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B and T cell prolymphocytic leukaemia

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ABSTRACT

Prolymphocytic leukaemias B-PLL and T-PLL are rare disorders, typically with an aggressive clinical course and poor prognosis. Combining morphology, immunophenotyping, cytogenetic and molecular diagnostics reliably separates B-PLL and T-PLL from one another and other disorders. In T-PLL discovery of frequent mutations in the *JAK-STAT* pathway have increased understanding of disease pathogenesis. Alemtuzumab (anti-CD52) produces excellent response rates but long-term remissions are only achieved in a minority following consolidation with allogeneic stem cell transplant. Molecular abnormalities in B-PLL are less understood. Disruption of *TP53* is a key finding, conveying chemotherapy resistance requiring novel therapies such as B-cell receptor inhibitors (BCRi). Both conditions require improved pathobiological knowledge to identify new treatment targets and guide therapy with novel pathway inhibitors.

Introduction

Prolymphocytic leukaemias (PLL) are mature lymphoid malignancies of either B-cell (B-PLL) or T-cell (T-PLL) lineage. They are rare, accounting for approximately 3% of all mature lymphoid leukaemias, T-PLL being more common than B-PLL.

They present with aggressive disease including B symptoms, splenomegaly and lymphocytosis of $> 100 \times 10^9$/L. A minority present with asymptomatic indolent disease suitable for initial conservative management. Progression requiring treatment is inevitable in a median of 33 months [1,2].

Combining morphology, immunophenotyping and molecular techniques is required to reliably confirm the diagnosis. Despite improved understanding of disease pathobiology treatment outcomes are still poor with median overall survival (OS) in B-PLL 36 months and T-PLL 20 months [2–4].

In T-PLL *JAK-STAT* pathway abnormalities are key, leading to novel therapeutic target possibilities. Many genetic drivers of B-PLL are still unknown although the high incidence of *TP53* and *MYC* abnormalities is recognised. Recent development of BCRi provides optimism for therapeutic response but lacks prospective trial data.

T-PLL

T-PLL is a rare post-thymic lymphoid neoplasm. It is the most common mature T-cell leukaemia but only accounts for approximately 2% of all mature lymphocytic leukaemias in adults > 30 years [2,3].

The majority of T-PLL cases are sporadic rather than inherited. Certain inherited genetic conditions carry an increased risk of developing T-PLL, e.g. ataxic telangiectasia (AT), an autosomal recessive condition caused by defects in ataxic telangiectasia mutated gene (*ATM*). The relative risk increase appears to be low with 3/279 patients with AT developing T-PLL in one report. Nijmegen

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breakage syndrome is also reported as a risk factor for developing T-PLL [3,5–7].

Clinical presentation

T-PLL is typically aggressive with rapid onset of symptoms. Common features are splenomegaly (73–81%), B symptoms (66%), lymphadenopathy (46–64%) and lymphocytosis. Cytopenias are a frequent initial presentation, particularly anaemia (15–55%) and thrombocytopenia (36–68%). Serous effusions can occur (14–21%), typically being pleural or peritoneal. Skin involvement (25%) most commonly affects the limbs or trunk with either maculopapular rash, erythroderma or a nodular appearance. Rarely other extranodal sites, including lung, liver and CNS, are affected [1,3,8,9].

Indolent disease was seen in 32% of a 78 patient cohort. Aggressive and indolent presentations had similar immunophenotype and morphology with less CD45RO + CD45RA-in indolent disease. The indolent phase can last many years, with median duration of 33 months (range 6–103 months). Progression is inevitable and can occur rapidly and aggressively just like the majority of first time T-PLL presentations [1].

Diagnosis

Accurate diagnosis requires combined morphology, immunophenotyping and genetics.

Morphology

Three morphological types are recognised. All typically have cytoplasmic blebs or projections.

1 Typical (75%). Peripheral blood (PB) shows small to medium sized lymphocytes with a basophilic cytoplasm devoid of granules. The nucleus shows partially condensed chromatin and is round or oval but can be irregular shaped with a prominent nucleolus.
2 Small cell variant (20%). Has a much smaller cell size with condensed nuclear chromatin and the nucleolus maybe inconspicuous under a light microscope.
3 Sézary cell-like variant (5%). Have a very irregular or 'cerebriform' nuclear outline similar to that seen in Sézary syndrome [2,3].

Immunophenotype

T-PLL cells are mature T-cells expressing CD2, CD3, CD5 and strong CD7 whilst CD1a and TdT are negative. CD4 and CD8 expression show variable combinations, the majority being CD4+/CD8- (38–74%) or CD4+/CD8+ (17–41%) whilst CD4-/CD8+ (13–17%) and CD4-/CD8- (1–8%) are much less frequent. In mature (post-thymic) T-cell leukaemias the co-expression of CD4 and CD8 is generally only seen in T-PLL with very rare occurrences in other mature T-cell disorders [2].

Molecular genetics

Clonal rearrangement of T-cell receptor (TCR) genes (TRB and TRG) demonstrates clonality. Cytogenetic abnormalities are common and some are relatively unique to T-PLL.

The most common abnormalities are of chromosome 14 (90%). They are either inversion 14 (80%) or t(14:14) (10%) involving the *TCL1A* and *TCL1B* locus, or t(X; 14) (q28; q11) involving a homolog of *TCL1, MTCP1* (mature T-cell proliferation 1 gene), located on the X-chromosome. In those with a normal karyoptype *TCL1* rearrangement occurs in approximately 80% versus 94% in complex karyotype. Transgenic mouse models have demonstrated the oncogenic roles of *MTCP1* and *TCL1* which promotes cell survival/ proliferation by co-activating Akt-kinase [10–12].

The 2nd most common finding is abnormalities of chromosome 8 (70–80%), including isochrome 8q (iso8q) (61%), idic(8p11), t (8; 8) and trisomy 8q. Abnormalities in chromosome 6 (33%), chromosome 17 (26%), and del(12p13) (50%) are also seen. Del (12p13) pathogenesis occurs via haplo-insufficiency of *CDKN1B*, encoding a protein essential in cell cycle regulation [13].

The most frequent genetic abnormality is of TCR A/D locus (86%). Deletions and mutations occur in *ATM* (69% and 73% respectively) and *TP53* (31% and 14% respectively). Mutations are also seen in *BCOR* (8%), *JAK1* (6%) and *JAK3* (21%) [14].

High-throughput sequencing identifies driver mutations, broadly split into 2 groups:

1) Gain of function involving *IL2RG*, *JAK1/3*, and *STAT5B* leading to constitutive *STAT5* signalling.
2) Loss of function involving *EZH2*, *FBXW10* and *CHEK2*. Their role in T-PLL pathogenesis is via proteasome degradation, DNA repair and epigenetic transcriptional regulation.

How these abnormalities evolve is unclear but given their high frequency, mutations in *TCL1* and *ATM* are most likely the early events with subsequent secondary mutations in *JAK/STAT* [15,16].

Table 1 shows a summary of PLL characteristics [1-3,14,17-19].

Table 1
Summary of characteristic features of PLL.

	T-PLL		B-PLL	
Presenting clinical and laboratory features	**Typical Clinical features:** ● Splenomegaly (73–81%) ● B symptoms (66%) ● Lymphadenopathy (46–64%) ● Skin rash (25%) ● Serous effusions (14–21%) ● Rare involvement - extranodal sites, such as lung, liver and CNS	**Typical Laboratory findings:** ● Significant lymphocytosis, > 100×10^9/L. ● Anaemia (15–55%) ● Thrombocytopenia (36–68%)	**Typical Clinical features:** ● Splenomegaly ~(2/3rds) ● B symptoms (~2/3rds) ● Lymphadenopathy (> 50%) usually low volume, bulk is rare Asymptomatic indolent disease at presentation in 10–15%	**Typical Clinical features:** ● Significant lymphocytosis, > 100×10^9/L. (66%) ● Anaemia (50%) ● Thrombocytopenia (50%)
Morphological features and differential diagnosis	**Peripheral blood:** ● Medium sized lymphocytes ● Round or oval nucleus, chromatin partially condensed with a visible nucleolus ● Basophilic cytoplasm, no granulation ● Cytoplasmic projections/blebs ● Small cell variant (20%) ● Cerebriform/Sézary cell-like variant (5%)	**Differential diagnoses:** ● B-cell prolymphocytic leukaemia (B-PLL) ● Sezary syndrome (SS) ● T-LGL leukaemia (T-LGLL) ● Adult T-cell leukaemia/lymphoma (ATLL)	**Peripheral blood:** ● > 55% prolymphocytes (often > 90%) ● Medium sized lymphocytes 2x size of normal lymphocytes ● Round nucleus, moderately condensed chromatin, prominent central nucleolus ● Weakly basophilic cytoplasm without granules	**Differential diagnoses:** ● Mantle cell Lymphoma (MCL) – pleomorphic variant in leukaemic phase ● Hairy Cell Leukaemia variant (HCLv) ● Chronic lymphocytic leukaemia (CLL) ● Splenic marginal zone lymphoma (SMZL) ● T-cell prolymphocytic leukaemia (T-PLL) ● Follicular Lymphoma (FL) ● Lymphoplasmacytic lymphoma (LPL)
Immunophenotyping	**Positive markers:** ● CD2 + (94–100%) ● CD3 + (81–94%) ● CD5 + (100%) ● CD7 + (93–100%) ● CD52 (100%) Variable markers: ● CD25 + ve (18–35%) Negative markers: ● CD1a-, Tdt-	**CD4/CD8 combinations:** ● CD4+/CD8- (38–74%) ● CD4+/CD8+ (17–41%) ● CD4-/CD8+ (13–17) ● CD4-/CD8- (1–8%)	**Positive markers:** ● Strong SmIG (M and often D) ● CD19, CD 20, CD22, CD79a, FMC7 ● CD38 (50%) ● ZAP70 (50%) – no correlation to IGHV mutational status	**Variable markers:** ● CD5 +ve (20–30%) ● CD23 + ve (10–20%) ● CD200 weak or negative in most CLL score (< 0–1) IGHV usage ● Un-mutated (46–53%) ● IGHV3 (68%) – especially V3-23 (50% of VH3 cases) ● IGHV4 (32%) ● VH1 and VH2 – not used
Genetic features	**Cytogenetics:** ● Chromosome 14 (90%). Either Inversion 14 (80%), t(14; 14) (10%), t(X; 14) ● Chromosome 8 (70–80%) including idic (8), t(8; 8), trisomy 8q, Isochrome 8q (61%) ● Abnormalities of chromosome 6 (33%) ● Abnormalities of chromosome 17 (26%) ● Complex karyotype (69%)	**Molecular features:** ● TCL1 ● MTCP1 ● ATM (69%) ● JAK1 (8%) ● JAK3 (30–42%) ● STAT5B (21–36%)	**Cytogenetics:** ● Complex karyotype - common ● Del 13q (55%) ● Del 17p (> 50%) ● Del 11q (39%) ● Trisomy 12q (uncommon) **Absence of t(11;14)**	**Molecular features:** ● TP53 mutation or deletion (75%) ● C-MYC defects (50%)
Treatment and prognosis	**Treatment options:** ● IV Alemtuzumab - ORR > 80% in first line and 50–76% in relapsed ● IV pentostatin - ORR 45% ● IV Bendamustine - ORR 53%	**Prognosis:** ● Median OS 1–2 years ● Median OS with Alemtuzumab 20 months ● Median OS with Alemtuzumab and allo-HSCT 48 months	**Treatment options:** ● TP53 wildtype – FCR or BR ● TP53 disrupted – BCRi	**Prognosis:** ● Significantly affected by presence of TP53 abnormality ● Median survival 3 years (pre Rituximab and BCRi eras)

Table 2
Alemtuzumab treatment protocol and supportive care.

Initiation schedule	Alemtuzumab is given intravenously (IV) with dose escalation in the first 3 doses: ● Day 1 3 mg ● Day 3 10 mg ● Day 5 30 mg
Further dosing schedule	On successful completion of dose escalation patient continues on 30 mg 3x/week, usually given on Monday, Wednesday and Friday for ease of organisation.
Treatment duration	Provided ongoing tolerance treatment continues at 30 mg 3x/week to maximum response. Often this will be achieved by 2 months of treatment.
Infusion reactions such as fevers, rigor, headache, nausea/vomiting, rash, hypotension	Initially infusion reactions are common and are managed with ● Prophylactic paracetamol (1g PO) and chlorphenamine (4 mg PO) 30 min before commencing infusion ● Hydrocortisone 100 mg IV to be used in the event of an infusion reaction ● IV Chlorphenamine 10 mg to be used in the event of an infusion reaction ● Pethidine 12.5–25 mg IV if severe rigor occurs
Supportive medications	● Allopurinol 300 mg OD for first 4 weeks of treatment ● PCP prophylaxis – Co-trimoxazole or suitable alternative. ● Anti-viral prophylaxis – aciclovir or valaciclovir ● Anti-fungal prophylaxis – fluconazole, itraconazole or posaconazole depending on institutional preference.
Virology	● Pre-treatment testing for Hepatitis B and C ● Pre-treatment serology for CMV ● If serology for CMV +ve then weekly CMV PCR monitoring.

Prognosis

Median OS from various studies is approximately 20 months (17–33). Complex karyotype occurs in approximately 2/3rds of T-PLL carrying a poor prognosis compared to normal karyoptype. No solitary cytogenetic abnormality influences OS, however patients with > 5 aberrations had an inferior OS of 11 months versus 22 months if < 5 aberrations.

Other poor prognostic factors include short lymphocyte doubling time, pleural effusion, WCC > 208K/L, lactate dehydrogenase (LDH) > 1668IU/L, Beta2 microglobulin > 8 mg/L and Haemoglobin (Hb) < 93 g/L which also conveyed an inferior PFS. Presence of JAK3 mutations and high expression of TCL1 also carry an adverse prognosis [11,14,20,21].

Treatment

In indolent disease a 'watch and wait' approach is appropriate. Candidates for allogeneic haematopoietic stem cell transplant (allo-HSCT) should have donor workup undertaken early, particularly where there is potential for a matched sibling donor [1].

Chemotherapy

Treatment in T-PLL previously focussed on anthracycline, alkylator and purine analogue therapy and combinations of these. Combination chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) showed a poor response with ORR approximately 33% and median survival only 7 months. Pentostatin induced an ORR of 45% in 55 T-PLL patients, 5/55 (9%) of these CR [3,17].

Single agent bendamustine administered in 15 T-PLL patients (6 frontline, 9 previously treated) achieved an ORR of 53% (3 Cr, 5 PR) with median PFS 5 months and median OS 8.7 months. ORR in 6 frontline patients was higher (67%) but duration remained short (2–10 months). Encouragingly, of 3 alemtuzumab refractory patients, 2 responded (1 CR, 1 PR) [19].

Combination therapy with fludarabine, mitoxantrone and cyclophosphamide (FMC) produced an ORR of 68%, increasing to 95% after the addition of IV alemtuzumab consolidation. A further trial from the German study group explored use of FMC given concurrently with subcutaneous (SC) alemtuzumab followed by alemtuzumab maintenance (FMCA + A). This did not improve on results from their earlier study of FMC followed by alemtuzumab or compared to single agent intravenous (IV) alemtuzumab [22,23].

Given the modest responses seen with chemotherapy approaches, this is not recommended as first-line treatment outside a clinical trial.

Alemtuzumab

In patients requiring treatment, alemtuzumab is currently first-line treatment of choice. Alemtuzumab is a recombinant DNA derived, fully humanized IgG1 kappa monoclonal antibody targeting CD52, which is strongly expressed in T-PLL and other mature lymphocytes, but importantly is absent on stem cells.

Table 2 Alemtuzumab treatment protocol.

There have been no randomised studies comparing alemtuzumab to single agent or combination chemotherapy. A number of studies have indicated superior ORR 51–76% (CR 40–60%) with alemtuzumab, when compared to any other therapy. Median PFS was 4.5–7 months and median OS 7.5–10 months but 14.8–16 months if achieving a CR. In the front-line setting ORR was significantly better at 91% (81% CR) with a PFS at 12 months of 67% [18,24–26].

Alemtuzumab should be administered IV based on three studies confirming the inferiority of SC administration compared to IV. They showed a significant survival difference with IV versus SC Alemtuzumab of 40.5 versus 13.7 months. SC group ORR was 31% versus 91% in the comparator IV group, with subsequent switching to IV alemtuzumab increasing ORR to 67% [22,26,27].

Alemtuzumab maintenance

Following induction treatment with alemtuzumab CD52 expression may be down-regulated or lost. A single study has investigated maintenance alemtuzumab, with 30 mg SC once monthly. This showed no benefit, however only 6 patients received maintenance, possibly due to increased toxicity from FMC-A induction. At present maintenance alemtuzumab is not recommended as it does not appear to improve outcome compared to standard single agent alemtuzumab [22].

Haematopoietic stem cell transplant (HSCT)

Autologous HSCT (auto-HSCT) and allo-HSCT have been used in T-PLL with variable success. Although auto-HSCT showed improved OS and PFS, relapse rates were higher than after allo-HSCT. Allo-HSCT is the best means of securing long-term remission and is recommended above auto-HSCT in patients with a suitable performance status (PS) and donor. Auto-HSCT may be reasonable for those where allo-HSCT is unfeasible [28].

Allo-HSCT is shown to improve OS and PFS allowing long-term survival for a minority of patients. However, post allo-HSCT relapse (33–47%) and transplant related mortality (TRM) (30–40%), remain high. Although most studies have found a survival benefit for allo-HSCT, others have not [21,28–32].

Somewhat reassuringly molecular evidence of graft versus leukaemia (GvL) activity in T-PLL is demonstrated via reduction in

Table 3
Summary of Allo-HSCT studies.

Study	N	Prior treatment	Median age and range (years)	M:F ratio	CR rate pre HSCT (%)	CR rate post HSCT (%)	Median OS	Median DFS	Median PFS	TRM rate (%)	Relapse rate (%)
Krishnan et al. 2010 Allogeneic [28]	13	Alemtuzumab in all	51 (39-61)	10:3	69%	92%	33 months	24 months		31	33
Krishnan et al. 2010 Autologous [28]	15	Alemtuzumab in all	58 (43-68)	8:7	87%	100%	52 months	28 months		7	60
Wiktor-Jedrzejczak et al. 2012 [29]	41	Various	51 (24 -71)	28:13	27%		21% at 3 years	19% at 3 years	10 months	41% at 3 years	41% at 3 years
Kalaycio et al. 2010 [31]	21	Various	54 (30–75) a				11.2 a		5.1	28% at 1 year [a]	39% at 1 year [a]
Guilaume et al. 2015 [30]	27	Various	53 (36–65)	17:10	52%	78%	36% at 3 years		26% at 3 years	31% at 3 years	47%
Bhagirathbhai et al. 2018 [32]	11	Various	56 (43–71)	7:4	91%	91%	56 months		15 months	34% at 4 years	21% at 4 years
Wiktor-Jedrzejczak et al. 2019 [34] [b]	37	95% Alemtuzumab	56 (47-59)	27:10	62%		Median OS 27.8 months 4 year OS 42%		Median PFS 19.2 months (11.6–46.7) 4 year PFS 30%	25% at 2 years and 32% at 4 years	38% at 4 years.

[a] Figures are for entire cohort of 47 B and T-PLL patients. 21/47 had a diagnosis of T-PLL.
[b] Study excluded patients age > 65, those with progressive disease and those allografted with a mismatched unrelated donor or cord blood.

minimal residual disease (MRD) following post allo-HSCT immunomodulation, although often transient. Either immunosuppression tapering or donor lymphocyte infusion (DLI) reduced MRD in 7/10 patients, but only 2 patients had durable MRD clearance [33].

The only prospective study of allo-HSCT in T-PLL showed that long-term disease control is achievable for some patients. Good prognostic factors of time from diagnosis to allo-HSCT of < 12 months and using a conditioning regimen containing total body irradiation (TBI) dosed with ≥6 Gray were identified. Of note this study excluded patients age > 65 or those undergoing a mismatched unrelated donor or cord blood allo-HSCT [34].

A table summarising allo-HSCT study findings is shown below.

Table 3 [28–32,34].

Relapsed/refractory disease

Relapsed/refractory disease options are usually limited and clinical trials or novel therapies should be considered if available. In alemtuzumab relapsed/refractory disease, expression of CD52 should be re-assessed as loss of CD52 can explain resistance. Following initial response and subsequent relapse, approximately 50% respond to further alemtuzumab therapy, although response duration is typically shorter. A phase II study using alemtuzumab with pentostatin in 13 T-PLL patients produced an ORR of 69%, median OS 10.2 months and PFS of 7.8 months. This confirms the rationale for adding pentostatin to alemtuzumab in both relapsed and refractory settings. Bendamustine is another option in relapsed/refractory disease [19,35].

Novel therapies

Preliminary data from cell signal pathway inhibitors show encouraging results suggesting these drug classes may be effective in T-PLL.

Ex-vivo drug sensitivity and resistance testing correlated with somatic mutations and gene expression profiling (GEP) identified potential drugs of interest to take forward into clinical trials. These included histone deacetylase inhibitors, phosphoinositide-3 kinase (PI3K) inhibitors, BCL inhibitors and p53 activators. Disappointingly, JAK-STAT inhibition response did not correlate with presence of JAK-STAT pathway mutations or other known T-PLL genetic lesions [36].

Next generation functional testing on 106 FDA–approved drugs in current clinical development found the highest T-PLL specific response was with venetoclax, a BCL-2 inhibitor. Responses correlated with expression of BCL-2 but not BCL-2 family members MCL-1 and BCL-XL.

Two relapsed/refractory patients were treated with single agent venetoclax, both patients achieving a PR. One patient responded rapidly with laboratory features of tumour lysis syndrome (TLS) however venetoclax was stopped during dose ramp up due to infection to which the patient succumbed. The 2nd patient completed dose ramp up to a maximum dose of 1.2g with no TLS and response duration of 131 days. Postulated mechanisms of resistance are via BCL-2 and BCL-XL induction. These responses showed promising efficacy of single agent venetoclax and the potential for combination therapy. Additional in patient and ex-vivo study highlighted ibrutinib as an effective combination partner for venetoclax [37].

Hasanali *et al.* showed that combining epigenetic therapy and immunotherapy could be a useful treatment in T-PLL and overcome resistance to alemtuzumab. They postulated that epigenetic agents could induce expression of silenced tumour suppressor genes or targetable markers, such as CD30, providing a target e.g. for brentuximab [38].

ATM mutant malignancies including T-PLL have impaired DNA double strand break repair. In-vitro/in-vivo testing showed potential for olaparib, a poly ADP-ribose polymerase (PARP) inhibitor, to sensitise *ATM* null tumour cells to DNA-damaging agents [39].

Chimeric antigen receptor natural killer (CAR-NK) cells targeting T-cell specific antigens, e.g. CD7 are in development with little in-vivo testing. Their potential issue is rendering the recipient immunocompromised lifelong via eradication of normal T-cells. This can be avoided by exploiting T-cell receptor β-chain constant (TRBC) locus clonality. Normal T-cells have a mixture of TRBC1 and TRBC2. In malignancy only one type is expressed. A CAR-NK specific to the malignant cell TRBC targets the malignant cells, sparing the normal T-cells and preserving immune function [40].

Whilst these studies provide evidence for further study and optimism for efficacy, prospective trials are needed to assess the utility of these drugs, particularly in novel combinations.

Practice points

- T-PLL typically presents with an aggressive clinical course characterised by B symptoms, splenomegaly and a lymphocytosis often $> 100 \times 10^9$/L
- 1/3rd of T-PLL cases present indolently and may be suitable for initial observation.
- The most frequent genetic abnormalities involve chromosome 14 and affect *TCL1* and *MTCP1*.
- *JAK-STAT* pathway mutations have been implicated in T-PLL pathogenesis.
- 1st line treatment should ideally be on a clinical trial. If this is not possible then 1st line treatment should be with IV alemtuzumab.
- If the patient has a suitable PS and donor for an allo-HSCT this should strongly be considered in 1st remission.
- Consider adding pentostatin treatment to alemtuzumab in patients with suboptimal response to alemtuzumab.

Research agenda

- Strategies to improve NRM and relapse post allo-HSCT.
- Randomised control trials exploring novel therapeutic options such as venetoclax, ibrutinib and ruxolitinib.
- Increased knowledge of underlying disease pathobiology through additional functional and molecular studies.

B-PLL

B-PLL is the rarer prolymphocytic leukaemia accounting for < 1% of lymphocytic leukaemias. Median age at presentation is 65–69, most patients being > 60. Incidence is highest in Caucasians, M:F ratio is equal [2].

First described in 1974 by Galton *et al*. as an aggressive variant of chronic lymphocytic leukaemia (CLL), B-PLL was only classed as a unique entity in the 2008 WHO classification [2,41].

Presenting features

B-PLL is a mature B-cell leukaemia with a wide range of clinical severity at diagnosis. A small proportion of patients have initially indolent asymptomatic disease. The classical presentation of B-PLL is more aggressive, 2/3rds of patients presenting with a brief history of B symptoms, splenomegaly and a lymphocytosis of $> 100 \times 10^9$/L. Peripheral lymphadenopathy occurs in > 50% of patients but is usually low volume with infrequent bulky disease. CNS involvement is uncommon, especially at first presentation, with only isolated case reports [42,43].

Diagnosis

The rarity of B-PLL and overlapping features with other lymphoproliferative disorders (LPDs) mean diagnosis can initially be challenging. Involvement of an expert haematologist and haemato-pathologist is recommended. The main differential diagnoses morphologically are T-PLL, CLL, Hairy cell leukaemia variant (HCLv), Mantle Cell Lymphoma (MCL), Lymphoplasmacytic lymphoma (LPL), Follicular lymphoma (FL) and splenic marginal zone lymphoma (SMZL). A combined approach is required for confirming the diagnosis including PB and bone marrow (BM) morphology, immunophenotyping, cytogenetics and molecular results [2].

Current diagnostic criteria require ≥55% of lymphocytes in the PB to be prolymphocytes, although these often account for > 90%. Morphologically the cells are larger than normal lymphocytes and CLL cells. The nucleus is typically round, occasionally being indented. Nuclear chromatin is moderately condensed with a prominent usually central nucleolus. Cytoplasm is weak to moderately basophilic and lacks granules or projections [41,43].

Immunophenotyping

B-PLL expresses mature B-cell markers including CD11c, CD19, CD20, CD22, CD24, CD79a, CD79b, and FMC7 whilst CD200 is variable. Surface membrane Immunoglobulin (SmIg) M and often SmIgD are brightly expressed, likewise bright surface immunoglobulin kappa or lambda restriction demonstrates clonality. CD5 and CD23 are variably positive occurring in approximately 1/3rd. These cases require additional analysis for t(11; 14) and cyclin D1 expression to differentiate them from MCL, although it has been postulated that MCL in leukaemic phase and B-PLL are a single entity [44].

ZAP-70 (57%) and CD38 (46%) are variably expressed but unlike CLL have no prognostic significance in B-PLL. Markers used to differentiate classical Hairy Cell Leukemia (HCLc), CD25, CD103, CD123, are typically negative in B-PLL [2,45,46].

The immunophenotypic profile of B-PLL has similarities to other B-cell LPDs, particularly MCL, SMZL and HCLv. Importantly immunophenotyping can reliably differentiate B-PLL from CLL, particularly due to expression of CD20 and surface immunoglobulin, both being bright in B-PLL but dim in CLL.

Genetic characteristics

B-cell clonality is demonstrable by showing immunoglobulin heavy chain variable (*IGHV*) gene rearrangement. Un-mutated *IGHV* occurs in 46–53% but like other CLL prognostic markers doesn't appear prognostically significant in B-PLL [45].

The most frequent molecular defects are *TP53* (75%) and *MYC* (50%). *MYC* defects are not associated with a more aggressive clinical course, with corresponding Ki67 often low [47–49].

GEP demonstrates a difference between B-PLL, CLL and SMZL, but considerable yet inconsistent overlap with MCL, especially MCL in leukemic phase. It is suggested that B-PLL is a sub-set of MCL, regardless of t(11; 14) status or expression of cyclin D1 or SOX11 [44].

Additional studies delineating the exact molecular pathogenesis of B-PLL would allow reliable separation from disorders presenting similarly with overlapping morphological, immunophenotypic and genetic features.

Prognosis

Prognosis is primarily affected by presence or absence of *TP53* disruption which conveys resistance to chemotherapy. Other prognostic factors are presence at diagnosis of anaemia < 110 g/L and lymphocytosis > 100 × 10^9/L. Features at diagnosis including B symptoms, thrombocytopenia, spleen size and age > 70 years are not prognostic. A median OS of 3 years was previously reported however this was prior to the advent of both rituximab and BCRi so is likely to have improved [50].

Treatment of B-PLL

Low incidence and often featuring in major trial exclusion criteria mean large data sets and prospective trial data are lacking in B-PLL. Paucity of evidence guiding treatment means there are no licensed treatments and many treatment recommendations are based on data in other B-cell LPDs e.g. CLL.

In the minority (10–15%) presenting with asymptomatic, indolent disease, a period of 'watch and wait' without treatment is appropriate. There is no evidence to support early intervention in this setting and the indolent phase can persist for several years [50].

First-line therapy for B-PLL

Various therapies have been used over time. In the pre-rituximab era purine analogues cladribine and pentostatin were used as single agent therapy with approximately 50% ORR and short duration of response (DOR). CHOP induced a PR in approximately 1/3rd of patients [50–52].

Addition of anthracyclines e.g. mitoxantrone and epirubicin to commonly used agents such as fludarabine, bendamustine and rituximab showed improved response rates though study numbers are small. It is unclear if anthracyclines are producing enough benefit to warrant their increased toxicity. Extrapolating trial data in CLL where adding anthracyclines shows no significant benefit, the current recommendation for chemo-immunotherapy is to consider fludarabine, cyclophosphamide and rituximab (FCR) or bendamustine and rituximab (BR) [53,54].

The aggressive clinical course and poor prognosis mean the treatment objective is achieving sufficient remission to allow allo-HSCT, where suitable PS and donor allow. This may change with the advent of novel more effective cell signal inhibitor therapies analogous to CLL.

First-line treatment should be based on the *TP53* mutation status. Those patients with *TP53* wild type (WT) should be considered for chemo-immunotherapy such as FCR or BR. In patients harbouring a *TP53* mutation resistance to chemotherapy can be anticipated. Prior to the advent of BCRi alemtuzumab has been used in these patients. Data on the utility of BCRi is mostly extrapolated from CLL data showing the efficacy of kinase inhibitors in *TP53* mutated CLL [55–57].

Compassionate use of idelalisib/rituximab was reported in 8 patients. *TP53* mutations were seen in 7/8 and 3/8 were treatment naive. All patients had rapid symptomatic improvement and 7/8 achieved CR with the other patient achieving PR and dying from an unrelated malignancy. Only 1 progression has been seen and this patient subsequently responded well to ibrutinib. Toxicity with idelalisib/rituximab was high, one patient dying of pneumonitis and 2 patients stopping treatment due to colitis, with only 5/8 patients completing 6 cycles. Remissions were durable, even for patients stopping treatment due to toxicity, with 5 patients remaining in CR at a median follow up of 21 months (2 still on Idelalisib, 2 stopped due to toxicity and 1 proceeded to allo-HSCT) [58].

Ibrutinib has not been studied in B-PLL and efficacy data is extrapolated from CLL. Gordon *et al.* reported 2 cases of B-PLL treated with ibrutinib both achieving a CR of > 12 months [59].

Data on consolidation with allo-HSCT is minimal and conflicting. Kalaycio *et al.* showed a very poor median PFS of only 3.5 months post allo-HSCT in 11 patients with B-PLL. Conversely there have been case reports of patients achieving very durable responses of > 60 months post allo-HSCT. The poor prognosis of B-PLL should prompt consideration of allo-HSCT in patients with a suitable donor and performance status. In particular patients who are young, have *TP53* disruption, respond poorly to initial therapy, fail to respond to BCRi or those with relapsed disease responsive to salvage therapy [31,60,61].

Relapsed/refractory treatment

Relapsed/refractory disease should ideally be treated on a suitable clinical trial if available. Retreatment with the previous line of therapy is also reasonable if sufficient depth and duration of response were achieved. If the relapse is linked to a known or newly acquired *TP53* mutation then chemotherapy-based options should be avoided. Idelalisib, ibrutinib, alemtuzumab, or venetoclax a BCL-2 inhibitor showing very significant activity in *TP53* disrupted CLL, would be suitable options in this setting. Consolidation with allo-HSCT should be strongly considered if responsive to salvage therapy [62].

Practice points

- B-PLL typically presents aggressively with B symptoms, splenomegaly and high WCC > 100 × 10^9/L with nodal involvement often present but clinically insignificant.
- Multiparametric diagnostics including morphology, immunophenotyping, immunohistochemistry, cytogenetics and molecular analysis should be used to secure the diagnosis due to the overlap of B-PLL with other conditions.
- 1st line therapy should be based on *TP53* status
  - o *TP53* WT should receive chemo-immunotherapy
  - o *TP53* disrupted should receive a BCR inhibitor e.g. idelalisib or ibrutinib, venetoclax or alemtuzumab.

- Relapsed/refractory treatment should ideally be on a clinical trial if possible.
- Consolidation with allo-HSCT should be considered

Research agenda

- Further understanding of B-PLL pathobiology from NGS studies, in particular identifying mutations of prognostic significance that could be therapeutic targets.
- Inclusion of B-PLL patients in randomised clinical trials using combinations of B-cell survival pathway inhibitors, either in the form of basket trials or ideally a specific B-PLL trial.

Summary

PLL encompasses two morphologically, immunophenotypically and genetically distinct subgroups, T-PLL and B-PLL. Both are rare, mature lymphoid leukaemias, classically with aggressive clinical presentation characterised by lymphocytosis, B symptoms, splenomegaly, non-bulky lymphadenopathy and cytopenias. Either can present indolently, not initially requiring treatment. Despite increased knowledge of underlying PLL molecular pathogenesis and novel cell signalling inhibitors the prognosis is still poor. First-line treatment in T-PLL should be IV alemtuzumab, with the addition of pentostatin in poor responders. In B-PLL 1st line treatment is dependent on *TP53* status. Those patients who are *TP53* WT receive chemo-immunotherapy and those with disrupted *TP53* receive either BCRi or alemtuzumab. In both conditions consolidation with allo-HSCT should be considered in 1st CR. Increased understanding of PLL molecular pathogenesis may identify novel targets and increase therapeutic options. At the present time trials are required to answer questions about the efficacy of drugs targeting cell signalling pathways in PLL.

Permissions

None.

Conflicts of interest

None.

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