospitals from March 2014 to March 2020 were screened and taken for analysis. It was a retrospective study in which cases were analyzed for demographic data, clinical presentation, complete blood counts, blood chemistry, peripheral blood film (PBF), autoimmune profile, immunophenotyping of blood, T-cell receptor (TCR) gene rearrangement by polymerase chain reaction (PCR), BM examination with immunohistochemistry in relevant cases, and importantly treatment outcome in each case. After fulfilling the diagnostic criteria for LGL leukemia, cases were further assessed. Diagnostic criteria used were: PBF documented LGLs $>500/\mu L$ and subsequent confirmation by immunophenotyping or immunohistochemistry of BM biopsy for LGL leukemia. For clonality assessment T-cell gene rearrangement by PCR was available in four cases because it was not available at our institutions and samples were outsourced in affording patients.

LGLs are large sized (15–18 µm), with abundant cytoplasm containing azurophilic granules, and a reniform or round nucleus with mature chromatin. In physiologic conditions, these cells represent 5 to 10% of total lymphocytes, do not exceed 250/µL, and are mainly NK type. Increased number of circulating LGLs forms the basic step of LGL leukemia diagnosis. A threshold of 500 LGLs/µL is now generally accepted. Only 40 to 50% of patients present with hyperlymphocytosis at diagnosis. LGL leukemia is typically characterized by a postthymic mature cell phenotype. Briefly, T-LGL patients express CD3+, CD8+, CD57+, and TCR-αβ or TCR-γδ, while NK-LGL patients express CD3+, CD8+, CD16+, and CD56+.[8,9]

Diagnosis is confirmed by the detection of clonality, making it possible to distinguish reactive LGL proliferation from real LGL leukemic proliferation. T-LGL can easily be tested for clonality on the basis of TCR gene rearrangement analysis. It is difficult to assess the clonality of NK-LGL because these cells do not express TCR.[10] All those patients in whom TCR gene rearrangement was not available the diagnosis was made on the basis of classical peripheral blood/BM picture along with immunophenotyping and immunohistochemistry markers.

All the patients were put on specific immunosuppressive therapy like prednisolone (0.5–1 mg/kg/day), methotrexate (10 mg/m^2/week), cyclosporine (3 mg/kg/day), and cyclophosphamide (100 mg/day) either as single agent or in various combinations and monitored for response every 6 weeks as per the data available in this retrospective study. Treatment was used in symptomatic patients with severe neutropenia (absolute neutrophil count [ANC] $<0.5\times10^9$/L) or moderate neutropenia (ANC 0.5×10^9/L to 1×10^9/L) associated with recurrent infections, or symptomatic or transfusion-dependent anemia and associated autoimmune disorders requiring treatment.[11] Response assessment was done by monitoring clinical features, complete blood counts, PBF, immunophenotyping of blood or immunohistochemistry of trephine biopsy, and imaging studies in relevant cases. Complete remission (CR) was defined by normalization of blood counts including PBF, hemoglobin (Hb) >10 g/dL, ANC $>1000\times10^9$/L and platelet count $>100\times10^9$/L), immunophenotypically documented absence of LGLs, and imaging-proven no organomegaly or lymphadenopathy. Partial remission (PR) was defined by at least 50% reduction in measurable disease and no transfusion dependence. Declaration of Helsinki (1975) guidelines as revised in 2013 were followed for the data analysis.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 23 (SPSS 23, IBM, Chicago, Illinois, United States). A p-value of <0.05 was considered as statistically significant. Categorical variables were presented in frequency (%). In this retrospective study, there are no patient-identifying data and no new tests or interventions were performed. Data analyzed were collected as part of routine diagnosis and treatment and hence no approval was required.

Results

Out of 384 cases of CLPDs analyzed, 14 cases of LGL leukemia were identified (3.64%) and subjected to further analyses.

Thirteen cases (90.85%) were T-LGL type and one case belonged to NK-LGL subtype (7.14%). Thus, T-LGL formed the most common subtype. There were six males (42.85%) and eight (57.14%) females (M:F = 1:1.33) with age group ranging from 42 to 82 years.

Anemia was the most common presentation, seen in 13 patients (92.85%) with median Hb of 7.8 g/dL. Twelve patients (85.70%) had lymphocytosis at presentation with median lymphocyte count of 9800/µL. Eleven patients (78.57%) presented with neutropenia with median neutrophil count of 1100/µL while four patients (28.57%) had thrombocytopenia with median platelet count of 167.5/µL. Splenomegaly was seen in two patients (14.28%) and lymphadenopathy in one patient (7.14%). One patient (7.14%) had RA and one (7.14%) had recurrent chest infections (►Table 1). Anemia, lymphocytosis, and neutropenia were frequent presentations. One patient was diagnosed incidentally during the evaluation process of diabetes mellitus. Overall, 2 patients (14.28%) were asymptomatic at presentation.

Of 14 cases, two patients received cyclosporine, both attained CR (median duration 5 months; range 4–6 months). Four patients received methotrexate, one attained CR, two attained PR, and one was resistant (median duration: 7 months; range 2–9 months). One patient received cyclophosphamide that attained CR (duration 6 weeks). Four patients received methotrexate plus prednisolone out of which one attained CR, two attained PR, and one was resistant (median duration 8 months: range 2–11 months). One patient received prednisolone only and responded to PR (duration 2 months) (►Table 2). Hence, 5 patients (35.70%) attained CR, 5 patients (35.70%) attained PR, 2 patients were resistant to first-line treatment, and 2 asymptomatic patients were closely followed with observation only (►Table 2). Overall treatment response was 83.33% (►Table 3). There was no significant treatment-related toxicity and all the patients tolerated the therapy well. Treatment toxicities were monitored by performing regular complete blood counts, liver function tests, kidney function tests, blood glucose levels, and pulmonary function tests in addition to the clinical history and physical examination. The resistant cases were put on second-line treatment (CHOP protocol).

Table 1 Clinical profile of LGL leukemia patients

Variable	Frequency (*N*: 14)	Percentage (%)
Males	6	42.85
Females	8	57.14
Anemia	13	92.85
Thrombocytopenia	4	28.57
Neutropenia	11	78.52
Pancytopenia	2	14.28
Recurrent chest infections	1	7.14
Splenomegaly	2	14.28
Lymphadenopathy	1	7.14
Lymphocytosis	12	85.71
Rheumatoid arthritis	1	7.14
Ulcerative colitis	1	7.14
T-LGL	13	92.85
NK-LGL	1	7.14

Abbreviations: LGL, large granular lymphocytic; NK, natural killer.

Table 2 Distribution of patients as per treatment used

Case	Treatment	Outcome
1	Cyclosporine	CR
2	Methotrexate	Resistant
3	Methotrexate + Prednisolone	PR
4	Cyclophosphamide	CR
5	Observation	Stable
6	Methotrexate + Prednisolone	PR
7	Prednisolone	PR
8	Methotrexate + Prednisolone	CR
9	Prednisolone + Methotrexate	Resistant
10	Observation	Stable
11	Methotrexate	CR
12	Methotrexate	PR
13	Cyclosporine	CR
14	Methotrexate	PR

Abbreviations: CR, complete response PR, partial response.

Table 3 Response to treatment in LGL leukemia

Variable	Frequency (*N*: 14)	Percentage (%)
Complete response	5	35.71
Partial response	5	35.71
Resistant	2	14.28
Observation only	2	14.28
Overall response rate	10/12	83.33

Abbreviation: LGL, large granular lymphocytic.

Discussion

LGL leukemia commonly affects either men or women with the same proportion at a median age of 60 years. Only 20 to 25% of patients are younger than 50 years. Our study showed slight female preponderance.

Predominant patient population is symptomatic at the time of diagnosis with neutropenia as the most common feature. However, the present study showed anemia (92.85% cases) followed by lymphocytosis (85.71% cases) and neutropenia (78.57% cases) as the common presenting features.

There are no significant differences in clinical features between the two main subtypes of LGL leukemia.[12]

Table 4 Comparison of various studies

Therapy	Type of study	No. of patients	ORR	CR
Methotrexate				
Sanikommu et al (2018)	Retrospective	34	44%	5%
Loughran et al (2015)	Prospective	54	38%	50%
Loughran et al (1994)	Prospective	10	60%	14%
Bareau et al (2010)	Retrospective	36	44%	
Cyclophosphamide				
Sanikommu et al (2018)	Retrospective	22	47%	47%
Moignet et al (2014)	Retrospective	45	72%	46%
Poullot et al (2014)	Retrospective	13	69%	38%
Dhodapkar et al (1994)	Retrospective	16	63%	38%
Cyclosporine				
Sanikommu et al (2018)	Retrospective	44	45%	
Osuji et al (2006)	Retrospective	14	92%	
Combination				
Present study	Retrospective	14	83.33%	35.71%

Abbreviations: CR, complete response; ORR, overall response rate.

Splenomegaly is seen in 25 to 50% of patients, whereas hepatomegaly and lymphadenopathy are rare features.[6,7] RA is present in 11 to 36% of patients and is mostly diagnosed before the onset of LGL leukemia. Recurrent infections associated with neutropenia occur in 15 to 56% of patients, mostly with mucocutaneous or respiratory involvement. In our study, splenomegaly was seen in two patients (14.28%) and lymphadenopathy in one patient (7.14%). One patient (7.14%) had RA prior to the diagnosis of LGL leukemia and one patient (7.14%) had recurrent chest infections. Additionally, four patients (28.57%) had thrombocytopenia and two patients (14.28%) presented with pancytopenia at the time of diagnosis.

T-LGL leukemia can be observed as posttransplant lymphoproliferative disorder.[13] Very rarely, pulmonary artery hypertension has been seen. Aggressive NK-LGL leukemia patients present with organomegaly, B symptoms, a high LGL count, and massive LGL marrow infiltration. The prognosis is very poor in these cases because patients are refractory to any treatment.[4]

Immunosuppressive therapy forms the cornerstone of LGL leukemia treatment. T-LGL leukemia and NK-LGL leukemia share the same treatment options. Treatment efficiency is related in several retrospective series, but only a few prospective trials are available (►**Table 4**). Sanikommu et al in a retrospective study of 34 patients documented overall response rate (ORR) of 44%.[14] Loughran et al in a prospective study of 54 patients showed ORR of 54% and complete response of 5%.[15] Moignet et al in a retrospective study of 45 patients demonstrated 72% ORR and 47% complete response.[16] Poullot et al in a retrospective study of 13 patients showed ORR of 69% and complete response of 46%.[17] In our study, out of 14 cases, 5 (35.71%) attained CR, 5 (35.71%) attained PR, and 2 patients (14.28%) were resistant to first-line therapy. ORR was 83.33%. Follow-up data was available in 7 out of 10 responding patients. Five patients attained long-term remission (> 30 months) while two patients relapsed within 18 months of treatment and were put on second-line therapy. The present study highlights the excellent response rates with immunosuppressive therapy as compared to the previous studies in this rare disorder.

Conclusion

LGL leukemia is a rare lymphoproliferative disorder which needs high index of suspicion for early diagnosis. Our study shows anemia as the predominant presentation especially in the presence of neutropenia and lymphocytosis that should alert the treating physician to look for peripheral LGLs and subsequent flow cytometry of blood or immunohistochemistry of BM trephine biopsy. This study highlights the excellent response rates with immunosuppressive therapy and forms the baseline data for future reference. However, it has limitation of smaller sample size which can be improved by future prospective observational study with larger sample size.

Funding
None.

Conflict of Interest
None declared.

Acknowledgment
We thank the Departmental staff of Clinical Hematology for helping us in data collection.

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