T-PLL (T-cell prolymphocytic leukemia)

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Here you can inform yourself about the characteristics, classification, diagnosis, prognosis and therapy of this rare T cell leukemia.

Diagnostic recommendation

Method	Anticoagulant	Recommendation
Cytomorphology	EDTA	mandatory
Immunophenotyping	EDTA or Heparin	mandatory
Chromosome analysis	Heparin	mandatory
FISH	EDTA or Heparin	mandatory
Molecular genetics	EDTA or Heparin	mandatory

Characteristics of T-PLL

T-cell prolymphocytic leukemia is a very rare, usually aggressive malignant disease of the lymphatic system. To gain further insights into this very rare entity, every newly diagnosed T-PLL should be included in the **German CLL Study Group Registry (DCLLSG)** for the purpose of systematic data collection.

The pathological cell population develops from mature T cells that have already undergone imprinting in the thymus. Often the pathological cells are CD4+/CD8-, but there are also cases with CD4-/CD8+ or CD4+/CD8+. Characteristic and also relatively specific for the disease are rearrangements involving the "T-cell leukemia/lymphoma 1" (*TCL1*) gene family, which lead to pathological overexpression of the oncogenes *TCL1A*, *TCL1B* or *MTCP1* (Staber et al. 2019). In recent years, patient survival has been significantly improved by treatment with anti-CD52 monoclonal antibodies (alemtuzumab) and stem cell transplantation.

Classification of T-PLL

T-cell prolymphocytic leukemia accounts for about 2% of all mature lymphocytic leukemias and is described by the WHO as a separate entity.

T-PLL WHO Classification 2017
(Swerdlow et al. 2017)

Mature T-cell neoplasm
- T-cell prolymphocytic leukemia

There are three morphological variants:
- typical variant
- small cell variant
- cerebriform variant

Diagnostics according to consensus criteria of the international T-PLL study group

The diagnosis according to the criteria of the T-PLL International Study Group (T-PLL-ISG) can usually be made on the basis of cytomorphology and immunophenotype. Genetic tests can significantly support the diagnosis. Table 1 gives an overview of the consensus criteria established for the diagnosis of T-cell prolymphocytic leukemia (Staber et al. 2019). T-PLL cells can be found in peripheral blood, bone marrow, lymph nodes, spleen, liver or skin. In clinical routine, peripheral blood is usually sufficient to confirm the diagnosis (Staber et al. 2019). Differentiation from other mature cell lymphomas must be made by differential diagnosis (Swerdlow et al. 2016).

Table 1: Consensus criteria of the T-PLL-ISG (after Staber et al. 2019). The diagnosis of a T-PLL can be made if either all three main criteria are met, or the first two main criteria and one secondary criterion are met.

Major criteria	Minor criteria
>5 x 10^9/l cells of T-PLL phenotype in peripheral blood or bone marrow	Abnormalities involving chromosome 11 (11q22.3; ATM)
T-cell clonality (by PCR for TRB/TRG, or by flow cytometry)	Abnormalities in chromosome 8: idic(8)(p11), t(8;8), trisomy 8q
Abnormalities of 14q32 or Xq28 OR expression of TCL1A/B, or MTCP1*	Abnormalities in chromosome 5, 12, 13, 22, or complex karyotype
	Involvement of T-PLL specific site (eg, splenomegaly, effusions)

*Cases without *TCL1A*, *TCL1B*, or *MTCP1* rearrangement or their respective overexpression are collected as *TCL1*-family negative T-PLL.

Diagnostics of T-PLL

Cytomorphology

Typical for the disease T-PLL is a predomination of the prolymphocytic cell population in three variants, which otherwise do not differ significantly clinically and immunophenotypically.

Variants of the prolymphocytic cell population:

- 75% typically medium-sized prolymphocytic with a slightly loosened nucleus of smooth contour with a distinct nucleolus; the basophilic cytoplasm has occasional protuberances.
- 20% small-cell with highly condensed chromatin and barely visible nucleolus.
- 5% cerebriform with irregular, furrowed nuclear circumference as in Sézary cells.

At diagnosis, cytomorphological assessment of the peripheral blood is usually sufficient. To control the response, however, the examination of bone marrow aspirate and biopsy is necessary, since the definition of complete remission (CR) or complete remission with incomplete marrow recovery (CRi) includes cytomorphological criteria. For example, the proportion of T-PLL cells among the bone marrow mononuclear cells must be less than 5% and for the detection of CR a recovery of the bone marrow must be measurable (platelet count ≥100 x 10^9/l, hemoglobin ≥11.0 g/dL, neutrophils ≥1.5 x 10^9/l) (Staber et al. 2019).

Immunophenotyping

The T-PLL shows a leucocytosis of mostly more than 100 x 10^9/l and the cells express characteristic surface markers (see Table 2).

T-cell lymphomas in patients can be detected by immunophenotyping via an aberrant phenotype. For example, they show a coexpression of the antigens CD4 and CD8. A loss or decreased expression of certain T-cell associated antigens such as CD5 or CD3 can also indicate T-cell lymphoma. The ratio of CD4- to CD8-positive T lymphocytes may be shifted to **δ/β** as well as from T cell receptor **δ/δ**.

Table 2: Characteristic findings for T-PLL

Antigene	Result
CD2	+
CD3	+
CD5	+
CD7	+
CD4+CD8-	+ (60%)
CD4+CD8+	+ (25%)
CD4-CD8+	+/- (15%)
CD52	+

Besides cytomorphology, immunophenotyping is also obligatory for diagnosis. It can be used for clonality detection as well as for the detection of overexpression of the involved *TCL1* oncogene (*TCL1A/B* or *MTCP1*) (see also Table 1). Furthermore, the immunophenotype can be used to differentiate the disease from other T cell diseases (Staber et al. 2019).

Chromosome analysis

Inversion of chromosome 14 characteristic for T-PLL

The most common chromosomal changes in T-PLL affect chromosome 14, with inversion 14 (inv(14)(q11q32)) being the most common aberration and being observed in 80% of all patients (Matutes et al. 1996). 10% of the cases show a reciprocal translocation between the homologous chromosomes 14 (t(14;14)(q11;q32)) (Brito-Babapulle & Catovsky 1991). In both cases there is a rearrangement of the gene locus of the T cell receptor alpha/delta (TRA/D) with the proto-oncogene *TCL1* at the molecular level, which leads to an increased expression of *TCL1* (Pekarsky et al. 1999). Another fusion partner of TRA/D is the proto-oncogene *MTCP1*, which is homologous to *TCL1* and is located on the X chromosome in the Xq28 band (Stern et al. 1993). Thus, the t(X;14)(q28;q11) represents another typical aberration in the T-PLL. In very rare cases, no rearrangement or corresponding overexpression of the *TCL1* gene family can be detected for a T-PLL despite the fulfillment of the further diagnostic criteria (see Table 1). They should be categorized as *TCL1* gene family negative T-PLL (Staber et al. 2019).

Further recurrent cytogenetic abnormalities in T-PLL
In addition, aberrations of chromosome 8 were observed in 70-80% of cases. These include i(8)(q10), idic(8)(p11), t(8;8)(p11~12;q12), and other unbalanced aberrations that cause trisomy 8q and thus overexpression of the *MYC* oncogene (Pekarsky et al. 1999). In addition, 12p13 deletions, 13q deletions, and aberrations of chromosome 6 (33%) and chromosome 17 (26%) were observed, the latter often leading to a deletion of the *TP53* gene (Soulier et al. 2001). 12p deletions cause a haploinsufficiency of *CDKN1B*, for which a function in the pathogenesis of T-PLL has been postulated (Le Toriellec et al. 2008).

Individual cytogenetic abnormalities do not seem to influence the prognosis, but there is evidence that the number of aberrations is of prognostic relevance. For example, median overall survival in T-PLL patients with a complex karyotype (≥3 aberrations) was 14 months, significantly shortened compared to cases with a normal karyotype (43 months). A particularly poor prognosis with a median overall survival of 11 months was observed in patients with five or more cytogenetic aberrations. When the number of aberrations was <5, median survival was 22 months (Hu et al. 2017).

FISH

Often deletions in the *ATM* locus on chromosome 11
By means of FISH-analysis and molecular genetic investigations, partly cytogenetic cryptic deletions on chromosome 11 in the chromosome band 11q23 could be detected in the majority of patients. 11q23 deletions occur in about 57% of cases (Stengel et al. 2016). This gene locus contains the *ATM* (Ataxia telangiectasia mutated) gene, which is also frequently mutated in T-PLL (Stilgenbauer 1997). In total, the *ATM* gene is affected by deletions and/or mutations in more than 70% of patients (Stengel et al. 2016, Staber et al. 2019). Patients with ataxia teleangiectatica (congenital homozygous *ATM* mutation) develop T-PLL more often than average (Brito-Babapulle & Catovsky 1991). Deletions of *TP53* can also be detected in 26% of cases, mutations in 14% (Stengel et al. 2016).

Molecular genetics

Activation of the STAT5 signal path often with T-PLL

In addition to *TP53*, frequent molecular genetic mutations in T-PLL affect the *JAK1* and *JAK3* genes, which leads to an activation of the *STAT5* signaling pathway, which thus appears to play an important role in the pathogenesis of T-PLL (Kiel et al. 2014). In addition, *JAK3* mutations have been shown to have a negative impact on patient survival, so that *JAK3* may act as an important prognostic marker (Stengel et al. 2016). Mutations of the *PTPRC* gene, which codes for *CD45*, have also been described as recurrent, including a negative regulator of the JAK-STAT pathway (Johannson et al. 2018).

Other recurrent mutations affect DNA repair and transcription
Various mutations that frequently occur in T-PLL affect factors of DNA repair. These include in particular *ATM* (see Diagnostics, FISH), a protein kinase that plays a key role in initiating DNA repair. In addition, genetic characterization has identified further mutations affecting repair factors:

SAMHD1, *PARP10*, *HERC1* and *HERC2* (Schrader et al. 2018, Johannson et al. 2018).

Further evidence suggests that transcription is also one of the dysregulated cellular processes in T-PLL, through mutations that affect factors directly involved in or epigenetically regulating transcription. Recurrent mutations of the transcription factor *FOXP1* (Johannson et al. 2018) have been described as well as mutations in the *BCOR* gene (Xp11), a BCL6 co-repressor (Stengel et al. 2016, López et al. 2016) and in the *ARID4B* gene, which also encodes a co-repressor (Johannson et al. 2018). Among the mutated epigenetic factors are *TET2*, which is involved in the regulation of DNA methylation, and a large number of histone modifying factors (*EZH2*, lysine methyltransferases of the *KMT2A* gene family and *KMT5A*, *EP300*, *PRDM2*) (López et al. 2016, Schrader et al. 2018, Johannson et al. 2018).

The importance of mutations both in the *JAK*-STAT pathway (*JAK3* and *STAT5B*) and in epigenetic regulators or regulators of transcription (e.g. *EZH2*, *TET2* and *BCOR*) for the development and possible therapy of T-PLL could be further illustrated by high mutation frequencies in the corresponding genes (López et al. 2016). Further pathological genetic aberrations lead to increased cell survival (through TP53 inactivation) or contribute to chromosomal instability (e.g. through *ATM* inactivation), as described with the high proportion of complex karyotypes (70-80% of patients) for T-PLL (Hu et al. 2017, Staber et al. 2019).

Prognosis

The overall rather uniformly poor prognosis for patients and the rarity of T-PLL hinder the prospective validation of clinical or biological prognostic factors. In clinical practice, there are currently no validated prognostic factors that can be used as a basis for specific stratification and therapeutic decisions.

T-PLL patients can be enrolled in the registry study of the German CLL Study Group (DCLLSG) "Long-Term Follow-Up of Patients with CLL, B-PLL, T-PLL, SLL, T/ NK-LGL, HCL and Richter Transformation" (NCT02863692) at the University of Cologne **(detailed information)**.

Therapy of T-PLL

With regard to the course of the T-PLL disease, two phases can be distinguished: the asymptomatic "inactive phase" and the "active phase", in which characteristic symptoms such as lymphadenopathy, leukocytosis, hepato- and/or splenomegaly occur. Only a small percentage is diagnosed in the inactive phase. Under these circumstances, a prudent watch-and-wait approach is usually indicated, which requires close monthly monitoring. After 1-2 years, even in diseases diagnosed in the inactive phase, a transition to the active phase requiring treatment occurs (Staber et al. 2019, Onkopedia Guideline T-PLL 2020).

The current gold standard in the treatment of T-PLL is treatment with the anti-CD52 monoclonal antibody alemtuzumab. Although the initial response is very good, with overall response rates of over 90% in some cases, recurrences almost always occur (Staber et al. 2019), with a median progression-free survival of approximately 12 months (Dearden et al. 2011, Hopfinger et al. 2013, Braun et al. 2020). Only stem cell transplantation represents a curative approach, but only about 30-50% of patients are eligible for this procedure (Onkopedia Guideline T-PLL 2020). Long-term remissions after allogeneic stem cell transplantation were observed in about 1/3 of the patients (Staber et al. 2019).

New therapeutic approaches result from the improved understanding of the pathobiology of the disease (see also Diagnostics, FISH and Molecular Genetics) and various drug screenings (Andersson et al. 2018, Dietrich et al. 2018, Schrader et al. 2018, Braun et al. 2020), which could lead to an improvement of the response time in first-line therapy as well as to new therapeutic strategies for the treatment of recurrent T-PLL and for maintenance therapy after stem cell transplantation.

In the class of small molecule inhibitors, the following agents in particular show ex vivo activity against T-PLL (Andersson et al. 2018, Braun et al. 2020) and are currently being investigated in clinical studies:
- HDAC inhibitors (epigenetic regulation and reactivation of p53)
- MDM2 inhibitors (reactivation of p53, thereby induction of apoptosis)
- BCL2 inhibitors (induction of apoptosis)
- Inhibitors of the JAK-STAT signaling pathway

T-PLL sensitivity to JAK inhibitors was also described in another ex vivo screening study (Dietrich et al. 2018). A Phase I study is currently investigating whether the response and especially the response time can be improved by combining alemtuzumab with the JAK1 inhibitor itacitinib **(NCT03989466)**.

Sensitivity to BCL2 inhibitors was also observed in a further ex vivo screening approach (Boidol et al. 2017). Under venetoclax monotherapy, a transient partial response was achieved in two individual treatment trials in refractory T-PLL (Boidol et al. 2017). Another screen identified the tyrosine kinase inhibitor ibrutinib as a potential synergistic agent (Kornauth et al. 2019). After observing a substantial clinical response to combination therapy in two patients with relapsed T-PLL, a Phase II study was initiated to evaluate venetoclax/ibrutinib therapy **(NCT03873493)**. A Phase I study is evaluating another potential synergism that may result in the induction of apoptosis by treatment with an MDM2 inhibitor and a BCL2 inhibitor **(NCT04496349)**.

References

You can find the corresponding references here:
https://www.mll.com/en/diagnostic-offer/mature-t-cell-neoplasms/t-pll-t-cell-prolymphocytic-leukemia.html#referenzen