Clinical and Laboratory Features of 78 Cases of T-Prolymphocytic Leukemia

By E. Matutes, V. Brito-Babapulle, J. Swansbury, J. Ellis, R. Morilla, C. Dearden, A. Sempere, and D. Catovsky

We describe the clinical and laboratory findings of 78 adult patients with T-prolymphocytic leukemia (T-PLL) studied over the last 12 years. The main disease features were splenomegaly (73%), lymphadenopathy (53%), hepatomegaly (40%), skin lesions (27%), and a high leukocyte count (> 100 x 10^9/L in 75%) with nucleolated prolymphocytes. A variant form with small, less typical cells was recognized in 19%. Membrane markers defined a postthymic phenotype Td^+, CD2^-, CD3^+, CD5^+, CD7^+, in 65%, the cells were CD4^+ CD8^-, in 21%, they coexpressed CD4 and CD8, and, in 13%, they were CD4^- CD8^. Serology for human T-cell leukemia/lymphoma virus Type-I (HTLV-I) was negative in the 27 cases investigated. Cytogenetic analysis in 30 cases showed a consistent abnormality of chromosome 14, usually inv(14), with breakpoints at q11 and q32 in 76% of cases. Trisomy 8, including iso8q, was shown in 53%; t(11;14)(q13;q32) was documented in one case; and one had a normal karyotype. The clinical course was progressive with a median survival of 7.5 months. Thirty-one patients were treated with 2-deoxycoformycin and 16 responded (3 complete remissions and 12 partial remissions); the response rate (48%) increased to 58% in patients with a CD4^+ CD8^- phenotype. The median survival of responders was 16 months and of nonresponders 10 months; other treatments were less effective. T-PLL is a distinct clinicopathologic entity with aggressive course and characteristic chromosome abnormalities. A subgroup of patients may benefit from deoxycoformycin.

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Table 1. Clinical Features of T-PLL

<table>
<thead>
<tr>
<th>Feature</th>
<th>% Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenomegaly*</td>
<td>73</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>53</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>40</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>27</td>
</tr>
<tr>
<td>Serous effusions</td>
<td>14</td>
</tr>
<tr>
<td>WBC (&gt; 100 × 10^9/L)†</td>
<td>75</td>
</tr>
<tr>
<td>Hemoglobin (&lt; 10 g/dL)</td>
<td>36</td>
</tr>
<tr>
<td>Platelets (&lt; 100 × 10^9/L)</td>
<td>51</td>
</tr>
</tbody>
</table>

*Splenomegaly (> 10 cm) in 51%.
†Median WBC 200 × 10^9/L (range, 16 to 1,000).

RESULTS

This series included 45 males and 33 females (male/female ratio, 1.33) with a median age of 69 years (range, 33 to 91). All but two patients were caucasian; two were black and born in the Caribbean. In one, T-PLL supervened on a preexistent ataxia telangiectasia. The main clinical features (Table 1) were splenomegaly, hepatomegaly, lymphadenopathy, serous effusions, and skin lesions. The skin lesions were generalized or local maculo-papular rashes or nodules; erythroderma was seen in two patients in whom a diagnosis of cutaneous T-cell lymphoma had been entertained. Skin biopsies performed in eight patients showed dermal lymphoid infiltration involving preferentially the appendages, sometimes extending to the subcutaneous fat but always without epidermotropism (Fig 1). All patients presented with a high leukocyte count with over 90% atypical prolymphocytes, and half of the patients were anemic and thrombocytopenic (Table 1). Bone marrow aspirate showed a variable degree of lymphoid infiltration (30% to 90%) and this was confirmed on the bone marrow trephines, which showed a diffuse or mixed pattern of infiltration as reported elsewhere; the aspirate was a dry-tap in two cases. Serum calcium levels were normal in all cases. Antibodies to human T-cell leukemia/lymphoma virus type-I (HTLV-1) performed by enzyme-linked immunosorbent assay (ELISA) or/and radioimmunoassay were not detected in any of the 27 samples tested, including two from the Caribbean-born patients.

Morphology. Peripheral blood provided the best material for diagnosis. The films showed a monomorphic population of medium-sized cells with features of prolymphocytes, ie, cells with a high nucleo-cytoplasmic ratio, moderately condensed chromatin, and a single prominent nucleolus. The nucleus was regular or oval in half of the cases, and irregular with convolutions and folds in the other; cells with regular and irregular nuclei coexisted in some cases. The degree of nuclear irregularity was usually less than in Sezary cells or in adult T-cell leukemia/lymphoma (ATLL), except in two cases in which half of the cells had a cerebriform nucleus resembling Sezary cells or were polylabeled as in ATLL. A distinct feature of T prolymphocytes was the presence of a nongranular deeply
basophilic cytoplasm that often showed protrusions or blebs. Immunoblast-like cells were rarely seen (<1%).

In 15 cases (19%), the cells were small and the nucleolus was not readily apparent by light microscopy but always visible by electron microscopy. This group was designated small cell variant.8 Ultrastructural analysis was useful to observe the heterochromatin marginalized to the periphery of the nucleus and to characterize as prolymphocytes the two cases with cells resembling Sezary and ATLL.9 Numerous ribosomes, polyribosomes, and profiles of rough endoplasmic reticulum accounted for the cytoplastic basophilia.

**Immunologic markers.** Membrane markers defined a postthymic phenotype (TdT, CD1a+) with negative B markers (CD19/CD20/CD22) (Table 2). Most cases were CD2, CD3, CD5, and CD7 positive. A minority of the cases were CD3 weak or negative when tested in suspension (mCD3), but positive by cytoplasmic staining (cCD3). The phenotype according to the major T-cell subsets was CD4+ CD8+, with a distinct subgroup coexpressing CD4 and CD8 (Table 2). Reactivity with CD38 and anti-TCR1 was seen in half of the cases; a minority reacted also with CD25 (Table 2). The absence of membrane CD3 expression did not correlate with negativity with anti-TCR1, nor with the expression of CD25 (six of eight mCD3 negative cases were also CD25 negative). There was no correlation either between the expression of CD25 and the reactivity with CD4 and CD8 (five of the CD25+ cases were CD4+, CD8−, two were CD4+, CD8+, and one CD8+CD4+). The MoAbs CD45RA, CD29, and CD45RO that define possible functional phenotypes within CD4+ cells were analyzed in 33 cases (Table 3). A "hybrid" phenotype or one like "memory" T cells was found in the majority of the cases. Markers of natural killer cells and LGL were rare: CD57 in 1 of 34. No case was CD16−.

**Cytogenetics.** Metaphases derived from the PHA + TPA cultures were obtained in 30 of 36 cases. The most consistent abnormalities were those involving chromosome 14 with breakpoints at q11 and q32, seen in 76% (Table 4). These abnormalities were inv (14)(q11;q32) in the majority, or involved both chromosomes 14 in complex translocations. Trisomy 8 involving iso 8q was seen in half of the cases and was often associated with rearrangements of chromosomes 14 or 7. No patient had abnormalities simultaneously affecting chromosomes 7 and 14. One case had a t(11;14) (q13;q32) with breakpoints similar to those found in B-cell PLL.25 No abnormalities were shown in 30 metaphases examined from one case and random abnormalities only were found in another. In a patient with preexistent ataxia telangiectasia, a rearrangement (X;14) (q28; q11), detected before the development of T-PLL,25 was still present and, in addition, all metaphases showed t(8;22) (q24;q11).

**Response to therapy and prognosis.** Four patients were not treated and died between 1 and 2 months after diagnosis. Another patient remained untreated for 19 months with progressive lymphocytosis and died 1 month after starting therapy without response. Thirty-two patients were treated with alkylating agents and nine (28%) had short-lived PRs. Five of 15 patients (33%) responded to CHOP, including a CR lasting 3 months. Responses to radiotherapy were seen in three of seven patients, including a PR after mediastinal irradiation maintained for 44 months and two other PR to mediastinal plus splenic or splenic irradiation lasting less than 6 months. Two patients treated with mitozantrone plus or minus cytosine arabinoside had PR.

Thirty-one of the patients treated with 2-deoxycoformycin (DCF) were evaluable for response as three are still undergoing therapy. Fifteen responses were documented, 3 CR and 12 PR, of which eight were in 15 patients treated with DCF as first line. The three patients in CR were treated for 5 to 6 months and all eventually relapsed (8, 10,

### Table 2. Immunologic Markers in T-PLL

<table>
<thead>
<tr>
<th>MoAb</th>
<th>No. of Cases</th>
<th>Tested</th>
<th>Positive*</th>
<th>% Positive</th>
</tr>
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<tbody>
<tr>
<td>CD1a</td>
<td>68</td>
<td>55</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CD2</td>
<td>68</td>
<td>77</td>
<td>65</td>
<td>99</td>
</tr>
<tr>
<td>CD3t</td>
<td>68</td>
<td>56</td>
<td>37</td>
<td>56</td>
</tr>
<tr>
<td>CD5</td>
<td>68</td>
<td>27</td>
<td>8</td>
<td>100</td>
</tr>
<tr>
<td>CD7</td>
<td>68</td>
<td>27</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>CD4+, CD8−</td>
<td>72</td>
<td>72</td>
<td>47</td>
<td>65</td>
</tr>
<tr>
<td>CD4+, CD8+</td>
<td>72</td>
<td>72</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td>CD4−, CD8−</td>
<td>72</td>
<td>72</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>CD4−, CD8+</td>
<td>72</td>
<td>72</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CD25</td>
<td>72</td>
<td>44</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>CD38</td>
<td>72</td>
<td>33</td>
<td>17</td>
<td>52</td>
</tr>
<tr>
<td>Anti-TCR1</td>
<td>72</td>
<td>25</td>
<td>15</td>
<td>60</td>
</tr>
<tr>
<td>HLA-DR</td>
<td>72</td>
<td>52</td>
<td>4</td>
<td>8</td>
</tr>
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</table>

*More than 20% of cells reactive; TdT was negative in all 49 cases tested.
†Membrane CD3 (tested in cell suspension); six of the mCD3− cases become CD3+ when tested on fixed cells (cCD3+).

### Table 3. Immunophenotype in 33 CD4+ T-PLL

<table>
<thead>
<tr>
<th>Functional Phenotype</th>
<th>MoAb</th>
<th>Positive Cases</th>
</tr>
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<tbody>
<tr>
<td>Hybrid</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Memory&quot; T cells</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>&quot;Naive&quot; T cells</td>
<td>+</td>
<td>-</td>
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</table>

### Table 4. Cytogenetic Findings in 30 Cases of T-PLL

<table>
<thead>
<tr>
<th>Chromosome Abnormality</th>
<th>No. of Cases</th>
</tr>
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<tbody>
<tr>
<td>Breakpoints</td>
<td></td>
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<tr>
<td>14q11−q32</td>
<td>23</td>
</tr>
<tr>
<td>inv (14)(q11;q32)</td>
<td>19</td>
</tr>
<tr>
<td>t(14;14)(q11;q32)</td>
<td>2</td>
</tr>
<tr>
<td>t(10;14)(p11;q11; q11)</td>
<td>1</td>
</tr>
<tr>
<td>(11;14)(p13;q11 q32; q11)</td>
<td>1</td>
</tr>
<tr>
<td>Trisomy 8q*</td>
<td>16</td>
</tr>
<tr>
<td>t(11;14)(q13;q32)</td>
<td>1</td>
</tr>
<tr>
<td>t(22;q24;q11) + t(8;22)(q24;q11)†</td>
<td>1</td>
</tr>
<tr>
<td>Random abnormalities</td>
<td>1</td>
</tr>
<tr>
<td>Normal karyotype</td>
<td>1</td>
</tr>
</tbody>
</table>

*Associated to 14q11 q32 abnormalities in 13 cases and with rearrangements of chromosome 7 q33-35 in two.
†Patient with preexistent ataxia telangiectasia.

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or below 100.

Better than older ones. Hepatomegaly (any size palpable) second time. The response rate was higher in cases with a

of sex, splenomegaly, skin lesions, or lymphocytosis above

analysis of prognostic factors showed no effect on survival

of therapy. Patients treated with DCF had a better median

survival for the whole group was 7.5 months (Fig 2). The

was shown in four of seven cases and trisomy 8q in three.

CDK.

CD4' CD8- phenotype (58%) compared with other pheno-

types (27%). All but two of the responders were CD4'

transient second response to DCF, but died of progressive
disease 6 months later. Another was unresponsive to DCF a

six are still alive. The median

and age reached statistical significance.

More importantly, the chromosome abnormality inv (14)

of prolymphocytes, with the most common phenotype

features suggestive of T-PLL.30,31

DISCUSSION

Within the spectrum of T-cell leukemias with a mature
phenotype, T-PLL is relatively common, accounting for
one-third of the cases. The disease affects mainly elderly
patients and is characterized by splenomegaly, lymphade-
nopathy, skin infiltration, and a high leukocyte count. The
findings are different from those of other mature T-cell
leukemias, such as ATLL, Sezary syndrome, and LGL
leukemia. In all these other leukemias, the WBC is, as a
rule, below $100 \times 10^9/L$ and massive splenomegaly is
uncommon; instead, they have other features, eg, hypercal-
caemia in ATLL, or erythroderma in Sezary syndrome, that
are rare in T-PLL. The pattern of skin involvement is
different from the cutaneous T-cell lymphomas; epidermo-
tropism is never seen in T-PLL. Furthermore, unlike
ATLL, we have not been able to establish an association
between T-PLL and HTLV-I, even in the two patients born
in the Caribbean.

The diagnosis of T-PLL could be made by light micros-
copy examination of blood films in most cases. The main
morphologic features are a prominent nucleolus and deep
cytoplasmic basophilia. In a minority of cases with small
prolymphocytes, the nucleolus is not easily visible by light
microscopy and ultrastructural analysis is necessary to
establish the diagnosis.16 Our observations in 15 cases with
small prolymphocytes do not support the view that the small
variant is a separate disease and suggest instead that it
corresponds to the same entity of T-PLL.

Immunologic markers showed the mature T-cell nature
of the prolymphocytes, with the most common phenotype
being CD4+, CD8-. The expression of CD7 was a consistent
feature of T-PLL and this contrasts with findings in ATLL,
in which CD7 is often negative, and in Sezary syndrome and
LGL leukemia, in which half of the cases are also CD7
negative.19 The lack of membrane expression of CD3
(mCD3) in 19% of the cases did not correlate with the
reactivity with anti-TCR1, which detects a determinant of
the $\beta$-chain of the T-cell receptor. A defective expression
of the CD3 TCR complex has also been reported in ATLL
and it has been suggested that it relates to the activation of
ATLL cells that express interleukin-2 (IL-2) receptors
(CD25+).24 This is unlikely to be the explanation in T-PLL
because there was no correlation between the expression
of CD25 in a minority of cases and the absence of mCD3 in
these cells. The pattern of staining with markers that define
functional subsets in CD4+ T-PLL cases was not uniform, as
found in other CD4+ T-cell malignancies.28

A consistent chromosome abnormality in T-PLL involves
chromosome 14 with breakpoints at bands q11 and q32,
which might result in the juxtaposition of the $\alpha$-chain or
$\delta$-chain gene locus located at q11 to a candidate oncogene
yet to be shown at q32.26 This abnormality seems to be
characteristic of T-PLL as it has not been found by us in 30
cases with other T-cell malignancies27 and has rarely been
reported in ATLL,28 peripheral T-cell lymphoma,29 and in
some "T-cell leukemias" with clinical and laboratory fea-
tures suggestive of T-PLL.20,30

These cytogenetic findings, together with the other dis-
ease features, support the concept of T-PLL as a distinct

![Fig 2. Kaplan-Meyer plot of the survival of 68 T-PLL patients.](image-url)
entity. It is of interest that patients with ataxia telangiectasia have in their peripheral blood T-cell clones carrying chromosomal rearrangements involving 14q11, 7p13-14, and 7q32-35 where the TCR genes have been mapped. These patients are at risk of developing T-cell malignancies that corresponded in some to T-PLL, as illustrated by one patient in this series. T-cell clones from patients with ataxia telangiectasia morphologically resemble T prolymphocytes. Molecular analysis of one such clone and of four cases of ataxia telangiectasia developing T-cell leukemia with inv(14) or the tandem translocation t(14;14) has shown that the 14q11 breakpoint was located within the TCR Jα locus and that the breakpoint on 14q32 was mapped to 14q32.1. Clonal abnormalities involving chromosome 14 are also seen in ataxia telangiectasia without leukemia, suggesting that this karyotypic change may be a preleukemic event and that a second event is required for the development of an overt neoplastic process. Indeed, in all but one of our T-PLL cases, the clonal abnormality of chromosome 14 was associated to other rearrangements, more frequently trisomy 8q. In the patient with ataxia telangiectasia developing T-PLL, additional chromosomal rearrangements (Table 4) were documented in the leukemic phase that had not been previously detected.

The clinical course of T-PLL is progressive in almost all patients who are, as a rule, resistant to alkylating agents. Responses to CHOP, mediastinal and abdominal irradiation, and DCF have been previously documented in single case reports, as well as the resistance to these or other types of treatment. Our results suggest that DCF is a moderately effective agent in T-PLL, particularly when the phenotype is CD4+ CD8+, and when it is used as the first line of treatment. However, the responses to DCF are not durable and have not yet been translated in an improved survival. It is possible that several therapeutic agents used sequentially or in combination may improve the outlook in this aggressive T-cell leukemia.

This study confirms the relevance of a multiparameter analysis to define disease entities. We have established that within the spectrum of postthymic T-cell malignancies, T-PLL has characteristic clinical, morphologic, and immunologic features and consistent karyotypic rearrangements involving chromosome 14 that are rare in other T-cell malignancies. The identification of T-PLL may provide the basis for molecular studies on the ethiopathogenesis of this disease and will facilitate comparisons with other T-cell malignancies. This analysis has allowed also to delineate therapeutic strategies that may subsequently result in improvements in survival.

ACKNOWLEDGMENT

We are grateful to Ann Gates for helping in the data collection, M. Pomfret and A. Crawford for performing some of the cytogenetic studies, Dr Tedder (University College, Middlesex Medical School) and Prof R. Weiss (Institute of Cancer Research) for assessing serology for HTLV-I, and to all the many hematologists in the UK that have referred samples and patients for this study.

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