



Alexey Bobylev. *Shuya River*, 2002. Oil on canvas, 55 × 75 cm. Courtesy of the St. Petersburg Art Salon, Russia.

LGL leukemia represents a variety of clinicopathologic entities with diverse etiologies, biologic behaviors, and prognoses.

Diseases of Large Granular Lymphocytes

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Background: Clonal diseases of large granular lymphocytes (LGLs) are rare lymphoproliferative malignancies that arise from either mature T-cell (CD3+) or natural killer (NK)-cell (CD3-) lineages. They manifest a distinct biologic behavior that ranges from indolent to very aggressive.

Methods: We discuss four distinct diseases involving LGLs: indolent T-cell LGL leukemia, aggressive T-cell LGL leukemia, chronic NK-cell leukemia, and aggressive NK-cell leukemia. Furthermore, we present an up-to-date systematic review of therapies for each entity.

Results: Sustained LGLs, characteristic immunophenotype, clonal origin of leukemic cells, and clinical presentation are the most important features that distinguish indolent from aggressive subtypes of LGL leukemia and guide the selection of therapy. Patients with symptomatic indolent T-cell or NK-cell LGL leukemia are usually treated with immunosuppressive therapies in contrast to aggressive T-cell and NK-cell LGL leukemia, which require intensive chemotherapy induction regimens. Novel targeted therapies using monoclonal antibodies against receptors, including CD2, CD52, the β subunit of the interleukin-2 receptor, and small molecules such as tipifarnib, are undergoing evaluation in clinical trials.

Conclusions: Future scientific advances focusing on the delineation of molecular pathogenic mechanisms and the development of new targeted therapies for each distinct LGL leukemia entity should lead to improved outcomes of patients with these disorders.

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The authors have disclosed that this article discusses unlabeled/unapproved uses of drugs methotrexate, cyclophosphamide, cyclosporine, alemtuzumab, siplizumab, fludarabine, tipifarnib, and MiK- β -1 for T-cell and NK-cell LGL leukemia.

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Abbreviations used in this paper: LGL = large granular lymphocyte, NK = natural killer, WHO = World Health Organization, MAPK/ERK = mitogen-activated protein kinase/extracellular signal-regulated kinase.

Introduction

Diseases of large granular lymphocytes (LGLs) are rare clonal lymphoproliferative neoplasms derived from either T-cell or natural killer (NK)-cell lineages.¹ LGLs represent 10% to 15% of the total peripheral blood mononuclear cells in healthy adults. T-cell LGLs (CD3+) are mature postthymic, antigen-primed CD8+ cytotoxic cells. NK-cell LGLs (CD3-) belong to the innate immune system and have the capability of non-major histocompatibility complex-restricted cytotoxicity. LGL leukemias may behave either in an indolent manner or as rapidly progressive hematologic neoplasms necessitating aggressive treatment.² Herein, we discuss the four distinct disorders involving LGLs: T-cell LGL leukemia, aggressive T-cell LGL leukemia, chronic NK-cell leukemia, and aggressive NK-cell leukemia.

T-Cell LGL Leukemia

Epidemiology and Pathogenesis

T-cell LGL leukemia is the most frequent LGL disorder in Western countries and accounts for 85% of all cases.² The median age at diagnosis is 60 years without gender predilection. The term *large granular lymphocyte leukemia* was first introduced by Loughran³ in 1985 and later accepted by all pathologic classification systems including the most recent World Health Organiza-

tion (WHO) classification of tumors of hematopoietic and lymphoid tissues.⁴ The etiology of T-cell LGL leukemia has not been entirely elucidated; however, chronic antigenic stimulation with exogenous antigens such as human T-cell lymphotropic virus (HTLV) or putative endogenous autoantigens may be responsible for inducing the activation and clonal expansion of effector CD8+ LGLs.⁵ Nonrandom clonal selection of malignant LGLs in patients with T-cell LGL leukemia was recently detected by sequencing the variable beta (V β)-chain complementarity-determining region 3 (CDR3).⁶ These data support the hypothesis of a common putative antigen responsible for proliferation of these cells. The exact role of retroviral infection as an etiologic agent has not been entirely established.⁷⁻¹⁰ Most patients with T-cell LGL leukemia are not infected with prototypical HTLV-I or HTLV-II, but they demonstrate seroindeterminate reactivity against a small peptide derived from the HTLV-I env protein p21e.^{9,10} There have been only two reported cases of patients with T-cell LGL leukemia whereby HTLV-II viral sequences have been detected.^{7,8} Another possible mechanism implicated in the pathogenesis of indolent T-cell LGL leukemia besides antigen-stimulated proliferation is inhibition of apoptosis with accumulation of leukemic LGLs.⁵ Dysregulation of several intracellular signaling pathways, including FAS/FAS-L, phosphatidylinositol-3 kinase (PI3K), and mitogen-activated protein-kinase/extracellular signal-regulated kinase (MAPK/ERK),

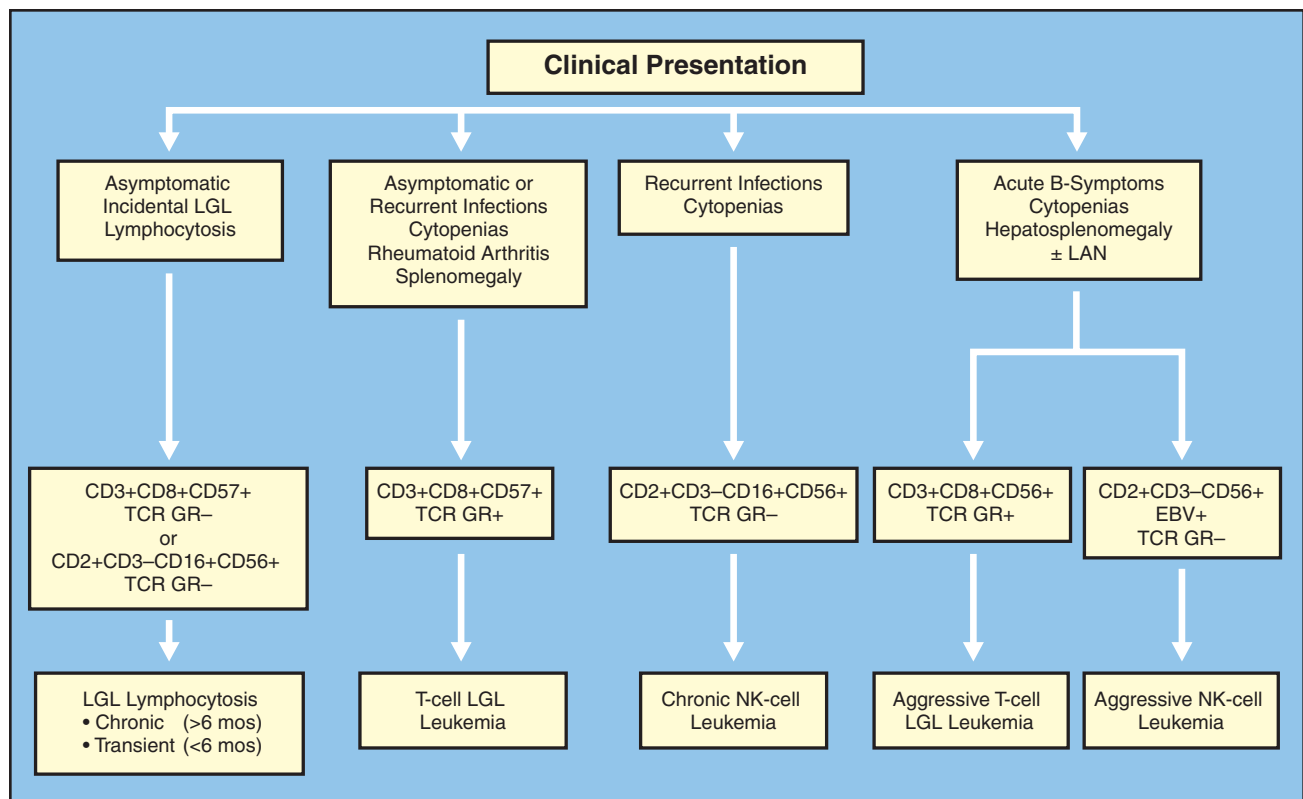


Fig 1. — Diagnostic algorithm based on clinical presentation. EBV = Epstein-Barr virus, LAN = lymphadenopathy, TCR-GR = T-cell receptor gene rearrangement.

were associated with intrinsic resistance to apoptosis in leukemic LGLs in *in vitro* studies.¹¹⁻¹³ Although no specific mutations in genes coding for key factors of the above signaling pathways were detected, these experiments revealed potential molecular targets for novel therapeutic approaches.

Clinical Manifestations

Although most cases of LGL leukemia behave in an indolent manner, approximately 60% of patients become symptomatic during the course of their disease.^{14,15} The majority of patients with LGL leukemia present with an absolute LGL count greater than $2.0 \times 10^9/L$ (normal range $0.2-0.4 \times 10^9/L$). Eighty percent of patients with LGL leukemia develop neutropenia, while approximately 45% of patients experience severe neutropenia as defined by an absolute neutrophil count $<0.5 \times 10^9/L$.^{1,2,16} Multiple mechanisms have been postulated for neutropenia associated with LGL leukemia including FAS/FAS-L-induced premature apoptosis of neutrophils and myeloid precursors, antibody- or immune-complex-mediated neutrophil destruction, hypersplenism, and direct inhibition of myeloid progenitors by leukemic LGLs in the bone marrow.^{2,16-18} Recurrent bacterial infections secondary to neutropenia are common initial clinical manifestations of LGL leukemia.^{15,17} Most of these infections are mucocutaneous. The development of opportunistic infections is not characteristic of LGL leukemia.¹⁵ Anemia caused by various pathogenic mechanisms was reported in 48% of patients.¹⁹ In a single institutional study, T-cell LGL leukemia was the most common cause of pure red cell aplasia.²⁰ Thrombocytopenia (detected in 20% of patients) and splenomegaly (detected in 20% to 50% of patients) are also frequently associated manifestations of T-cell LGL leukemia (Fig 1).^{2,19} The presence of lymphadenopathy would be considered an unusual disease manifestation.¹ Acute onset of B symptoms is a rare manifestation of indolent LGL leukemia; however, chronic fatigue is common. Autoimmune disorders such as rheumatoid arthritis occur in 25% to 35% of patients with T-cell LGL leukemia.^{1,2} Rheumatoid arthritis, neutropenia, and splenomegaly known as Felty syndrome can be difficult to distinguish from T-cell LGL leukemia associated with rheumatoid arthritis.²¹ Both conditions have a higher frequency of HLA-DR4 haplotype compared to the general population, suggesting a common immunologic mechanism. It is still debated whether these two conditions represent the same disease entity.¹⁷ Increased prevalence of Sjögren's syndrome (27%) in patients with T-cell LGL leukemia has recently been reported.²² Other autoimmune disorders including systemic lupus erythematosus, and Hashimoto's thyroiditis can occur in patients with this disorder, but less frequently.^{1,23} Immune serologic abnormalities such as positivity for rheumatoid factor, antinuclear antibodies,

and circulating immune-complexes were demonstrated in 40% to 60% of patients.¹⁹ Dysregulation of the normal function of B-cells due to the presence of malignant LGLs and production of proapoptotic and proinflammatory cytokines is most probably responsible for increased autoimmunity in patients with T-cell LGL leukemia.^{24,25} Additionally, concurrent manifestations of indolent T-cell LGL leukemia with various bone marrow failure disorders including myelodysplastic syndromes, aplastic anemia, and paroxysmal nocturnal hemoglobinuria have also been described.^{19,26,27} Since all of these hematologic diseases are relatively rare, increased coincidence suggests possible causative association.²⁷ Several reports have suggested that clonal T-cells might be derived from pluripotent hematopoietic stem cells in patients with myelodysplastic syndromes.^{28,29} On the other hand, a clonal expansion of T-cell LGLs could be explained by chronic antigenic stimulation by an abnormal clone of bone marrow myeloid cells.²⁷ Autoreactive cytotoxic T-cell clones could contribute to the development of cytopenias in T-cell LGL leukemia and other bone marrow failure disorders.

Diagnosis

The diagnosis of T-cell LGL leukemia is based on the presence of an LGL lymphocytosis, characteristic immunophenotype, and confirmation of clonality using TCR β and γ gene rearrangement studies.^{1,2,4} Morphologically, LGLs are medium to large cells containing abundant cytoplasm, coarse azurophilic granules, and eccentric nuclei (Fig 2).^{1,2,4} T-cell LGL leukemic cells typically coexpress CD3+CD8+CD57+ markers.^{1,4} The majority of patients with T-cell LGL leukemia express type $\alpha\beta$ of the T-cell receptor (TCR $\alpha\beta$). Rare immunophenotypic variants such as CD3+CD4+CD8+CD57+TCR $\alpha\beta$, CD3+CD4+CD8-CD57+TCR $\alpha\beta$, and CD3+CD4-CD8-CD57+TCR $\gamma\delta$ have also been described.^{4,19,30} Aberrantly weaker expression of pan-T-cell markers such as CD5 and CD7 can also be helpful in differentiating malignant T-cell LGL populations from reactive expansions of LGLs.³¹ A confirmation of the clonal origin of LGLs can be accomplished with the use of several tech-

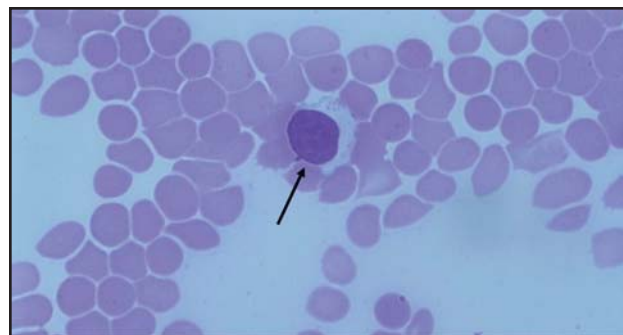


Fig 2. — Peripheral blood smear demonstrating circulating atypical cell with an irregular nuclear contour, coarse chromatin, and azurophilic granules consistent with a large granular lymphocyte (arrow).

niques. Restriction fragment length polymorphism (RFLP) of the TCR β gene detected with Southern blotting, polymerase chain reaction (PCR) of TCR γ gene rearrangement, and reverse-transcriptase PCR (RT-PCR) analysis of V β repertoire are the most commonly used clonality techniques in T-cell malignancies. The recent availability of a panel of monoclonal antibodies directed against V β repertoire was also found to be a valuable clonality assay. Langerak et al³² demonstrated that detection limits of Southern blotting (5% to 10%) and PCR-based techniques (1% to 5%) were superior to flow cytometric analysis of the V β repertoire with sensitivity of 20%.

A bone marrow biopsy/aspirate is not required for diagnosing the majority of T-cell LGL cases. However, in asymptomatic patients with absolute LGL counts that are $<0.5 \times 10^9/L$, an evaluation of the marrow is essential.^{1,2} Examination of the marrow will demonstrate clonal populations of LGLs in an interstitial pattern.¹⁶ Immunohistochemistry using anti-CD3 antibodies can be helpful in visualization and enumeration of the malignant T-cell population. The extent of marrow involvement is highly variable and does not correlate with the severity of symptoms or the degree of cytopenias.^{2,19} The majority of T-cell LGL cases will manifest a normal karyotype.¹ Fewer than 10% of cases will exhibit karyotypic abnormalities, which include trisomies of chromosomes 3, 8, and 14, deletions of chromosomes 6 and 5q, and inversions of 12p and 14q.^{2,3,33,34}

Reactive LGL lymphocytosis and persistent polyclonal LGL lymphocytosis, due to viral infections, aging, and hematopoietic cell transplantation, should be considered prior to establishing a diagnosis of T-cell LGL

leukemia.³⁵ Recently, polyclonal expansions of LGLs were also detected in patients with combined variable immunodeficiency associated with neutropenia.³⁶

Treatment

No randomized phase III trials have been conducted to evaluate therapeutic interventions in patients with T-cell LGL leukemia. Most treatment data are derived from retrospective and prospective case series, as well as from case reports from single institutions.^{2,37} The management of asymptomatic patients with this disorder is careful observation.^{1,2} The indications for treating patients with T-cell LGL leukemia are the development of recurrent infections, severe neutropenia, symptomatic anemia or thrombocytopenia, symptomatic splenomegaly, and the presence of systemic symptoms (Fig 3). The improvement of symptoms secondary to therapy may occur despite the failure to normalize neutrophil counts. Similarly, the failure to eradicate the malignant leukemic clone with therapy does not prevent improvements in underlying cytopenias.^{37,38} Low-dose methotrexate at 10 mg/m² per week has been effective in inducing responses (Table 1).^{37,39,40} Approximately 50% of patients with T-cell LGL leukemia who are treated with single-agent methotrexate develop a complete response; however, patients may require indefinite treatment to maintain sustained responses.⁴⁰ Cyclophosphamide at 50 to 100 mg daily or cyclosporine A at 5 to 10 mg/kg daily are also effective therapeutic alternatives to methotrexate.^{37,38,41,42} Treatment should be continued for at least 4 months prior to altering the therapeutic regimen for lack of response.² It has been postulated that these therapies

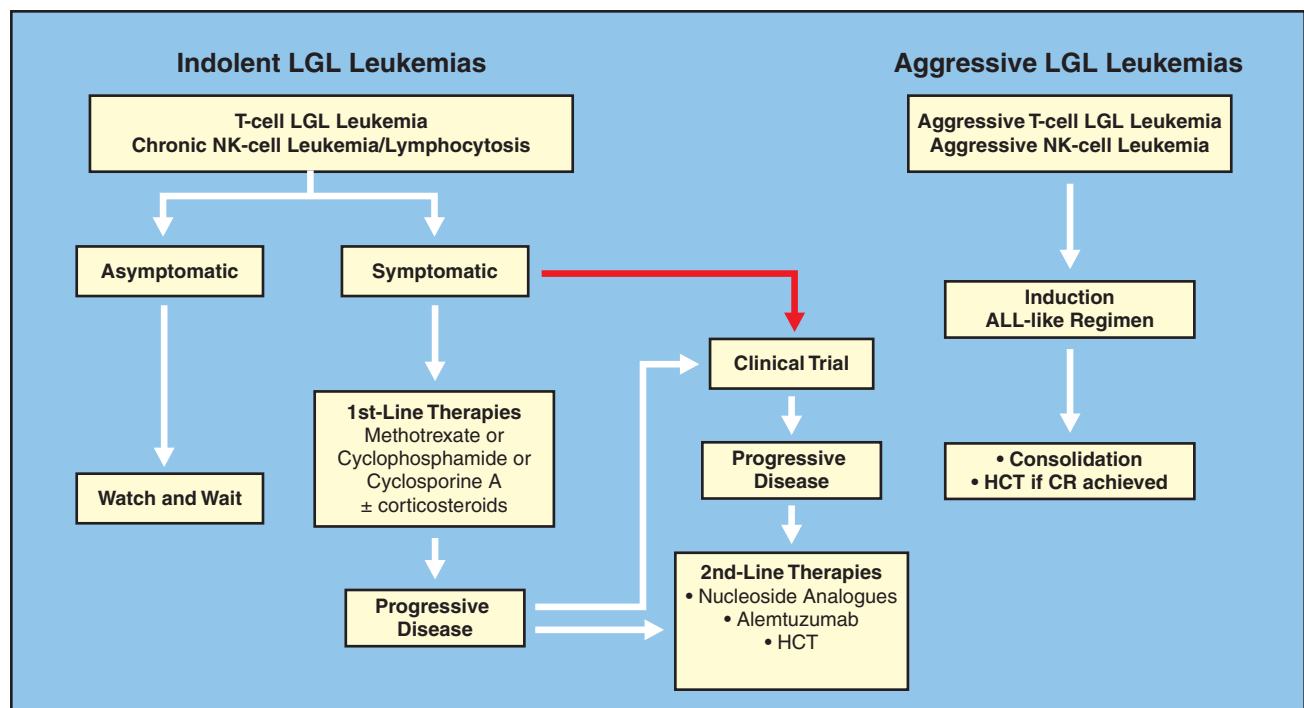


Fig 3. — Therapeutic algorithm of LGL disorders. ALL = acute lymphoblastic leukemia, HCT = hematopoietic cell transplantation, CR = complete response.

act via immunomodulatory mechanisms rather than by exerting cytotoxic effects on leukemic T-cell LGLs.¹⁹ The selection of an immunosuppressive agent for first-line therapy is usually practitioner-dependent since no randomized studies have been conducted to compare efficacy of these agents.^{2,19} Although cyclosporine A is used as the first choice in some institutions, our observations suggest that side effects are greater with cyclosporine A compared with the toxicities due to therapy with low-dose methotrexate or cyclophosphamide, especially in elderly patients.² After normalization of the neutrophil count or achievement of the best response, the dose of cyclosporine A should be tapered down to obtain the

lowest effective maintenance dose. Monotherapy with corticosteroids has activity in treating this disorder, but response duration seems to be less than with methotrexate, cyclosporine A, or cyclophosphamide alone. However, resolution of B symptoms and hematologic improvements may be more rapid if corticosteroids are used in combination with methotrexate or cyclophosphamide during the first month of therapy.^{2,16} Due to adverse side effects, prolonged administration (>1 month) of high-dose corticosteroids is not usually recommended. Prophylactic use of antibiotics can be beneficial, especially in patients with severe neutropenia, with concurrent corticosteroid treatment.

Table 1. — Selected Trials Assessing Therapies for LGL Leukemia

Therapy	Investigator (Year)	No. of Patients	Results
Methotrexate			
Methotrexate 5–13.5 mg/m ² q wk ± prednisolone	Osuji et al ³⁷ (2006)	7	ORR = 85.7% (patients were mostly pretreated) 1 hematologic CR, 5 PR
Methotrexate 7.5 mg/m ² q wk	Hamidou et al ³⁹ (2000)	4	ORR = 100% 3 hematologic CR, 1 PR Molecular CR in 50%
Methotrexate 10 mg/m ² q wk ± prednisolone	Loughran et al ⁴⁰ (1994)	10	ORR = 60% 5 CR, 1 PR Molecular CR in 30%
Methotrexate + prednisone	Dhodapkar et al ³⁸ (1994)	2	ORR = 100% 1 hematologic CR, 1 molecular CR
Cyclophosphamide			
Cyclophosphamide 50–100 mg p.o. qd or 250–500 mg IV q wk	Osuji et al ³⁷ (2006)	3	1 hematologic CR lasting >7 yrs with complete resolution of bone marrow infiltrate Dose of cyclophosphamide resulting in 1 hematologic CR was not stated
Cyclophosphamide 25–100 mg p.o. qd ± prednisone	Dhodapkar et al ³⁸ (1994)	16	ORR = 69% 3 hematologic CR, 3 molecular CR, 4 hematologic PR
Cyclosporine A			
Cyclosporine A 1–6.7 mg/kg b.i.d	Osuji et al ³⁷ (2006)	23	ORR = 92% treatment-naïve (n=13) 5 hematologic CR, 7 PR ORR = 78% all patients 7 hematologic CR, 11 PR Women responded better than men (<i>P</i> = .04)
Cyclosporine A 5–10 mg/kg/day	Battiwalla et al ⁴¹ (2003)	25	ORR = 56% Normalization of blood counts in 7 patients Sustained responses required continued cyclosporine A HLA-DR4 was predictive of cyclosporine A response
Cyclosporine A 1–1.5 mg/kg b.i.d.	Sood et al ⁴² (1998)	5	4 patients achieved normal neutrophil counts 1 patient required concomitant GM-CSF Maintenance of neutrophil counts with continued cyclosporine A in 3 patients for 2, 8, and 8.5 yrs
ORR = overall response rate, CR = complete response, PR = partial response, GM-CSF = granulocyte-macrophage colony stimulating factor.			

Table 2. — Selected Active Clinical Trials for the Treatment of LGL Leukemia

Therapy	Clinicaltrials.gov Identifier	Sponsor	Comments
Phase I			
MiK-β-1	NCT 00079196	NCI	Humanized monoclonal antibody that binds to the β subunit of the IL-2 and IL-15 receptors
Siplizumab (MEDI-507)	NCT 00075361 NCT 00105313	NCI MedImmune	Humanized monoclonal antibody directed against CD2
Phase II			
ECOG 5998	NCT 00003910	NCI/ECOG	Oral methotrexate + prednisone or oral cyclophosphamide + prednisone
Tipifarnib	NCT 00331591	Office of Rare Diseases	Farnesyltransferase inhibitor
Alemtuzumab	NCT 00345345	NHLBI	Humanized monoclonal antibody directed against the cell surface glycoprotein,CD-52
Methotrexate/fludarabine	NCT 00278265	German CLL-Study Group	Methotrexate subcutaneously once weekly; patients not achieving a response to methotrexate receive fludarabine
Cyclosporine A	NCT 00363779	NCI	Oral cyclosporine; gene expression analysis is performed on pre- and post-treatment samples at baseline and 12 wks
ECOG = Eastern Cooperative Oncology Group, NCI = National Cancer Institute, NHLBI = National Heart, Lung, and Blood Institute, CLL = chronic lymphocytic leukemia.			

Hematopoietic growth factors, specifically erythropoietin, granulocyte-macrophage colony-stimulating factor (GM-CSF), and granulocyte colony-stimulating factor (G-CSF), also have been employed as first-line therapy with beneficial effects for the treatment of anemia and neutropenia due to LGL leukemia.^{17,43}

Currently, within the United States, a few phase II trials are assessing treatment strategies (Table 2). One such trial, ECOG 5998 by the Eastern Cooperative Oncology Group, a phase II clinical trial sponsored by the National Cancer Institute (NCI), is evaluating the efficacy of methotrexate in the treatment of T-cell LGL leukemia associated with severe neutropenia and/or symptomatic or transfusion-dependent anemia. Patients are treated with oral methotrexate at 10 mg/m² once weekly for 4 months plus prednisone 1 mg/kg daily for 30 days followed by a prednisone taper. Those achieving at least a partial response to methotrexate can continue this therapy for up to 1 year. Patients who do not respond to this therapy after 4 months then receive oral cyclophosphamide at 100 mg daily for up to 1 year in addition to prednisone for the first 30 days of this regimen. Another NCI-sponsored phase II study is evaluating the efficacy of cyclosporine in patients with LGL leukemia. Laboratory correlative studies with microarray analysis of the effects of cyclosporine therapy on gene expression patterns in leukemic LGLs both pre- and post-therapy are important parts of this protocol. Preclinical data implicating constitutive activation of the MAPK/ERK/Ras pathway in the pathogenesis of LGL leukemia has been the foundation for evaluating tipifarnib.¹² In addition, the efficacy of tipifarnib, a farnesyl-

transferase inhibitor, in the treatment of symptomatic individuals with T-cell LGL leukemia is undergoing evaluation in an NCI-sponsored phase II clinical trial. Patients are treated with oral tipifarnib at 300 mg twice daily for 21 consecutive days of a 28-day cycle. Patients achieving a complete response after 4 cycles will receive one additional course of therapy. Patients who achieve a partial response receive four additional cycles of therapy. Correlative studies that include *K-ras* and *N-ras* gene mutational analysis are being performed.

Osuji et al⁴⁴ reported the expression of CD52 on all abnormal cells in patients with T-cell LGL leukemia and NK-cell leukemia using flow cytometry. Anecdotal reports describe the successful use of alemtuzumab, an anti-CD52 humanized monoclonal antibody (Campath®, Berlex, Montville, NJ), in the therapy of refractory T-cell LGL leukemia.⁴⁵⁻⁴⁷ Currently, a single phase II study sponsored by the National Heart, Blood, and Lung Institute is evaluating the efficacy and safety of alemtuzumab for the first-line treatment of T-cell LGL leukemia. Alemtuzumab at 10 mg per day is administered intravenously for 10 days. Response rates will be assessed at 3 months.

CD2, an E-rosette receptor, is expressed on mature T cells, NK cells, and thymocytes. Siplizumab, a humanized anti-CD2 monoclonal antibody (MEDI-507, MedImmune, Gaithersburg, Md), is undergoing testing in two phase I dose escalation studies in patients with relapsed/refractory CD2+ T-cell lymphoma/leukemia including T-cell LGL leukemia sponsored by NCI and MedImmune. Siplizumab is administered for 3 consecutive days every other week for 16 weeks. A once-weekly dosing sched-

ule has been tested. Safety, tolerability, and responses will be evaluated.

Humanized MiK- β -1 monoclonal antibody is undergoing testing in a phase I open-label study in patients with T-cell LGL leukemia. This antibody is directed toward CD122, a common β subunit of interleukin-2 (IL-2) and interleukin-15 (IL-15) receptors. Patients receive a single dose of this MiK- β -1 monoclonal antibody intravenously. The safety and tolerability of this antibody are assessed. The cytokines IL-2 and IL-15 are implicated in the proliferation, survival, and cytotoxic activity of LGLs.^{19,48}

Durable responses have been anecdotally reported with the use of second-line therapies such as fludarabine, chlorodeoxyadenosine, and deoxycoformycin.⁴⁹ In a phase II clinical study, the German Chronic Lymphocytic Leukemia Study Group is investigating the efficacy of fludarabine in patients with T-cell LGL leukemia who have failed first-line therapy with methotrexate (Table 2). Since there are no standards by which patients with LGL leukemia should be treated, investigating novel therapeutic approaches within the context of clinical trials should be encouraged. Patients should also be recommended to participate in the national LGL leukemia registry established at Penn State University (www.hmc.psu.edu/cancer/research/index.htm) to further investigate this disease.

Aggressive T-Cell LGL Leukemia

Epidemiology and Pathogenesis

Aggressive T-cell LGL leukemia is a rare clinical entity that is distinct from the more commonly encountered indolent T-cell LGL leukemia, as both diseases significantly differ with respect to clinical behavior, treatment, and prognosis.⁵⁰ Aggressive T-cell LGL leukemia primarily affects younger people, with a median age of 41 years (range 9 to 64 years), without ethnic predilection. This disorder is not yet recognized by the WHO as a separate lymphoproliferative neoplasm due to the small number of reported cases.⁵⁰⁻⁵⁴ Several cases of aggressive T-cell LGL leukemia have been reported using different terms including CD3+CD56+ aggressive variant T-cell LGL leukemia, aggressive lymphoma of T-cell LGLs, aggressive acute LGL leukemia, and NK-like T-cell LGL leukemia.⁵¹⁻⁵⁴ The pathogenesis of aggressive T-cell LGL leukemia is not known. It has been speculated that this disorder may develop from clonal evolution of indolent T-cell LGL leukemia.^{55,56} However, the majority of reported cases appear to arise de novo.⁵⁰⁻⁵⁴

Clinical Manifestations

The majority of patients with this disease present with rapidly progressive B symptoms, hepatosplenomegaly, lymphadenopathy, lymphocytosis, and variable degrees

of anemia and/or thrombocytopenia (Fig 1). In general, these patients have poor prognosis, and their survival ranges from several months to 2 years.⁵⁰⁻⁵⁴

Diagnosis

A diagnosis of aggressive T-cell LGL leukemia can be established based on several clinical and laboratory features including large granular lymphocytosis in the peripheral blood ($>0.5 \times 10^9/L$, and in many cases $>10 \times 10^9/L$), presence of a characteristic immunophenotype CD3+CD8+CD56+TCR $\alpha\beta$ or variants, demonstration of clonally rearranged TCR β and γ genes and development of acute onset of systemic B symptoms, hepatosplenomegaly, peripheral cytopenias, and lymphadenopathy.⁵⁰ Indolent T-cell LGL leukemia must be considered in the differential diagnosis since this disorder cytologically resembles and shares a similar immunophenotype with aggressive T-cell LGL leukemia. However, indolent T-cell LGL leukemia usually lacks expression of the NK-cell marker CD56 and frequently manifests with neutropenia and autoimmune diseases. The clinical presentation of aggressive T-cell LGL leukemia is similar to the manifestations of aggressive NK-cell leukemia. However, at least four characteristics distinguish these two conditions. Aggressive NK-cell LGL leukemic cells do not express surface CD3 (sCD3-) marker, possess TCR genes in a germline configuration, or demonstrate intracellular clonal episomal EBV. Additionally, aggressive NK-cell LGL leukemia appears to be more prevalent in the Asian population.^{16,57}

Treatment

Patients who develop aggressive T-cell LGL leukemia will have a poor prognosis if treated with conventional doses of systemic chemotherapy. Despite limited data, treatment with more intensive acute lymphoblastic leukemia (ALL)-like induction regimens, including central nervous system (CNS) prophylaxis followed by consolidation with hematopoietic cell transplantation in the first remission may potentially render better responses and outcomes (Fig 3).⁵¹

Chronic NK-Cell Leukemia

Epidemiology and Pathogenesis

Chronic NK-cell leukemia constitutes approximately 5% of LGL disorders.¹⁶ This entity is also known as chronic NK-cell lymphocytosis or NK-cell LGL lymphocytosis.⁵⁷ The median age at diagnosis is 58 years with increased predilection for males (male:female ratio of 3.2:1).¹⁹ This disorder was discussed in the WHO classification of lymphoid malignancies. However, since the clonal origin of malignant NK cells is difficult to determine, it did not receive the status of a separate disease entity.⁵⁷ The pathogenesis of chronic NK-cell

leukemia is not known, but the presence of viral infections has been suggested.^{58,59}

Clinical Manifestations

Chronic NK-cell leukemia is an indolent hematologic disorder with a favorable prognosis. This disease usually manifests with persistent elevations of circulating LGLs without associated fever, hepatomegaly, splenomegaly, or lymphadenopathy (Fig 1). The median absolute leukemic NK-cell count is $2.3 \times 10^9/L$.¹⁹ Lymphadenopathy and tissue invasion do not occur. Neutropenia and anemia may be present; however, compared with T-cell LGL leukemia, these two cytopenias occur less frequently and in the majority of cases are less severe.⁶⁰ Leukocytoclastic vasculitis and acute glomerulonephritis have been described in patients with chronic NK-cell lymphocytosis.⁶⁰

Diagnosis

The diagnosis of chronic NK-cell leukemia can be difficult to establish because of a lack of clonal markers.² Rarely, clonality studies using X-chromosome inactivation patterns have assessed the clonal origin of cells in informative female patients.⁶¹ Altered expressions of all three NK-associated antigen families including KIR (killer-immunoglobulin-like receptors), C-type lectin-like receptors, and natural cytotoxicity receptors (NCR) were reported in patients with chronic NK-cell leukemia compared to normal lymphocyte subpopulations.⁶²⁻⁶⁵ Diagnostic panels consisting of antibodies against some of these receptors could be useful in the differential diagnosis of chronic NK-cell leukemia and reactive NK-cell lymphocytosis.⁶⁵ Reactive or persistent benign NK-cell lymphocytosis has been reportedly associated with viral infections and connective tissue disorders.^{16,59} The persistence (>6 months) of an NK-cell population detected in the peripheral blood has been arbitrarily proposed for categorizing this disorder as chronic.^{1,19} The majority of reactive LGL proliferations usually will not persist for longer than 4 to 6 months.¹⁶ Typically, chronic NK-cell leukemia displays a CD2+CD3-CD16+CD56+ immunophenotype.^{19,60} CD57 is expressed variably.¹⁹ The most powerful predictors are the clinical manifestations. Those patients who present with systemic symptoms or who have hepatic, splenic, or bone marrow involvement most probably have chronic NK-cell leukemia. Asymptomatic patients probably have a benign chronic NK-cell lymphocytosis. Careful observation is needed when the diagnosis is uncertain or when patients are asymptomatic.²

Treatment

The treatment of chronic NK-cell leukemia is similar to the treatment algorithm for T-cell LGL leukemia (Fig 3). In the absence of a clinical trial, immunosuppressive therapies should be considered as the first-line treatment.

Aggressive NK-Cell Leukemia

Epidemiology and Pathogenesis

Aggressive NK-cell leukemia is a fulminant sCD3- neoplasm with a poor prognosis that is most prevalent in younger patients of Asian descent.^{16,66} The median age of patients with this disorder at diagnosis is 39 years, and males and females are usually affected equally.¹ This clinicopathologic entity is recognized by the WHO classification as a distinct neoplasm that constitutes approximately 10% of all LGL lymphoproliferative disorders.^{16,57} There is an association between NK-cell leukemia and Epstein-Barr virus (EBV), thereby implicating EBV as a possible etiology in the pathogenesis of this leukemia.^{57,67}

Clinical Manifestations

This disease presents in an acute manner and manifests with B symptoms, organomegaly, and cytopenias (Fig 1). Disseminated intravascular coagulopathy (DIC) and multiorgan failure can also occur.^{57,66}

Diagnosis

Neoplastic cells display CD2+CD3-CD56+ immunophenotype with TCR genes in a germinal configuration, along with clonal episomal EBV.^{57,66} These leukemic cells usually lack CD57 expression. The most common cytogenetic abnormalities are deletion 6q21-q25 and loss of 17p13.^{66,68,69} Analysis of bone marrow will reveal diffuse infiltration with neoplastic cells, and involved organs will demonstrate destructive infiltrates with necrosis.⁵⁷

Treatment

Standard therapies such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) are ineffective when used to treat aggressive NK-cell leukemia.⁷⁰ Intensive ALL-like therapies with CNS prophylaxis should be considered as an initial treatment for aggressive NK-cell leukemia. Consolidation therapy with hematopoietic cell transplantation should also be considered for those patients achieving responses to induction therapy (Fig 3).⁷¹

Conclusions

Since the first description of LGL leukemia more than 20 years ago,³ our understanding of this fascinating group of lymphoid disorders has improved significantly. LGL leukemia is not a single disease but rather a spectrum of clinicopathologic entities with diverse etiologies, biologic behaviors, and prognoses. Clinical presentation remains the most important prognostic predictor due to poor correlation between cytomorphology and prognosis. Patients with indolent T-cell LGL and NK-cell

leukemia usually have a favorable prognosis, with median survival rates exceeding 10 years. In contrast, patients with aggressive T-cell LGL and NK-cell leukemias have poor outcomes. An accurate diagnosis should be based on the clinical presentation, determination of sustained large granular lymphocytosis, characteristic immunophenotype, and clonal origin of cells. Recent increased interest in this disease by several groups of basic scientists and clinical investigators has suggested that some important questions about the etiology, key pathogenic mechanisms, and optimal therapy of LGL leukemia could be answered in the near future.

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