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State of the Art Review: New Insights in T Cell Prolymphocytic Leukemia

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Abstract

T cell ProLymphocytic Leukemia (T-PLL) is a rare lymphoid malignancy and is typified by its aggressive presentation and chemo-resistance. Given its rarity, haemato-oncologists are likely to manage only a handful of cases across their career and therefore making the diagnosis is the initial challenge. This diagnosis is critical, as recent data suggests that choosing specific treatment options, such as alemtuzumab, is important in improving outcomes.

Keywords: T cell Prolymphocytic leukemia; Alemtuzumab, JAK3; JAK1; Stem cell transplantation

Introduction

Clinical features and laboratory investigations are characteristic. The disease is twice as common in men as women, and the median age of presentation is 61 years. T-PLL is also more common in ataxia telangiectasia (AT) an autosomal recessive disorder resulting from mutations of the ATM gene [1]. Patients almost universally present with an increasing lymphocytosis and / or splenomegaly. The disease can initially follow a relatively indolent phase for a short period of time in a minority, invariably followed by more aggressive progression. Other clinical associations include skin infiltration leading to purple, dusky, nodular infiltrates, conjunctival injection and periorbital oedema, pleural and pericardial involvement with effusions, hepatomegaly, and occasional CNS involvement [2].

A marked peripheral blood lymphocytosis is common, often exceeding 100×109/L, with a rapid lymphocyte doubling time. Peripheral blood morphology and flow cytometry results are diagnostically critical. T cell prolymphocytes dominate the peripheral blood film, and are often relatively small compared to B cell prolymphocytes. The nucleoli are less apparent, while the cytoplasm is deeply basophilic with very characteristic cytoplasmic 'blebbing'. Thrombocytopenia may be particularly prominent due to hypersplenism and bone marrow infiltration. As the disease progresses, extensive bone marrow infiltration leads to marrow failure and death.

Peripheral blood film morphology typically raises the suspicion of the diagnosis, which can be confirmed by peripheral blood or bone marrow immunophenotyping. T-PLL cells are classically very strongly CD7 positive [2], as well as expressing the post-thymic phenotypic markers CD2, CD3 and CD5. Importantly, CD25 is negative (positive in Adult T cell leukemia / Lymphoma (ATLL)), B cell markers are negative (positive in B cell PLL), and TdT and CD1a are negative (positive in T cell acute lymphoblastic leukemia (T-ALL)).

Thus, the elucidation of an additional factor is expected to facilitate a better understanding of ATL.

The characteristic cytogenetic abnormalities of T-PLL described in Western populations are the chromosomal inversion inv(14)(q11q32) and variant translocation t(14;14)(q11;q32) present in approximately 70% of cases [3], and the rarer translocations t(X;14)(q28;q11) and t(X;7)(q28;q11) found in up to 20% of patients [4]. These abnormalities all juxtapose a member of the oncogenic TCL1 family next to a TCR locus; inv(14)(q11q32) and t(14;14)(q11;q32) TCRA/D locus to TCL1A and TCL1B [5], t(X;14)(q28;q11) TCRA/D locus to MTCP1 [6] and t(X;7)(q28;q11) TCRB locus to MTCP1 [4]. The net result of all these chromosomal aberrations is overexpression of TCL1 family oncoproteins which via their interaction with the serine/threonine protein kinase AKT are able to effect cell proliferation and survival [7] and through their inhibition of the PKCθ and ERK pathways inhibit activation induced cell death [8]. These changes often co-exist with trisomy 8q [4]. Mutations in the ATM gene at 11q23 are seen in many cases [9], including those patients without ataxic telangiectasia. As is true for many haematological malignancies, given the different parameters used to formalise the diagnosis it is critical that the results are reported and integrated together to reduce the risk of misdiagnosis [10].

Although some transgenic mouse models suggest that overexpression of TCL1A or MTCP1 alone is sufficient to produce a T-PLL (or at least lymphoproliferative) phenotype [11,12] this is not universally observed amongst such models [13] or repeated in human subjects: Cytogenetic analyses of clonal T cell expansions observed in some patients with ataxia telangiectasia prior to the development of overt leukemia [1,14] frequently show chromosomal rearrangements involving TCL1 family proteins suggesting that although this is an important initiating event in leukaemogenesis, by itself it is insufficient to cause transformation.

Unlike studies performed in Western populations, cytogenetic analyses of patients with T-PLL from Japan and China have not demonstrated frequent translocations involving TCL1 family proteins [15-17]. In the study by Yokohama et al. however, aberrant TCL1A expression could be detected in 6 of 11 cases using qRT-PCR or flow cytometry/immunohistochemistry. Further investigations using split signal FISH probes revealed 3 of 7 cases had a rearrangement of the TCL1 locus. Together these results suggest that overexpression of

TCL1 family proteins can occur in the absence of the characteristic chromosomal aberrations and alternative fusion partners to the TCR genes can induce abnormal expression of TCL1A protein.

In addition to chromosomal rearrangements involving TCL1 family proteins, T-PLL is associated with a number of secondary chromosomal abnormalities including gains in 6p and 8q (often associated with a loss of 8p resulting in an isochromosome 8q) and losses of 6q, 10p, 11, 12p, 18p and 22q. One explanation for this chromosomal instability is the frequent disruption (by deletion or mutation) even in non-AT patients of the ATM gene resulting in loss of its critical function in mobilising the cellular response to double-strand DNA breaks [18].

Loss of chromosome 11q has been reported in more than 50% of patients with T-PLL and is frequently associated with mutations in the other ATM allele [9,19,20] resulting in biallelic disruption demonstrating it acts as a classic tumour suppressor gene. Unlike B-CLL where the mutations are distributed across the gene, in T-PLL the mutations cluster in the PI3-K domain [21]. One hypothesis suggests that in sporadic T-PLL ATM disruption precedes and facilitates both TCL1 loci rearrangements (as is seen in AT-associated T-PLL) and the subsequent transforming genetic event(s).

Attempts have been made to identify genes involved in other recurrent chromosomal rearrangements using high density Single Nucleotide Polymorphism (SNP) arrays and Gene Expression Profiling (GEP) [22,23]. Although these studies have reinforced the genetic complexity of the T-PLL karyotype and demonstrated common chromosomal lesions such as isochromosome 8q, they have not revealed any common breakpoints for translocations, rather yielded a list of recurrently disrupted (e.g. in 2 of 18 samples) genes (e.g. PLEKHA2, NBN, NOV and MYST3) which may be involved in pathogenesis but have yet to be confirmed by independent investigations [23].

Examination of a combination of karyotype, FISH, SNP and GEP data has been more successful at identifying minimally deleted regions and the constituent genes which may be contributing to the aetiology of T-PLL. One such investigation of chromosome 12 demonstrated a 216 kb minimally deleted region at 12p13 which occurred in approximately half of all cases [13]. This region includes the CDKN1B gene which encodes the p27KIP1 protein which has an essential role in cell cycle regulation and shows a gene dose effect; high levels of p27KIP1 are able to bind to and inhibit cyclin-dependent kinases, preventing progression through the cell cycle whereas lower levels of the protein permit continued cell-cycling and are associated with a poor prognosis in a number of malignancies [24].

Only one somatic mutation was found in the CDKN1B gene amongst this series in a patient who did not have an accompanying deletion. The lack of biallelic disruption suggests it is not acting as a classic tumour suppressor gene. Gene expression profiling using qRT-PCR demonstrated reduced transcription of CDKN1B amongst all those patients with a deletion or mutation of the gene and some who did not appear to have a disruption of the gene suggesting other mechanisms of down-regulation (e.g. epigenetic modification) may be being utilised.

Further evidence for the role of CDKN1B in the pathogenesis of T-PLL comes from a double transgenic mouse model where transgenic MTCP1 mice were crossed with animals with a heterozygous inactivation of CDKN1B. In these experiments MTCP1/CDKN1B+/+ mice developed normally with no clonal expansion of T cells in contrast to MTCP1/CDKN1B+/- animals who developed pre-leukemic clones. Of note, early data from MTCP1/CDKN1B-/- mice revealed a similar phenotype to MTCP1/CDKN1B+/- animals with no earlier accumulation of T cell clones [13]. Together these data suggest a role for CDKN1B in the aetiology of T-PLL as a haploinsufficient tumour suppressor gene. Similar investigations of chromosome 22 (found to be disrupted in approximately a third of cases in several different cohorts) revealed a 25.3 Mb minimally deleted region extending from the centromere to 22q12.1 [25]. Two previously described tumour suppressor genes are located within this region; SMARCB1 and CHEK2. The former is the core subunit of the SWI/SNF chromatin remodelling complex which alters histone-DNA interactions therefore influencing gene expression [26] while the latter is down-stream of ATM in the cellular response to double-strand DNA breaks [27]. In cases where deletions of 22q were detected sequencing was undertaken of the other SMARCB1 and CHEK2 alleles to look for inactivating mutations; none were found in either gene suggesting if these are acting as tumour suppressor genes in the pathogenesis of T-PLL they are doing so via a haploinsufficient mechanism.

It is of note that this genetic complexity observed in American and European patient cohorts was not replicated in the Japanese and Chinese cohorts described previously where the disease was generally more indolent and associated with a less marked lymphocytosis [15-17]. It is particularly striking that the characteristic chromosomal aberrations involving the TCL1 family gene loci are largely absent in these latter populations. It would therefore be interesting to perform arrays comparing more indolent and aggressive disease phenotypes amongst both Eastern and Western populations.

The genes most recently found to be recurrently mutated in T-PLL are JAK1 and JAK3, both members of the Janus kinase family [28,29]; non-receptor tyrosine kinases involved in the transduction of cytokine signals from the cell surface to the nucleus via the JAK-STAT signalling pathway. The hypothesis that members of the JAK family may be mutated in T-PLL arose from the discovery that activating mutations of JAK3 were present in other T cell malignancies [30,31] and MTCP1/TEL-JAK2 double transgenic mice rapidly developed a T cell malignancy [29]. In one study 4 of 45 and 19 of 45 cases showed mutations in JAK1 and JAK3 respectively, many of which had been described previously in other malignancies (as evidenced by entry in the COSMIC database) and had been shown to be activating in vitro [29]. The JAK1 mutations were all located in the pseudokinase domain while the JAK3 mutations were found in the kinase domain, pseudokinase domain and linker region. Of note, the linker region contained a hotspot mutation M511I which in vitro was the most efficient oncokinase out of a panel of JAK3 mutations identified in acute leukemias [32]. In a separate cohort 11 of 32 patients had JAK3 mutations distributed across the linker and pseudokinase domains [28]. As with the cohort described in Bellanger et al the most frequently occurring mutation was M511I which was found in 8 cases.

Across the two patient populations, several patients had more than one JAK family mutation (either a JAK1 and JAK3 mutation or two JAK3 mutations) meaning they either have cumulative/complementary effects or are found in different subclones. The finding of recurrent JAK family mutations is of particular interest as in addition to providing further insights into the pathogenesis of the disease it provides a potential new therapeutic avenue as JAK3 inhibitors exist and in vitro have shown some promising results inhibiting proliferation in cell lines expressing activating JAK3 mutations [33]. The discovery of JAK family mutations in T-PLL

provides an incentive to perform more extensive sequencing studies (whole genome or whole exome sequencing) as these may reveal other recurrently mutated genes which are potential therapeutic targets. Given the rarity of the disease, large multicentre prospective randomised clinical trials are nearly impossible to perform in T-PLL. As a result, there are no randomised trials in T-PLL, and the best data consists of collaborative phase II single arm studies. T-PLL has shown limited, non-durable responses to traditional chemotherapy with a median Overall Survival (OS) of 7 months in historical series [2]. T-PLL cells express CD52 on their cell surface. Alemtuzumab is a recombinant, humanized IgG1 monoclonal antibody directed against the surface glycoprotein CD52. Three key publications have shown that the use of alemtuzumab significantly improves the Overall Response Rates (ORR) and Progression Free Survival (PFS) of patient cohorts with T-PLL in both the first line and relapsed setting. These are summarised in Table 1. The first such report by [34] treated 39 patients with intravenous (iv) alemtuzumab between 1993 and 2000 [34], Nearly all patients had received a previous treatment. The ORR was impressive (76%), with 60% achieving Complete Response (CR) and 16% partial response (PR). A small proportion of responding patients within this study were consolidated with autologous or allogeneic Stem Cell Transplantation (SCT). The median PFS was 7.5 months, but this was the first study to describe these response rates.

This was rapidly followed by a report of similar results in a retrospective analysis of relapsed T-PLL used as part of a compassionate use programme. Using the standard 30mg iv dose three times per week, Keating et al found an ORR of 51% (95% CI 40-63%), with a 39.5% CR rate (95% CI, 28-51%). OS in this group at relapse was still poor, with a median OS of 7.5 months from time of treatment. More recently, the prospective non-randomised UKCLL05 study has been published in which previously untreated T-PLL patients were treated with subcutaneous alemtuzumab. The response rates using subcutaneous alemtuzumab in this study were compared retrospectively to a cohort of 32 patients treated with iv alemtuzumab before and after the UKCLL05 study recruitment period. Demographics including age, sex and extranodal disease were similar in the two cohorts. The ORR using iv alemtuzumab was an outstanding 91% with an 81% CR rate. This compared with an ORR of 33% in the subcutaneous group on study (P=0.001). Further recruitment was terminated as the independent data monitoring committee deemed it unethical to continue [35]. The iv administration route is now considered as standard of care in T-PLL.

The most promising non-SCT data in term of PFS and disease control to date is the recently published prospective multicentre phase II trial investigating the use of Fludarabine, Mitoxantrone and Cyclophosphamide (FMC) induction for up to four cycles, followed by up to 12 weeks of alemtuzumab consolidation [36]. 9 pre-treated and 16 treatment-naïve patients with T-PLL were enrolled. 25 received FMC and 21 subsequent alemtuzumab consolidation. The ORR to FMC was 68%, which increased to 92% (12 CR, 11PR) on an intention-to-treat basis with the addition of alemtuzumab consolidation. FMC-A improved the median OS and PFS when compared to previous studies to 17.1 months (95% CI 12.1-22.1 months) and 11.9 months (95% CI 9.3-14.6 months) respectively. Interestingly, the group found that PFS was shorter (10.6 versus 24.8 months, p=0.05) in those with the TCL-1 oncogene mutation. Clearly this regimen is particularly immunosuppressive, and as with the other trial data presented, Cytomegalovirus (CMV) reactivation and cytopenias were clinically important adverse events. 13 of the 21 patients who received alemtuzumab consolidation reactivated CMV, of which 9 were symptomatic. It is imperative both to pre-emptively monitor (by Polymerase Chain Reaction (PCR)) and where elevated to treat CMV viral load to avoid clinical CMV disease.

Therapy	Patient details	ORR	CR	PR	Median PFS	Reference
IV Alemtuzumab	39 patients, relapsed TPLL	76%	60%	16%	7.5 months	Dearden et al., [34]
IV Alemtuzumab	76 patients, relapsed T-PLL, retrospective cohort: compassionate use programme	51%	39.5%	11.5%	7.5 months	Keating et al., [10]
Subcutaneous Alemtuzumab	UKCLL05 pilot study, 9 untreated patients	33%	33%	0%	67% at 12 months	Dearden et al., [34]
Fludarabine, mitoxantrone and cyclophosphamide (FMC) induction (up to 4 cycles, followed by up to 12 weeks IV alemtuzumab consolidation	9 relapsed and 16 treatment-naïve T-PLL patients	68% after FMC, 92% (ITT) post-consolidation	44%	48%	11.9 months	Hopfinger et al., [36]

Table 1: Key studies in T-PLL

Given the generally unsatisfactory overall PFS following alemtuzumab-based treatment, consolidation strategies have been investigated. Collaborative data from 28 patients was retrospectively reviewed in T-PLL patients who had undergone consolidation autologous SCT (n=15) or allogeneic SCT (n=13) across a number of countries [37]. Although subject to selection bias, this data suggested that consolidation with either type of SCT substantially improved the OS of patients with T-PLL (48 months verses 20 months in an historical cohort treated with alemtuzumab). OS was not statistically significantly different when comparing SCT strategies, although allogeneic SCT could potentially cure some patients with adequate performance status and minimal comorbidities.

The largest retrospective study of allogeneic SCT was subsequently constructed by pooling together the European Group for Blood and Marrow Transplantation (EBMT) database with the large Royal Marsden cohort [38]. The three year PFS and OS was 19 and 21%, respectively. Those who had not progressed at three years remained in remission up to 60 months from transplantation, suggesting the potential for long-term disease control. Although these results are relatively disappointing, more patients in this cohort entered conditioning without optimal disease control when compared with the

cohort of Krishnan et al. These series again highlight the importance of inducing a good remission prior to allogeneic SCT when aiming to achieve long-term disease control.

Further understanding of key genetic pathways will hopefully enable targeted, intelligent combination therapy in the future for patients with T-PLL. Although much progress has been made in the treatment of T-PLL with the introduction of iv alemtuzumab followed by SCT consolidation strategies, there is still much to do to improve the outlook for patients with this aggressive disease. It is hoped that further understanding of the key genetic pathways driving leukaemogenesis will allow both the introduction of new targeted therapies and more intelligent combinations of existing treatments with the net effect of increasing survival from current levels.

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