

Recent Insights Into Large Granular Lymphocytic Leukemia



Loretta J. Nastoupil, MD
Director, Lymphoma Outcomes Database
Assistant Professor, Department of Lymphoma/Myeloma
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

H&O How does LGLL manifest?

LN Large granular lymphocytic leukemia (LGLL) is an uncommon lymphoproliferation of mature cytotoxic T cells or natural killer (NK) cells. The disease is characterized by cytopenias, which contribute to the majority of the morbidity. LGLL generally affects elderly patients and is often associated with an underlying autoimmune disease, such as rheumatoid arthritis, or a malignancy, including hematologic disorders and solid tumors. Approximately one-third of patients are asymptomatic at presentation. Symptoms associated with this disease can include neutropenia with recurrent infections; splenomegaly; and B symptoms, such as fatigue, weight loss, and night sweats.

An interesting aspect of LGLL concerns the pathogenesis, which is incompletely understood. The current understanding recognizes a shift in the balance of cell proliferation with expansion of cytotoxic T cells or NK cells, which can resemble a chronic reactive process. Clonal expansion and increased survival of mature T cells may be driven by chronic antigen stimulation from viral, autoimmune, or tumor antigens. Supporting this hypothesis is the frequent occurrence of LGLL in patients with underlying chronic B-cell leukemia, lymphoma, or autoimmune disease, or who underwent an allogeneic stem cell transplant. Chronic and persistent antigen exposure may lead to *STAT3* activation and emergence of a dominant clone. In the case of T-cell LGLL, the cytotoxic T cells may develop survival mechanisms to avoid normal cell death. For example,

STAT3 mutations confer a survival advantage, leading to accumulation of aberrant T cells in comparison with normal hematopoietic cells. This process is thought to impact the hematopoiesis of normal cells, such as neutrophils, red blood cells, and platelets. Patients often present with cytopenias or recurrent infections as a result of neutropenia or pancytopenia, and may require transfusions or growth factor support.

H&O How does LGLL differ from other lymphoid malignancies?

LN LGLL cells are mature, which distinguishes this disorder from acute leukemia. The T-cell variant is more commonly associated with an indolent course, whereas the NK variant may behave more aggressively. Patients can live with LGLL for years. In addition, LGLL tends to manifest as a blood disorder and is typically detected when routine laboratory assessment shows abnormal blood counts associated with splenomegaly. Less often, patients have enlarged lymph nodes or significant symptoms.

H&O What are the standard treatments?

LN LGLL is relatively rare, and few prospective clinical trials have been conducted to address the preferred management. LGLL often arises in a chronic inflammatory state, and therefore most treatment options have focused on immunosuppression. Treatment often begins with methotrexate. If methotrexate is not effective, then cyclosporine is used. Recently, targeted therapy

has been explored with alemtuzumab (Campath, Millennium and ILEX Partners/Berlex Laboratories), but the limited availability of this drug has impacted its use in this disease.

Ongoing research has explored whether it is possible to predict which patients will respond to a given therapy. Recent insights into the role of *STAT3* mutations in the pathogenesis of LGLL have generated interest in whether the status of this mutation can be used to predict prognosis or guide treatment decisions. *STAT3* mutations occur in approximately half of patients. Emerging data from a small study suggested that patients with a *STAT3* mutation were more likely to have rheumatoid arthritis

The transcription factor *STAT3* plays a critical role in regulating the intracellular signaling pathways, and it may be involved in immunosuppressive signaling.

and neutropenia that required initiation of therapy, and they responded well to methotrexate. Patients who were *STAT3* wild-type were more likely to have pure red cell aplasia, which responded well to cyclophosphamide. This small study should be validated in a larger subset. However, *STAT3* mutation status appears to be associated with distinct clinical disease presentation, which could potentially inform treatment.

Constitutive activity of the nuclear factor- κ B (NF- κ B) signaling pathway has also been an area of interest and may be pursued as a potential therapeutic target. Bortezomib (Velcade, Takeda), for example, has been studied in other malignancies with NF- κ B signaling that is constitutively activated, and this agent might be an interesting option for LGLL.

H&O How might the biology or genetics of LGLL inform treatment?

LN It may be possible to target the microenvironment. It appears that a proinflammatory state drives the clonal expansion of T cells, which are reacting against an antigen. It may be possible to identify which cells in the microenvironment play a critical role, and then target these cells with therapies such as checkpoint inhibitors or immunomodulating agents.

H&O Are checkpoint inhibitors being studied in LGLL?

LN I am not aware of any prospective studies exploring the efficacy of checkpoint inhibitors in LGLL, likely because this tumor is rare and the pathogenesis is not completely understood. The transcription factor *STAT3* plays a critical role in regulating the intracellular signaling pathways, and it may be involved in immunosuppressive signaling. As mentioned, LGLL tends to occur in patients with underlying autoimmune conditions. The activity of *STAT3* and proinflammatory cytokines in the pathogenesis of this disease suggests that this tumor type might respond to immuno-oncology therapies. It may be possible to enhance a patient's innate and adaptive immune cell system to target the tumor cells. It is difficult to model the microenvironment, but it would be interesting to identify the number and types of immune cells within this tumor, in addition to exploring the mutational burden. It may be possible to develop new therapeutic options that target the chronic inflammatory state associated with this tumor, particularly the impact on immune surveillance.

H&O Are there any particular challenges for these patients in terms of clinical trial design and treatment?

LN The biggest challenge is finding enough patients for enrollment in a prospective clinical trial. This will likely require a multicenter study. It may be difficult to generate enough enthusiasm for drug development in this rare, indolent disease, given the heterogeneous outcomes. Another important issue is the underlying clinical feature of LGLL, which is cytopenia. Cytopenias can often disqualify patients from trial enrollment when applying traditional inclusion/exclusion criteria. As LGLL is a disease often impacting elderly patients, unintentional barriers to trial participation, including decreased renal function or vigorous treatment schedules, may limit enrollment in prospective clinical studies. Lastly, efforts to explore novel agents in this disease have been limited.

H&O Do you have any other insights into LGLL?

LN The goal of therapy is to minimize morbidity. Clinicians should aim to identify the underlying driver of the proliferating clone, so as to ensure that an underlying malignancy is not missed. If the LGLL is driven by an underlying autoimmune condition, and the self-antigen is driving the clonal proliferation of cells, oftentimes treatment decisions are based on minimizing morbidities, such as cytopenias, fatigue, and risk of infection. In LGLL, treatment is often a reaction to the potential risks

associated with cell proliferation and the impact on other normal cells in the bone marrow, such as white blood cells, red cells, and platelets. Less is understood about the pathogenesis, including the most effective therapeutic target that may alter the natural history of the disease.

H&O Are you involved in any other research in lymphoma?

LN Applying immune therapy in the management of lymphoma has been my area of interest. Given the promising efficacy of checkpoint inhibitors across several cancer types, Dr Sattva Neelapu and I have worked on an investigator-initiated trial to explore potential synergy between pembrolizumab (Keytruda, Merck) and rituximab (Rituxan, Genentech/Biogen) in patients with relapsed follicular lymphoma. The rationale was that the infiltrating T cells in the tumors of patients with follicular lymphoma have overexpression of programmed death 1 (PD-1) and, therefore, blocking PD-1 on T cells and NK cells may enhance their anti-tumor activity. Rituximab, an anti-CD20 antibody, has significantly improved outcomes in follicular lymphoma via antibody-dependent cell-mediated cytotoxicity. The combination of rituximab and pembrolizumab should result in activity of the innate and adaptive immune response. The study enrolled 30 patients with relapsed follicular lymphoma. We found a robust response, with an overall response rate of approximately 65%. A complete response was seen in 50% of patients. However, somewhat disappointing was a median progression-free survival of 11 months, raising the question of whether the combination was more effective than rituximab monotherapy.

In general, the combination was well-tolerated. Most adverse events were mild. The immune-mediated adverse events were mostly grade 1 or 2. Among the 30 patients enrolled, 7 patients discontinued treatment as a result of persistent grade 2 immune-mediated adverse events, such as colitis, pneumonitis, and rash. All of these patients had achieved a complete response, which also factored into the decision to discontinue therapy.

We concluded that the regimen of pembrolizumab and rituximab was associated with robust response rates and a manageable toxicity profile in relapsed follicular

lymphoma. The response rate was much higher than that observed in previous studies evaluating checkpoint inhibitors as monotherapy in follicular lymphoma, which demonstrated modest activity, at best.

Our study raises an important question. We enrolled patients who were relapsed, but not refractory. Before enrollment, all patients had demonstrated a prior response to rituximab that lasted at least 6 months. We are now doing correlative work to determine whether the efficacy was driven primarily by rituximab, which is known to be an effective agent in follicular lymphoma, or if there was true synergism between the therapies. This research is ongoing, but we have shown that a gene expression signature that predicted high antitumor activity pretreatment predicted for those patients who would achieve a complete response. This gene signature could potentially serve as a predictor of clinical response to PD-1 blockade in follicular lymphoma.

Disclosure

Dr Nastoupil has received honoraria from Celgene, Genentech, Merck, and Novartis.

Suggested Readings

- Coppe A, Andersson EI, Binatti A, et al. Genomic landscape characterization of large granular lymphocyte leukemia with a systems genetics approach. *Leukemia*. 2017;31(5):1243-1246.
- Dumitriu B, Ito S, Feng X, et al. Alemtuzumab in T-cell large granular lymphocytic leukaemia: interim results from a single-arm, open-label, phase 2 study. *Lancet Haematol*. 2016;3(1):e22-e29.
- Lamy T, Moignet A, Loughran TP Jr. LGL leukemia: from pathogenesis to treatment. *Blood*. 2017;129(9):1082-1094.
- Matutes E. Large granular lymphocytic leukemia. Current diagnostic and therapeutic approaches and novel treatment options. *Expert Rev Hematol*. 2017;10(3):251-258.
- Nastoupil LJ, Westin JR, Fowler NH, et al. Response rates with pembrolizumab in combination with rituximab in patients with relapsed follicular lymphoma: interim results of an open-label, phase II study [ASCO abstract 7519]. *J Clin Oncol*. 2017;35(15 suppl).
- Sanikommu SR, Clemente MJ, Chomczynski P, et al. Clinical features and treatment outcomes in large granular lymphocytic leukemia (LGLL). *Leuk Lymphoma*. 2018;59(2):416-422.
- Shi M, He R, Feldman AL, et al. *STAT3* mutation and its clinical and histopathologic correlation in T-cell large granular lymphocytic leukemia. *Hum Pathol*. 2018;73:74-81.
- Teramo A, Barilà G, Calabretto G, et al. *STAT3* mutation impacts biological and clinical features of T-LGL leukemia. *Oncotarget*. 2017;8(37):61876-61889.