T-cell Large Granular Lymphocytic Leukemia
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**DIAGNOSIS**

**ESSENTIAL:**
- Peripheral blood smear analysis for cytology; presence of larger lymphocytes characterized by reniform or round nucleus and abundant cytoplasm containing azurophilic granules
- Flow cytometry on peripheral blood
- Bone marrow aspirate and biopsy
- Adequate immunophenotyping to establish diagnosis
  - Cell surface marker analysis by flow cytometry: CD3, CD4, CD5, CD7, CD8, CD16, CD56, CD57, CD28, TCRβ, TCRγδ, CD45RA, CD62L
  - IHC panel: CD3, CD4, CD5, CD7, CD8, CD56, CD57, EBER, TCRβ, TCRγ, TIA1, granzyme B, granzyme M
- Molecular analysis to detect gene rearrangement
  - Flow cytometry to assess clonality: TCR Vβ
  - Mutational analysis: STAT3 and STAT5B

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Flow cytometry to assess clonality: TCR Vβ
- Mutational analysis: STAT3 and STAT5B

**WORKUP**

**ESSENTIAL:**
- History and physical examination: evaluation of enlarged spleen, liver; presence of lymphadenopathy (rare)
- Presence of autoimmune disease (especially rheumatoid arthritis [RA])
- Performance status
- CBC, differential, platelets
- Comprehensive metabolic panel
- Serologic studies: HIV-1,2, HTLV-1,2,
- PCR for viral DNA or RNA: HBV, HCV, EBV, CMV

**USEFUL IN SELECTED CASES:**
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Echocardiography

\[ \text{See Indication for Treatment (LGLL-2)} \]

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\[^a^\] Autoimmune disorders such as rheumatoid arthritis can occur in patients with T-cell large granular lymphocytic (LGL) leukemia. Small, clinically non-significant clones of T-cell LGLs can be detected concurrently in patients with bone marrow failure disorders.

\[^b^\] Rule out reactive LGL lymphocytosis. Repeat peripheral blood flow cytometry and TCR gene rearrangement studies in 6 months in asymptomatic patients with small clonal LGL populations (<0.5 × 10^9/L) or polyclonal LGL lymphocytosis.

\[^c^\] Typically needed to confirm diagnosis; essential for cases with low T-LGL counts (<0.5 × 10^9/L) and cases suspicious for concurrent bone marrow failure disorders.

\[^d^\] Typical immunophenotype for T-LGL: CD3+ CD8+ CD16+ CD57+ CD56- CD28- CD5 dim and/or CD7 dim CD45RA+ CD62L- TCRαβ+ TIA1+ granzyme B+ granzyme M+.

\[^e^\] TCR gene rearrangement results should be interpreted with caution. Clonal TCR gene rearrangement without cytologic and immunophenotypic evidence of abnormal T-cell population does not constitute a diagnosis of T-cell malignancy since it can be seen in healthy subjects.

\[^f^\] In patients with unexplained shortness of breath and/or right heart failure.

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Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
## INDICATION FOR TREATMENT

- ANC < 0.5 x 10^9/L
- Hemoglobin < 10 g/dL or need for RBC transfusion
- Platelets < 50 x 10^9/L
- Autoimmune conditions requiring therapy (typically RA)
- Symptomatic splenomegaly
- Severe B symptoms
- Pulmonary artery hypertension

### FIRST-LINE THERAPY

- Low-dose methotrexate ± corticosteroids
- Cyclophosphamide ± corticosteroids
- Cyclosporine

### FOLLOW-UP

- CR/PR: Continue with initial treatment
- No response: Continue with alternate first-line therapy

### SECOND-LINE THERAPY

- No response or progressive or refractory disease to all first-line therapies
  - Clinical trial
  - Purine analogues
  - Alemtuzumab
  - Splenectomy

### RESPONSE (at 4 mo)

- Complete response (CR/PR)
- Partial response

### NOTE

- Methotrexate with or without steroids may be beneficial in patients with autoimmune disease; cyclophosphamide or cyclosporine may be used as a first- or second-line option in patients with anemia. Lamy T, Loughran TP Jr. How I treat LGL leukemia. Blood 2011;117(10):2764-74.
- Complete response is defined as: recovery of blood counts to Hgb > 12 g/dL, ANC > 1.5 x 10^9/L, platelet > 150 x 10^9/L, resolution of lymphocytosis (< 4 x 10^9/L) and circulating LGL counts within normal range (< 0.5 x 10^9/L). Partial response is defined as: recovery of hematologic parameters to Hgb > 8 g/dL, ANC > 0.5 x 10^9/L, platelet > 50 x 10^9/L and absence of transfusions. Bareau B, Rey J, Hamidou M, et al. Analysis of a French cohort of patients with large granular lymphocyte leukemia: a report on 229 cases. Hematologica 2010;95:1534-1541.
- Limit therapy with cyclophosphamide to 4 mo if no response and to ≤ 12 mo if PR observed at 4 mo due to increased risk of leukemogenesis. Pentostatin, cladribine, and fludarabine have been used in LGL.
- While alemtuzumab is no longer commercially available, it may be obtained for clinical use.

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