**T-cell prolymphocytic leukemia**

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**Synopsis**

T-cell prolymphocytic leukemia (T-PLL) is a rare and aggressive T-cell malignancy. T-PLL can be distinguished from other lymphoid diseases by the evaluation and integration of clinical features, morphology, immunophenotyping, cytogenetics and
molecular features. The current therapeutic approach relies upon immunotherapy followed by a hematopoietic stem cell transplant (HSCT) in selected cases. Clinical outcomes are generally poor, although insights from genomic and molecular studies may increase our understanding of this disease, with the promise of additional effective therapeutic options.

**Key Points:**

- T-cell prolymphocytic leukemia (T-PLL) is a rare and aggressive leukemia.
- The current therapeutic approach utilizes immunotherapy followed by a hematopoietic stem cell transplant (HSCT) in eligible cases.
- Genomic and molecular studies may increase our understanding of this disease, with the promise of novel therapeutic options.
INTRODUCTION

T-cell prolymphocytic leukemia (T-PLL) is a rare and aggressive T-cell malignancy first described by Catovsky et al over 40 years ago. Although termed ‘prolymphocytic’, the disease is characterized by the proliferation of post-thymic T-lymphocytes. T-PLL can be distinguished from other lymphoid diseases by the evaluation and integration of clinical features, morphology, immunophenotyping, cytogenetics and molecular features. The current therapeutic approach relies upon immunotherapy followed by a hematopoietic stem cell transplant (HSCT) in selected cases. Clinical outcomes are generally poor, although insights from genomic and molecular studies may increase our understanding of this disease, with the promise of additional effective therapeutic options.

EPIDEMIOLOGY

T-PLL accounts for 2% of mature lymphocytic leukemia in adults. The median age at presentation is 61 years of age and there is a male predominance. Three cases of children with T-PLL have been reported, although incomplete diagnostics were reported in one. Patients with ataxia telangiectasia are at increased risk of developing T-PLL (as well as other lymphoid malignancies) with a younger median age at presentation of approximately 31 years of age. An individual with Nijmegen breakage syndrome developing T-PLL has been reported. Aside from these findings, no other genetic or environmental risk factor has been robustly identified thus far.

CLINICAL FEATURES

Most patients with T-PLL present with a brief history of B symptoms, hepatosplenomegaly (splenomegaly is often massive) and a marked lymphocytosis.
(typically >100x10^9/l).\textsuperscript{3} Lymphadenopathy, although present in a majority of patients, is rarely bulky. Anemia and thrombocytopenia are seen in up to half of patients.\textsuperscript{3} Erythematous or nodular skin rashes involving the trunk or limbs, peripheral edema and pleuro-peritoneal effusions may be seen in up to a quarter of patients with T-PLL.\textsuperscript{9} T-PLL may also involve the face, where it manifests as purpura and edema, often in a periorbital distribution.\textsuperscript{10,11} Central nervous system (CNS) involvement is rare. A minority of patients have no symptoms at diagnosis. This ‘indolent’ phase can persist for a variable length of time, and can be as long as years. Disease progression may be rapid when it occurs.

**LABORATORY DIAGNOSIS**

The diagnosis of T-PLL relies on an integrated evaluation of clinical features, peripheral blood, morphology, immunophenotyping, bone marrow, cytogenetics and molecular tests.

**Morphology**

The ‘typical’ morphology observed in 75 percent of cases consists of medium sized lymphoid cells with partial chromatin condensation, a visible nucleolus and a round or oval nucleus (Figure 1).\textsuperscript{2,9} A slight basophilic cytoplasm is present, often with protrusions and an absence of granules. A ‘small cell variant’ is seen in 20% of cases. These small cells possess condensed chromatin with a small nucleolus (observed only by electron microscopy). Finally, the ‘cerebriform (Sézary cell-like) variant’ is seen in 5% of patients in which the morphology resembles the Sézary cells seen in Sézary syndrome (SS)/mycosis fungoides (MF). The bone marrow is infiltrated in an interstitial pattern by cells with a similar morphology to that seen in the peripheral blood. Skin
biopsy of affected areas demonstrates a wide cyto-morphological spectrum similar to that observed in the peripheral blood with a perivascular or diffuse dermal infiltrate, sometimes with accompanying haemorrhage. These findings are distinct from MF in which atypical small to medium sized T-cells (with characteristic ‘cerebriform’ nuclei), infiltrate the epidermis and upper dermis, form Pautrier microabscesses with Langerhans cells, and accumulate along the basal layer of the epidermis (termed ‘string of pearls’). The spleen demonstrates an atrophied white pulp with dense lymphoid infiltrates in the red pulp that invade the capsule. Lymph node involvement is diffuse, often with prominent high-endothelial venules.

**Immunophenotype**

Flow cytometry confirms a post-thymic T-cell population (TDT-, CD1A-, CD5+, CD2+, CD7+). The majority of cases are CD4+/CD8-. Dual CD4+/CD8+ cells occur in approximately 25% of cases (this is unique to the post-thymic T-cell malignancies) and only a minority of cases express a CD4-/CD8+ phenotype. CD52 is expressed strongly. Cytoplasmic CD3 is always present, but membrane expression may be weak or negative. NK and cytoplasmic granule markers are consistently negative. Typically CD7 expression is strong, whilst CD25 may be negative, thus helping to distinguish T-PLL from adult T-cell leukemia (ATL) and SS. T-PLL patients are also negative for human T-cell leukemia virus type 1 (HTLV-1).

**Molecular genetics**

T-cell receptor genes are rearranged and are identical, confirming a clonal expansion of T-cells. Although cytogenetic and mutational analysis does not alter management, the
identification of abnormalities can aid diagnosis as well as provide insight into the pathogenesis of T-PLL.

The most frequently observed group of cytogenetic abnormalities involve chromosome 14 (90%). These may take the form of inv(14), t(14;14)(q11;q32) which involve the TCL1A and TCL1B locus and t(X;14)(q28;q11) involving a homolog of TCL1, MTCP1 (mature T cell proliferation 1 gene), which is located on the X-chromosome. Transgenic mouse models have confirmed the oncogenic roles of TCL1 and MTCP1, and functional work identifies TCL1 as an Akt kinase coactivator, promoting cell survival and proliferation. Cytogenetic abnormalities involving chromosome 8 are the next most frequently observed (idic(8p11), t(8;8) and trisomy 8q). Other recurrent abnormalities seen with conventional techniques include loss of 11q23 (ATM inactivation) together with additional losses (22q, 13q, 6q, 9p, 12p, 17p) and gains (22q and 6p). 12p13 deletion, which probably occurs in up to half of T-PLL cases, is thought to contribute to the pathogenesis of T-PLL by causing haploinsufficiency of CDKN1B. With the advent of high-throughput sequencing, additional mutations in T-PLL have been identified. These include highly recurrent, largely exclusive, gain-of-function mutations involving IL2RG, JAK1/3, and STAT5B, which lead to constitutive STAT5 signaling (Figure 2). Deleterious mutations in EZH2, FBXW10 and CHEK2 may further contribute to the pathogenesis of T-PLL through their roles in DNA repair, epigenetic transcriptional regulation and proteasome degradation pathways. Further genomic analysis including sequential tumor sequencing may define driver mutations and also the clonal architecture of T-PLL. Understanding the functional consequence of these mutations is essential in furthering our understanding of T-PLL and developing novel therapeutics.
TREATMENT

Due to the rarity of T-PLL, little published data exists regarding treatment. No randomized clinical trials have been conducted. The following recommendations are based on best available evidence and personal experience.

Watch and wait

Not all patients diagnosed with T-PLL require treatment immediately. Chemo-immunotherapy can be associated with significant toxicity and, aside from HSCT, current chemo-immunotherapy regimens in T-PLL are not curative. Furthermore, some patients present with an ‘indolent phase’ of the disease. Although disease progression eventually occurs, patients can be monitored for years before requiring intervention. Close monitoring (for example, blood count and clinical examination at regular intervals) is required as disease progression can be rapid and fatal. A pre-treatment lymphocyte doubling time (LDT) of less than 8.5 months has been shown to be associated with a worse outcome,\(^2\) although an absolute lymphocyte count with LDT should be taken into consideration when deciding upon treatment initiation. Indications for treatment include B symptoms, symptomatic anemia or thrombocytopenia, disease infiltration in the skin, lungs or CNS, and progressive disease demonstrated by an increasing lymphocytosis or rapidly enlarging spleen, liver or lymph nodes.

First line therapy

Treatment is initiated with the aim of attaining a complete response (CR) and patients should be offered a clinical trial when available. There is a limited response to conventional treatment regimens such as alkylating agents or anthracyclines, with a median overall survival (OS) of 7 months in historical series.\(^3\) In the absence of a clinical
trial, patients should be offered an alemtuzumab (anti-CD52) – regimen. This was initially employed over 2 decades ago and was first used due to the strong CD52 expression on treatment-naïve T-PLL cells. Studies suggest an overall response rate (ORR) of >80% in the first-line setting and in 50-76% of relapsed-refractory cases (Table 1). Although progression-free survival (PFS) is longer when compared to other therapies (over a year in responders), relapse invariably occurs and there are few long-term survivors, with a median overall survival (OS) from treatment of less than 2 years. For this reason, eligible patients should be considered for consolidation therapies such as HSCT. The results of alemtuzumab therapy compare favorably with outcomes reported with the use of purine analogues in which ORR are <50% and remission durations are less than one year. Single-agent pentostatin has shown the greatest efficacy of all purine analogues in T-PLL, although no randomized controlled trials have directly compared single agent pentostatin and alemtuzumab. The use of pentostatin is discussed further in relapsed/refractory disease. Small prospective studies have evaluated the use of alemtuzumab in combination with chemotherapy agents. For example, Hopfinger et al reported a prospective multi-center phase II trial investigating the use of fludarabine, mitoxantrone and cyclophosphamide (FMC) induction followed by alemtuzumab in 16 treatment-naïve patients and 9 previously-treated patients. The ORR to FMC was 68% increasing to 92% following the addition of alemtuzumab. Median OS and PFS were 17.1 months and 11.9 months respectively. Alemtuzumab increases an individual’s susceptibility to opportunistic infections. Patients should therefore be on appropriate antibacterial and antiviral prophylaxis and undergo serology testing for cytomegalovirus (CMV), herpes simplex virus (HSV) and hepatitis B and C prior to commencement of treatment. In individuals who are seropositive for CMV prior to commencing alemtuzumab, serial CMV viral load should
be monitored for the early detection and management of CMV reactivation. Due to the risk of infertility with chemotherapy and HSCT, men and women should receive appropriate counselling and options for fertility preservation prior to commencing any treatment. Intravenous administration of alemtuzumab is more effective than subcutaneous administration.\textsuperscript{32} Infusion reactions are common with alemtuzumab and measures should be employed to reduce the severity and occurrence of infusional reactions. One month following completion of therapy response to treatment should be measured by history, physical examination, full blood count, bone marrow aspirate and biopsy and computed tomography of the chest, abdomen and pelvis. Response is defined using the criteria created for disease assessment in chronic lymphocytic leukemia (CLL).

**Post remission therapy**

Approximately 80\% of patients achieve a CR following alemtuzumab treatment. However, without additional therapy, a majority of patients will relapse within two years. HSCT is used to consolidate responses in eligible patients. A number of studies have investigated the use of HSCT in T-PLL and suggest that OS can be improved and in a minority of cases can achieve a cure (\textbf{Table 2}).\textsuperscript{33-36} The main challenges to contend with are the treatment-related mortality (TRM) and risk of relapse. A retrospective study by Guillaume \textit{et al} reported 27 patients undergoing allogeneic HSCT (14 of who were in CR at time of HSCT).\textsuperscript{35} The relapse rate at 3 years was 47\%, with a TRM of 31\% and an OS of 36\%. The European Group for Blood and Marrow Transplantation (EBMT) registry had 41 patients with T-PLL who had received an allogeneic HCT.\textsuperscript{34} 3 year OS was 21\% with TRM and relapse rates of 41 percent (although nearly half of the patients had refractory disease at transplant time). We reported a similar TRM rate and lower 3
year relapse rate from a smaller cohort of patients although a larger proportion of patients in our study were in CR, highlighting the importance of disease-status at time of HSCT.\textsuperscript{33} Although the number of patients is small, we also demonstrated similar OS in patients who received an autologous-SCT compared to those who received an allogenic-SCT.\textsuperscript{33} Although not offering a cure, given lower risk of treatment-related toxicity, autologous-SCT may be an option for less fit patients. Relapse following HSCT is usually within 2 years but can occur late. Given the increasing use of reduced-intensity conditioning and matched unrelated donors, as well as improvements in supportive care, more patients are eligible for HSCT, and the data which exists currently regarding HSCT may not be applicable to prospective cohorts of T-PLL patients.

**Therapy for relapsed and refractory disease**

Little data exists regarding the treatment of relapsed or refractory disease. Approximately half of the patients who relapse following a previous response to alemtuzumab can achieve a second disease remission with further alemtuzumab therapy, although this is usually of shorter duration. Flow cytometry should be repeated as T-PLL cells can lose CD52 expression.

Patients who fail to achieve a remission with single-agent alemtuzumab should have pentostatin added to the treatment regimen. Although no randomized trials have compared single-agent therapy with combination therapy, pentostatin has demonstrated efficacy as a single-agent in a small retrospective study. The ORR was 45% independent of previous treatment with a median PFS and OS of 6 months and 9 months respectively.\textsuperscript{28} A phase II study evaluated combination alemtuzumab with pentostatin in 13 patients with newly diagnosed or relapsed or refractory T-PLL. The
ORR was 69% with a median OS and PFS of 10.2 and 7.8 months, respectively. Despite adequate prophylaxis, common side effects included infection (including CMV reactivation) as well as neutropenia, thrombocytopenia, anemia and nausea.

Other treatment options include nelarabine or bendamustine, although durable remissions with these therapies are uncommon. Herbaux et al report 15 patients with T-PLL treated with bendamustine, 7 of whom had failed front-line therapy with alemtuzumab. The ORR was 53% (20% CR), median PFS of 5 months and OS of 8.7 months, independent of prior exposure to alemtuzumab. Treatment of patients with relapsed or refractory disease is currently suboptimal. Effective novel therapies are needed to improve the outcome for these patients.

**Novel therapies**

New approaches aim to utilize our expanding knowledge of T-PLL in order to target pathways involved in disease pathogenesis and resistance. Given the high frequency of mutations observed, and the perturbed signaling pathways, small molecule inhibitors targeting JAK-STAT pathway represents a therapeutic strategy available for patients. Pimozide, a STAT5 inhibitor, has been shown to induce apoptosis in primary T-PLL cells. Histone-deacetylase inhibitors (HDACi) in combination with hypomethylating agents aim to act synergistically to increase expression of silenced tumor suppressor genes. The combination of cladribine and alemtuzumab with or without an HDACi can overcome alemtuzumab resistance and induce expression of other molecules liable to targeting with additional agents. Cells with inactive ATM demonstrate impaired DNA double strand break repair capabilities. Poly (ADP-ribose) polymerase (PARP) inhibition imposes the requirement for DNA double strand break repair capabilities and
therefore selectively sensitize ATM-deficient tumor cells to killing.\textsuperscript{40} Finally, chimeric antigen receptor natural killer cells targeting CD7 may represent a novel therapeutic avenue not yet explored.

**SUMMARY**

T-PLL is a rare lymphoid malignancy with an aggressive clinical course and poor prognosis. Careful evaluation of clinical features and laboratory tests is necessary to make an accurate diagnosis and ensure appropriate prognostication and treatment. Current therapy relies upon alemtuzumab followed by an HSCT in eligible patients achieving a CR. In patients with relapsed or refractory disease, pentostatin can be added. Clinical outcomes are generally poor, although our increased understanding of the biology of T-PLL offers the promise of additional effective therapeutic options.
REFERENCES


Table 1: Treatment Trials in T-PLL (> 10 patients)
CR, complete remission; ORR, overall response rate; MPFS, median progression-free survival; MS, median overall survival; IV, intravenous; FMC, fludarabine, mitoxantrone and cyclophosphamide.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Number of patients</th>
<th>CR</th>
<th>ORR</th>
<th>MPFS months</th>
<th>MS months</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab (IV)</td>
<td>39 pre-treated</td>
<td>60%</td>
<td>76%</td>
<td>7</td>
<td>10</td>
<td>Dearden&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>32 untreated</td>
<td>81%</td>
<td>91%</td>
<td></td>
<td></td>
<td>Dearden&lt;sup&gt;12&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bendamustine</td>
<td>9 pre-treated</td>
<td>20%</td>
<td>53.3%</td>
<td>5</td>
<td>8.7</td>
<td>Herbaux&lt;sup&gt;38&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>6 untreated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMC, then Alemtuzumab (IV)</td>
<td>9 pre-treated</td>
<td>24%</td>
<td>92%</td>
<td>11.5</td>
<td>17.1</td>
<td>Hopfinger&lt;sup&gt;31&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>16 untreated</td>
<td>48%</td>
<td>68%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentostatin + alemtuzumab (IV)</td>
<td>13 (pre-treated +</td>
<td>62%</td>
<td>69%</td>
<td>7.8</td>
<td>10.2</td>
<td>Ravandi&lt;sup&gt;37&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>untreated)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
Table 2: Allogeneic Stem Cell Transplant in T-PLL
TRM, transplant related mortality; OS, overall survival; CR, complete remission; PR, partial remission.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Median age in years (range)</th>
<th>Disease status at transplant</th>
<th>TRM at 3 years</th>
<th>Relapse Rate at 3 years</th>
<th>Median OS (months)</th>
<th>3 year OS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>51 (39-61)</td>
<td>10 CR, 1PR</td>
<td>31%</td>
<td>33%</td>
<td>33 months</td>
<td>62%</td>
<td>Krishnan 33</td>
</tr>
<tr>
<td>41</td>
<td>51 (24-71)</td>
<td>11 CR, 12 PR</td>
<td>41%</td>
<td>41%</td>
<td></td>
<td>21%</td>
<td>Wiktor-Jedrzejczak 34</td>
</tr>
<tr>
<td>27</td>
<td>54 (36-65)</td>
<td>14 CR</td>
<td>31%</td>
<td>47%</td>
<td></td>
<td>36%</td>
<td>Guillaume 35</td>
</tr>
</tbody>
</table>
Figure 1: Peripheral blood smear from a patient with T-prolymphocytic leukemia demonstrating a ‘typical’ morphology.
The T-prolymphocytic leukemia cells are medium sized lymphoid cells with partial chromatin condensation and a visible nucleolus. The cytoplasm is basophilic with protrusions and an absence of granules.

Figure 2: A pathway diagram illustrates the interaction of JAK1, JAK3, and STAT5B during cytokine activation. Cytokine binding results in JAK autophosphorylation, leading to STAT recruitment and activation through tyrosine phosphorylation. Activated STAT proteins then dimerize and translocate to the nucleus to regulate transcription of numerous genes involved in differentiation, proliferation, and survival. Mutated components of the JAK1-JAK3-STAT5B pathway are highlighted. Mutations have also been described in IL2RG, which is a cytokine receptor.