Non-Hodgkin’s Lymphomas

Version 2.2015

NCCN.org
T-Cell Prolymphocytic Leukemia
**DIAGNOSIS**

**ESSENTIAL:**
- Tissue histology not essential for diagnosis
- Peripheral blood smear analysis for morphology
- Peripheral blood flow cytometry to establish diagnosis
  - TdT, CD 1a, CD2, CD3, CD4, CD5, CD7, CD8, CD52, TCRαβ
- Cytogenetics: inv(14)(q11;q32); t(14;14)(q11;q32); t(X;14)(q28;q11); trisomy 8

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Molecular analysis to detect: TCRβ, TCRγ gene rearrangement; MTCP1 gene rearrangement; ATM mutation; TCL1 overexpression
- Bone marrow biopsy
  - IHC panel: CD1a, TdT, CD2, CD3, CD5, TCL1

**WORKUP**

**ESSENTIAL:**
- Complete H&P examination, including complete skin exam, and evaluation of lymph nodes, spleen, and liver.
- Performance status
- LDH, electrolytes, BUN, creatinine
- CBC, differential
- Chest/abdomen/pelvis CT

**USEFUL IN SELECTED CASES:**
- MUGA scan/echocardiogram if treatment includes regimens containing anthracyclines or anthracenediones
- Bone marrow evaluation
- PET-CT scan
- HTLV-1 serology: ELISA and confirmatory Western blot if ELISA positive
- Consider screening for active infections and CMV serology if therapy with alemtuzumab is contemplated

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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.

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aTypical immunophenotype: CD1a−, TdT−, CD2+, sCD3+/−, cCD3+/−, CD5+, CD7++, CD52++, TCRαβ+, CD4+/CD8− (65%), CD4+/CD8+ (21%), CD4-/CD8+ (13%).

bIn a minority of patients, the disease may be asymptomatic and can follow an indolent course of variable duration. In these selected cases expectant observation is a reasonable option.
### T-Cell Prolymphocytic Leukemia (T-PLL)

**Symptomatic Disease**

<table>
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<tr>
<th>Primary Treatment</th>
<th>Initial Response</th>
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| - Clinical trial (preferred)  
- Intravenous alemtuzumab alone  
- Alemtuzumab-containing regimens  
  - FMC (fludarabine, mitoxantrone, cyclophosphamide) followed by IV alemtuzumab  
  - IV alemtuzumab and pentostatin | Complete or partial response  
No response or progressive disease | Consider allogeneic stem cell transplant (if donor available)  
- Clinical trial (preferred)  
- Consider alternate regimens not used in primary treatment |

**SECOND-LINE THERAPY**

- Consider allogeneic stem cell transplant (if donor available)

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**Consider prophylaxis for tumor lysis syndrome (See NHODG-B)**

See monoclonal antibody and viral reactivation (NHODG-B)

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**See Treatment References (TPLL-A).**


- Monitor for CMV reactivation; anti-infective prophylaxis for herpes virus and PCP recommended when treating with alemtuzumab ± purine analogs.
TREATMENT REFERENCES

**Alemtuzumab**

**Alemtuzumab + pentostatin**

**FMC (fludarabine, mitoxantrone, cyclophosphamide) followed by alemtuzumab**

**Allogeneic stem cell transplant**
T-cell Prolymphocytic Leukemia

Diagnosis

T-cell prolymphocytic leukemia (T-PLL) is a rare malignancy, comprising approximately 2% of all mature lymphoid malignancies.\(^1\) Clinically, patients frequently present with lymphadenopathy, hepatomegaly, splenomegaly, and elevated WBC counts.\(^1\,2\) Skin lesions can also be present in about 30% of patients.\(^2\)

Morphological examinations of peripheral blood, as well as adequate immunophenotyping by flow cytometry, are essential to establish the diagnosis of T-PLL. Peripheral blood smears show prolymphocytes with round or oval nuclei in about half of the cases, and irregular nuclei (often with convolutions) in the remaining cases; in most cases (about 75%), the typically morphology comprises medium-sized prolymphocytes with agranular basophilic cytoplasm and a single visible nucleolus, while in about 20% to 25% of cases, the cell is small and the nucleolus may not be readily visible.\(^1,3\) Peripheral blood flow cytometry analysis should include the following markers: TdT, CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD52, and TCRαβ. Under certain circumstances, immunohistochemistry (IHC) analysis on bone marrow biopsy samples may be useful. In such cases, the IHC panel should include TdT, CD1a, CD2, CD3, CD5, and TCL-1. However, in general, bone marrow biopsy is not essential for establishing a diagnosis of T-PLL. The immunophenotype of T-PLL is consistent with a mature post-thymic T-cell phenotype, with a typical immunophenotype that is TdT-, CD1a-, CD2+, CD5+, and CD7+.\(^1,3\) CD3 expression may be weak on the cell surface but is usually expressed in the cytoplasm. In 65% of cases, the cells are CD4+/CD8- but cases with CD4+/CD8+ (21%) and CD4-/CD8+ (13%) can also be seen.\(^1,2\) CD52 is often highly expressed.\(^1,4\) Diffuse infiltration in the bone marrow is typically observed with T-PLL, but diagnosis is difficult to establish based on bone marrow evaluation alone. Tissue histology is not considered essential to establish the diagnosis. Frequent cytogenetic abnormalities in T-PLL include inversions or translocations involving chromosome 14, most commonly, inv(14)(q11;q32) or t(14;14)(q11;q32), which are associated with the TCL-1 oncogene.\(^2,5,6\) Although less frequent, the translocation t(X;14)(q28;q11), associated with the MTCP-1 oncogene, may also occur. Overexpression of TCL-1 and MTCP-1 has been implicated in the pathogenesis of T-PLL.\(^7,9\) Abnormalities in chromosome 8, mainly trisomy 8q, are also frequently observed.\(^2,5,6\) Deletions or mutations to the tumor suppressor gene ATM, which localizes to the chromosome region 11q22-23, have also been detected in patients with T-PLL.\(^10,11\) This gene is mutated in patients with ataxia telangiectasia, and these patients appear to be predisposed to developing T-cell malignancies, including T-PLL; thus, it is postulated that abnormalities in the ATM gene may also be one of the key events in the pathogenesis of T-PLL.\(^10,11\) Cytogenetics by conventional karyotyping and/or FISH to detect chromosome 14 abnormalities and trisomy 8 should be performed at the time of diagnostic workup. Under certain circumstances, molecular genetics to detect TCR gene rearrangements, MTCP-1 gene rearrangements, ATM mutations, or TCL-1 overexpression, may be useful.

Workup

The initial workup for T-PLL should comprise a comprehensive medical history and physical examination, including careful evaluation of lymph nodes, spleen, and liver, in addition to a complete skin examination and evaluation of performance status. Laboratory assessments should include standard blood work including CBC with differential, and a comprehensive metabolic panel, as well as measurements of serum lactate dehydrogenase (LDH). Bone marrow evaluation is generally unnecessary, as evaluation of peripheral blood...
smears and immunophenotyping are sufficient to establish the
diagnosis of T-PLL, as discussed above; however, bone marrow
assessments may be useful in some cases. CT scans of the chest,
abdomen and pelvis should also be performed at the time of initial
workup. PET-CT scans may also be useful in selected cases. If
treatment regimens containing anthracyclines or anthracenediones are
being considered, a MUGA scan or echocardiogram may be useful,
particularly for older patients or for patients with a prior history of
cardiac disease. Serology for detection of antibodies against the
human T-lymphotropic leukemia virus type 1 (HTLV-1) may be useful,
especially to distinguish adult T-cell leukemia/lymphoma from T-PLL
(HTLV-1 should be negative in the latter). If serology shows positivity
for HTLV-1 by ELISA, a confirmatory Western blot should be
performed. Screening for active infections and cytomegalovirus (CMV)
sérology should be strongly considered prior to initiation of treatment
with alemtuzumab-containing regimens.

Treatment Options

In the minority of cases where patients are asymptomatic and have a
more indolent course of disease, observation is a reasonable
approach until symptoms develop. In most cases of T-PLL, however,
patients are symptomatic at the time of presentation. T-PLL is an
aggressive malignancy associated with rapid disease progression. In
an early study of patients with T-PLL (N=78) treated with alkylating
agents, pentostatin, or CHOP (cyclophosphamide, doxorubicin,
vincristine, prednisone), the median overall survival (OS) was only 7.5
months; among the subgroup of patients who responded to pentostatin
(n=15), the median OS was 16 months.\textsuperscript{2} In a retrospective analysis of
patients (both previously untreated and treated) with post-thymic T-cell
malignancies treated with pentostatin, the overall response rate (ORR)
was 45\% and complete response (CR) 9\% in the subgroup of patients
with T-PLL (n=55).\textsuperscript{12} The median duration of response was short,
however, at 6 months (range, 3–16 months). The median OS from
treatment initiation was 17.5 months for responding patients and 9
months for non-responders.\textsuperscript{12}

More recently, treatment with the anti-CD52 monoclonal antibody
alemtuzumab has shown high response rates in both previously
treated and untreated patients with T-PLL.\textsuperscript{13–16} In a study that primarily
included pretreated patients with T-PLL (N=39; previously treated,
n=37), intravenous (IV) alemtuzumab resulted in an ORR of 76\% (CR
in 60\%).\textsuperscript{14} The median disease-free interval (from end of therapy to
relapse) was 7 months. Among the patients who were pretreated
(n=37), none had achieved a CR to previous therapy and 61.5\% were
resistant to prior treatments.\textsuperscript{14} The median OS for all patients was 10
months, and was 16 months for patients with a CR. Following
alemtuzumab, 11 patients proceeded to hematopoietic stem cell
transplant (HSCT; autologous HSCT, n=7; allogeneic HSCT, n=4).\textsuperscript{14} Outcomes were similar in a subsequent report, in which IV
alemtuzumab induced an ORR of 74\% (CR in 60\%) in patients with
relapsed/refractory T-PLL (n=45); the 4-year OS rate in this patient
group was 18\%.\textsuperscript{13} In a larger study in patients with T-PLL (N=76;
previously treated, n=72), treatment with IV alemtuzumab induced an
ORR of 51\% (CR in 39.5\%); among the 4 patients who received
alemtuzumab as first-line therapy, 3 achieved a CR.\textsuperscript{15} The median
time to progression (TTP) for all patients was 4.5 months, and the
median OS was 7.5 months. Among the patients who achieved a CR,
the median response duration and OS was 9 months and 15 months,
respectively.\textsuperscript{15} In a recent study that evaluated alemtuzumab in the
first-line setting using the IV route or subcutaneous (SC) delivery in
patients with T-PLL, response rates were found to be inferior with the
SC route of alemtuzumab.\textsuperscript{13} In the small number of patients who were
treated with first-line SC alemtuzumab (n=9), the ORR was 33% with no CRs; moreover, 2 of the patients (22%) died of progression of disease during therapy. In contrast, first-line IV alemtuzumab (n=32) induced an ORR of 91% with CR in 81% of patients. The most common toxicities reported with alemtuzumab in patients with T-PLL included infusion-related reactions, prolonged lymphocytopenia, and infectious events, including opportunistic infections.\textsuperscript{14,15}

Alemtuzumab has also been evaluated as part of combination regimens in patients with T-PLL. In a phase II study that evaluated the combination of alemtuzumab and pentostatin in patients with T-cell malignancies, the subgroup of patients with T-PLL (n=13) showed an ORR of 69%, with a CR in 62% of patients.\textsuperscript{17} The median PFS and OS for this subgroup of patients were 8 months and 10 months, respectively. The study included both patients with previously treated and untreated disease.\textsuperscript{17} In a study conducted by the German CLL Study Group in patients with T-PLL (N=18 evaluable; previously treated, n=6), alemtuzumab was given sequentially (as consolidation therapy) to patients who responded to initial courses of chemotherapy with FCM (fludarabine, cyclophosphamide, mitoxantrone).\textsuperscript{18} Patients with stable disease or progression after 2 courses of FCM were also eligible to receive alemtuzumab. Following FCM chemotherapy, 15 patients received consolidation with IV alemtuzumab. The ORR after FCM and after alemtuzumab was 66% and 88%, respectively. The median PFS and OS following FCM with alemtuzumab was 11 months and 19 months, respectively.\textsuperscript{18} In a recent follow-up report from this study (N=25; previously treated, n=9), the ORR after FCM was 68% with a CR in 24%.\textsuperscript{19} After consolidation with alemtuzumab, the ORR increased to 92% with a CR in 48% (intent-to-treat population). The median PFS and OS were 12 months and 17 months, respectively. PFS was shorter among patients with higher TCL-1 expression levels. Among the patients who received consolidation with alemtuzumab (n=21), CMV reactivation occurred in 13 patients (62%); 9 of these cases were clinical relevant CMV infections (43%).\textsuperscript{19} Outcomes with this treatment approach appear promising; however, the high rate of CMV reactivation warrants careful monitoring (and preemptive antiviral therapy upon increasing viral load) to prevent the development of CMV-related complications.

The potential utility of allogeneic hematopoietic stem cell transplant (HSCT) in patients with T-PLL has been reported in a number of individual case studies.\textsuperscript{14,20-23} A retrospective study investigated the role of HSCT (allogeneic or autologous) following treatment with alemtuzumab in patients with T-PLL (N=28), and compared the outcomes to a retrospective cohort of patients who received alemtuzumab alone.\textsuperscript{24} Among the group of patients who received allogeneic HSCT after alemtuzumab (n=13), all patients achieved a CR following HSCT (except one patient who was not evaluable), and 5 were alive in CR at a median of 28 months (range, 25 to 110 months) follow-up from transplant. Four patients had relapsed (at 5, 9, 24, and 31 months from transplant) and died; in addition, 4 patients died in CR, resulting in a treatment-related mortality (TRM) rate of 31%. The median OS (from start of alemtuzumab therapy) for all patients who underwent allogeneic HSCT was 33 months; this appeared more favorable to the median OS of 20 months among patients who did not receive transplant after alemtuzumab.\textsuperscript{24} Retrospective analyses of data from databases have evaluated the role of allogeneic HSCT in T-PLL.\textsuperscript{25-27} In a review of data from the CIBMTR database, which included patients with PLL treated with allogeneic HSCT (N=47; T-PLL, n=21 [45%]; B-PLL or unspecified lineage in the remaining cases), the 1-year PFS and OS rates were 33% and 48%, respectively.\textsuperscript{25} The median OS for these patients was 11 months. For the subgroup of patients with T-PLL (n=21), the median PFS with allogeneic HSCT was 5 months. The 1-year cumulative incidence of
TRM was 28%; the 1-year incidence of relapse or disease progression was 39%. In another study, outcomes of allogeneic HSCT in patients with T-PLL were evaluated based on data from the EBMT database (N=41). The median PFS and OS were 10 months and 12 months, respectively. The 3-year relapse-free survival (RFS) and OS rates were 19% and 21%, respectively. The 3-year TRM and relapse rates were 41% for both endpoints; most relapses (71% of cases) occurred within the first year following transplant. Patients who underwent HSCT in first remission (CR or partial remission [PR]) tended to have a lower relapse rate (2-year rate: 30% vs. 46%) and higher event-free survival rate (2-year rate: 39% vs. 15%) compared with those transplanted with advanced disease. Based upon multivariate analysis, the use of total body irradiation (TBI) conditioning and a shorter interval between diagnosis and transplant were significant independent predictors of longer RFS with allogeneic HSCT. None of the variables evaluated were independent predictors of OS outcomes. In another recent retrospective study, outcomes of allogeneic HSCT in patients with T-PLL were evaluated based on data from a multicenter French registry (N=20; transplanted in CR, n=9). The majority of these patients (85%) had received alemtuzumab prior to HSCT. The CR rate after allogeneic HSCT was 85%. At a median follow up of 29 months, 10 patients remain alive with 7 patients in CR. TRM occurred in 6 patients (30%), with early TRM in 2 of the patients. Four deaths occurred due to disease progression. The estimated 3-year PFS and OS were 29% and 42%, respectively. The 3-year incidence of TRM was 38%. The incidence of relapse was 51%, with a median time to relapse (post-HSCT) of 14 months. Although the available data are based on retrospective evaluations, allogeneic HSCT may offer the best chance for long-term disease control in a subgroup of patients with T-PLL.

Only limited data have been published on the use of autologous HSCT in patients with T-PLL. In the aforementioned study of alemtuzumab in patients with primarily pretreated T-PLL, a small group of patients (n=7) underwent autologous HSCT after achieving a CR with alemtuzumab therapy. Five of these patients were in first CR at the time of HSCT while 2 patients were in second CR. Among these patients, the median OS from time of transplant was 12 months (range, 5 to 19 months). Four patients (including the 2 patients transplanted in second CR) relapsed after 5 to 14 months and died due to progressive disease. At the time of the report, 3 patients were alive at 5, 7, and 15 months after transplant. In a more recent update, a retrospective analysis evaluated additional patients with T-PLL who underwent autologous HSCT following treatment with alemtuzumab (n=15). All of these patients achieved a CR following HSCT, and 5 were alive in CR at a median of 81 months (range, 8 to 115 months) follow-up from transplant. Nine patients had relapsed at a median of 15 months (range, 5 to 56 months) from transplant, and died; 1 patient died in CR due to an infection and multi-organ failure (TRM of 7%). The median OS (from start of alemtuzumab therapy) for all patients who underwent autologous HSCT was 52 months, which appeared to compare favorably to that of patients who received alemtuzumab alone (20 months). No statistically significant difference in OS was observed between autologous versus allogeneic HSCT (52 months vs. 33 months). At this time, however, the limited availability of data precludes any definitive conclusions regarding the role of autologous HSCT in the management of T-PLL.

NCCN Recommendations

Given the poor prognosis associated with T-PLL, the NCCN Guidelines panel recommends that patients be managed in a clinical trial for novel therapies. In the absence of suitable clinical trials, regimens containing
alemtuzumab are recommended as the initial treatment for patients with symptomatic T-PLL. Based on data showing inferior response rates with the SC route of alemtuzumab, the panel recommends that alemtuzumab be administered via IV delivery. Initial treatment options include single-agent therapy with IV alemtuzumab, or alemtuzumab in combination with pentostatin. Sequential therapy with FCM followed by IV alemtuzumab may also be considered. Given the potential risks for viral reactivation and opportunistic infections (e.g., CMV reactivation/infection, *Pneumocystis jiroveci* pneumonia [PCP]) with alemtuzumab therapy, patients should be given antiviral prophylaxis and prophylactic therapy for PCP (e.g., TMP-SMX). In addition, patients should be routinely monitored for CMV reactivation using quantitative PCR test, and treated with preemptive antiviral therapy, as appropriate (see Guidelines section for Supportive Care for NHL).

In patients who achieve a response (CR or partial response [PR]) following initial therapy, consolidation with allogeneic HSCT is recommended if a donor is available, and if the patient is physically fit enough to undergo the transplant procedure. For patients who relapse following an initial response to therapy, or for those who do not respond to therapy (or have progressive disease during therapy), second-line therapy options include clinical trial participation (preferred) or alternate regimens not used during first-line therapy.
References


