







POSITION PAPER

Chronic lymphocytic leukaemia Australasian consensus practice statement

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Abstract

Chronic lymphocytic leukaemia (CLL) is the most common haematological malignancy in Australia and New Zealand (ANZ). Considerable changes to diagnostic and management algorithms have occurred within the last decade. The availability of next-generation sequencing and measurable residual disease assessment by flow cytometry allow for advanced prognostication and response assessments. Novel therapies, including inhibitors of Bruton's tyrosine kinase (BTKi) and B-cell lymphoma 2 (BCL2) inhibitors, have transformed the treatment landscape for both treatment-naïve and relapsed/

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refractory disease, particularly for patients with high-risk genetic aberrations. Recommendations regarding appropriate supportive management continue to evolve, and special considerations are required for patients with CLL with respect to the global SARS-CoV-2 pandemic. The unique funding and treatment environments in Australasia highlight the need for specific local guidance with respect to the investigation and management of CLL. This consensus practice statement was developed by a broadly representative group of ANZ experts in CLL with endorsement by peak haematology bodies, with a view to providing this standardised guidance.

Introduction

The management and diagnostic paradigms for chronic lymphocytic leukaemia (CLL) have undergone dramatic change over the last decade. This consensus practice statement has been developed by a broadly representative group of Australian and New Zealand (ANZ) experts in CLL with endorsement by peak haematology bodies, with a view to providing standardised guidance to ANZ haematologists and oncologists for the investigation and management of CLL.

Methodology

This consensus practice statement was undertaken by a panel of CLL experts in collaboration with

1. The CLL Working Group of the Australasian Leukaemia and Lymphoma Group
2. Chronic Lymphocytic Leukaemia Australian Research Consortium
3. The Haematology Society of Australia and New Zealand
4. The Australasian Lymphoma Alliance (ALA) and the ALA policy for Consensus Practice Statement development

The authors performed a systematic review of all available literature pertaining to CLL as of April 2023. Relevant literature was selected by the authors following a survey of current literature and international guidelines. The statement was drafted by the authors through an iterative consensus approach¹ during three meetings and subsequent inclusive communication both to the opinions provided and the evidence available. Consensus was reached for all recommendations made with agreed wording per this document. A summary of recommendations is shown after each section with levels of evidence referenced per National Health and Medical Research Council criteria.² This practice statement does not necessarily represent the treatment policies of the individual institutions where the authors are employed.

Diagnosis and presentation

Presentation and indications for treatment

CLL is the most common haematological malignancy in ANZ. In Australia, the age-standardised incidence rate is 7.1/100 000 (9.3 for males and 5.1 for females). The median age of diagnosis is 70.9 years, with a risk of diagnosis before age 75 of 0.54% and before age 85 of 0.97%.³ CLL is a low-grade lymphoproliferative disorder with a peripheral blood lymphocytosis, often identified as an incidental finding on routine blood tests. Most patients are asymptomatic at presentation, and the disease commonly takes an indolent course. A 'watch and wait' strategy is often employed for many years before treatment is required, as there is no survival benefit for early treatment with chemotherapy, chemoimmunotherapy (CIT) or targeted agents.^{4–7} The indications for commencement of treatment in the targeted therapy era remain unchanged as per iwCLL⁸ criteria.

A significant proportion of patients will never require CLL treatment. The absolute lymphocyte count should not be used as a sole indication for treatment and leukostasis is rare even with markedly elevated lymphocyte counts. Similarly, hypogammaglobulinaemia or recurrent infections are not considered indications to commence CLL-directed therapy, as these disease manifestations are not commonly ameliorated by current CLL-directed therapies. Bone marrow biopsy and CT scanning may be considered appropriate prior to commencement of treatment.

Immunophenotyping

The iwCLL,⁸ WHO⁹ and NCCN¹⁰ diagnostic criteria for CLL are based on the morphology and immunophenotype of the neoplastic B-cells. CLL cells in peripheral blood (PB) and/or bone marrow (BM) typically co-express CD5, CD19 and CD23 and are light chain restricted with weak/dim expression of surface immunoglobulin (SIg) and CD20. The minimum set of markers required for the diagnosis of CLL is CD19, CD5, CD20, CD23 and light chain clonality.¹¹

The WHO 2017⁹ and NCCN 2020¹⁰ guidelines for the diagnosis of CLL require $\geq 5 \times 10^9/L$ circulating monoclonal B-lymphocytes with a typical CLL immunophenotype in the PB.¹² The diagnosis of small lymphocytic lymphoma (SLL) is made if the circulating clone is $< 5 \times 10^9/L$ with nodal, splenic or other extramedullary involvement and is otherwise identical to CLL. Monoclonal B-Lymphocytosis (MBL) is a circulating B-cell clone $< 5.0 \times 10^9/L$ in the absence of associated lymphadenopathy, organomegaly or other features of B-cell lymphoproliferative disorder.¹³ Most MBLs have a CLL-like immunophenotype.

Genetic testing

Molecular analysis of CLL is generally not required until treatment is indicated. Recommended prognostic tests for CLL are summarised in Table 1. Immunoglobulin heavy chain variable gene (IGHV) mutational status and V-gene usage are important factors for prognosis and prediction of treatment outcome. IGHV mutational status retains its independent prognostic significance except when the patient is treated with Bruton's tyrosine kinase inhibition (BTKi).¹⁸

Fluorescence *in-situ* hybridisation (FISH) detects focal deletions of chromosomes 13q, 11q and 17p and trisomy 12, which are of prognostic significance.^{8,19,20} In the CIT era, del(17p) and del(11q) conferred an unfavourable prognosis^{8,21,22} and trisomy 12 an intermediate prognosis.²³ Deletion of 13q as a sole abnormality is associated with a favourable outcome, although deletions encompassing RB1 are often associated with a complex karyotype, altering the

prognostic significance.^{21,22} Cases may harbour more than one abnormality.

G-band karyotype analysis or single-nucleotide polymorphism or 'chromosomal' microarray provides genome-wide analysis and can detect multiple and complex chromosomal abnormalities. Hence, these may be considered more informative than FISH. The complexity and heterogeneity of chromosomal rearrangements may indicate genomic instability.²¹ The presence of mutations affecting *TP53* and/or del(17p) abnormality (collectively referred to as *TP53* aberrancy) remains among the strongest predictors of poor disease response and early relapse.²⁴ A complex karyotype, defined as ≥ 5 aberrations,²⁵ is a marker of adverse prognosis.²⁶

Frontline management

Treatment recommendations for CLL requiring therapy are depicted in Figure 1.

The definition of a 'fit' patient with respect to frontline treatment for CLL was initially derived in the era of CIT, most frequently defined as age < 65 – 70 years with a cumulative illness rating scale (CIRS)²⁷ < 6 and a creatinine clearance (CrCl) ≥ 70 mL/min, while 'unfit' patients are accepted to have advanced age, or CIRS ≥ 6 and/or CrCl < 70 mL/min. These definitions have been used in the design of the major studies comparing novel therapies to CIT.^{28–31}

The therapeutic landscape in ANZ is substantially influenced by the Pharmaceutical Benefits Scheme (PBS, Australia) or PHARMAC (NZ), which provides reimbursed

Table 1 Recommended prognostic tests in CLL

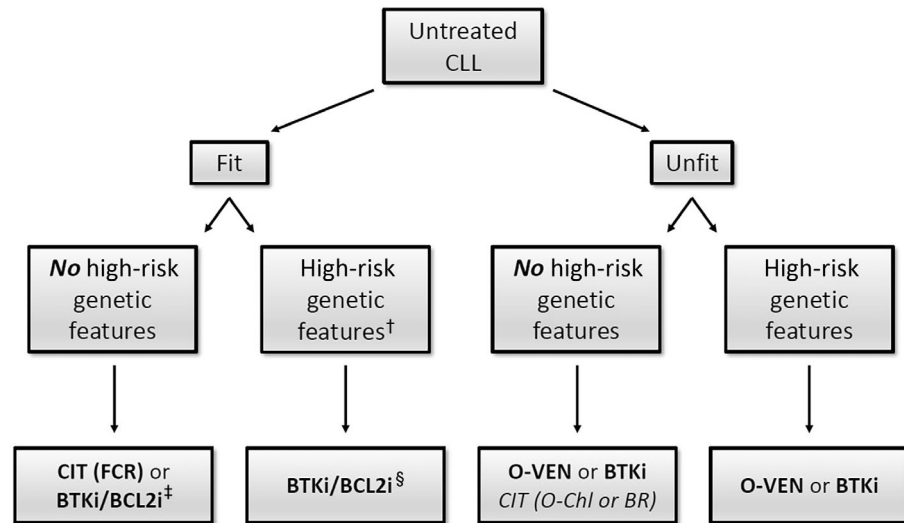
Laboratory test	Prior to firstline therapy	Disease response assessment	Prior to subsequent lines of therapy
FISH (17p; 13q; 11q; trisomy 12)	Yes – not required if CMA or standard karyotype performed	No	Yes
Chromosomal (SNP) Microarray (CMA)	Yes, may be used as an alternative to FISH	No	Yes, may be used as an alternative to FISH
Standard karyotype (chromosomal G-banding analysis)	Yes, (i) where CMA is not available, (ii) characterisation of CMA/FISH results	No	No
IGHV mutational status, V-gene use and BCR stereotype	Yes, if not done at diagnosis†‡	No	No
TP53 mutation	Yes	No	Yes, particularly if evidence of clonal evolution by other molecular testing
MRD analysis	N/A	Yes – usually flow cytometry	N/A
NGS lymphoid panel	Where considered appropriate, although not currently influencing treatment decisions		

†IgHV test not rebated by PBS.

‡IgHV may be performed on peripheral blood satisfying diagnostic criteria for CLL.

BCR, B-cell receptor; CLL, chronic lymphocytic leukaemia; CMA, chromosomal microarray; FISH, fluorescent *in-situ* hybridisation; IGHV, immunoglobulin heavy chain variable; MRD, minimal residual disease; NGS, next-generation sequencing; PBS, Pharmaceutical Benefits Scheme; *TP53*, tumour protein p53; tris 12, trisomy 12.

Figure 1 Frontline treatment of CLL requiring therapy. [†]High-risk genetic features defined by unmutated IGHV, complex karyotype (≥ 3), *TP53* dysfunction by del(17p) or *TP53* mutation. [‡]Clinical trial. [§]For IGHV unmutated disease, treatment with FCR is acceptable with acknowledgement of inferior PFS (~4 years) compared to IGHV-mutated (>50% cure rate). CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide and rituximab; IGHV, immunoglobulin heavy chain variable gene; PFS, progression-free survival.



treatment options. Reimbursed frontline novel therapies in ANZ are currently limited to venetoclax-obinutuzumab (VenO; *Australia only*; patients who are unfit or unsuitable for CIT) and venetoclax monotherapy (*NZ only*; patients with CLL with *TP53* dysfunction). CIT is therefore the only currently funded option for frontline treatment of fit patients in Australia and for patients with non-*TP53* aberrant CLL of any age in New Zealand.

Unfit patients

Chemoimmunotherapy

The CLL 11 trial³² randomised unfit patients to chlorambucil alone or combined with either rituximab or obinutuzumab and demonstrated chlorambucil-obinutuzumab was superior. For patients >65 years old, no significant difference in median progression-free survival (PFS) was demonstrated following bendamustine-rituximab (BR) compared with fludarabine, cyclophosphamide and rituximab (FCR) and BR was associated with better tolerability of therapy.³³

BTK inhibitors

Superior PFS and overall survival (OS) were observed with continuous ibrutinib over fixed-duration chlorambucil in unfit patients with CLL without del(17p) in RESONATE 2.³⁴ The ILLUMINATE³⁵ and ELEVATE TN²⁸ studies demonstrated improved PFS with both ibrutinib-obinutuzumab and acalabrutinib (\pm obinutuzumab) over chlorambucil-obinutuzumab respectively. The ALLIANCE trial²⁹ (patients ≥ 65 years) demonstrated superior PFS with both ibrutinib monotherapy or ibrutinib-rituximab (PFS identical for I vs I + R) over BR (2-year estimated PFS – 87%, 88% vs

74%, $P < 0.001$) sustained in long-term follow-up.³⁶ Similarly, in SEQUOIA,³⁷ zanubrutinib was compared to six cycles of BR in CLL without del(17p), resulting in an estimated 2-year PFS of 85% versus 69% ($P < 0.0001$). Subgroup analysis of several studies (ALLIANCE,²⁹ ILLUMINATE,³⁵ ELEVATE TN²⁸ and SEQUOIA³⁸) note the more pronounced PFS advantage of the BTKi arms in patients with adverse CLL biology. A drawback of BTKi therapy is the continuous use schedule until progression or intolerance. Adverse events with BTKi include hypertension and cardiac events (arrhythmias, cardiac failure and sudden death), although these risks are variably lower with second-generation agents. Optimisation of hypertension and cardiac risk factors is important.

The role of BTKi combination therapies has been partially addressed. Adding rituximab to single-agent ibrutinib offers no benefit^{29,39}; however, the merits of combining obinutuzumab with other BTKi remain less clear.^{28,35} The phase 3 trial GLOW⁴⁰ randomised elderly patients with no del(17p) or *TP53* mutation to chlorambucil-obinutuzumab or 12 cycles of venetoclax-ibrutinib preceded by a 3 months lead in with single-agent ibrutinib. Venetoclax-ibrutinib was associated with improved PFS (30 months PFS 80.5% vs 35.8%; $P < 0.0001$); however, increased grade 3/4 adverse events (75.5%; predominantly haematologic) and four sudden cardiac deaths occurred in this arm of the study.

Venetoclax-obinutuzumab

VenO is a generally well-tolerated, time-limited and highly effective regimen in the frontline setting treating elderly unfit patients, as shown in the CLL14 study.^{41–43} This study demonstrated that compared to chlorambucil-

obinutuzumab, VenO has higher PFS at 4 years (74% vs 35%) and frequently achieved uMRD remissions (76% in PB 3 months after completion of therapy).⁴⁴

Recommendations. For older/unfit patients BTKi or VenO is superior to CIT, particularly for CLL with high-risk genetic features such as del(17p), unmutated IGHV or complex karyotype (level II). Optimal control of hypertension and cardiac risk factors when using a BTKi and of TLS risk factors when using BCL2i is recommended (level II). If reimbursed access to BCL2i or BTKi is not possible, treatment with chlorambucil-obinutuzumab is reasonable in the absence of high-risk genetic features. Those who have high-risk genetics should be enrolled in a clinical study whenever possible (level II).

Fit patients

Chemoimmunotherapy

The CLL8 trial confirmed that FCR is a highly effective treatment for fit patients with CLL,⁴⁵ resulting in high overall response rates (ORR), prolonged PFS, OS and high rates of undetectable minimal residual disease (uMRD) compared to FC without rituximab. Long-term disease control was observed in the majority of IGHV-mutated CLL (PFS at 12.8 years 53.9%; plateaued after 10 years),^{46,47} while CLL with unmutated IGHV had an inferior PFS (4.2 years; 12 years PFS 8.9%) with a continuous pattern of relapse. CLL with del(17p) or mutated *TP53* had exceptionally poor outcomes with PFS of ~1 year.⁴⁶ Adverse events with CIT include cytopenias, infection and secondary haematological neoplasia (2–3%) with FCR.⁴⁶ The CLL10 trial compared BR versus FCR in fit patients with CLL without *TP53* disruption.³³ FCR was associated with a superior PFS in patients less than 65 years of age, but in unplanned *post hoc* analysis, no difference was observed in patients older than 65 years or females.⁴⁸

BTK inhibitors

The NCI-sponsored E1912 trial randomised 529 patients ≤70 years of age (median 57 years) with no del(17p) or *TP53* mutation in a 2:1 ratio to ibrutinib-rituximab (IR) for six cycles, then ibrutinib continuously until disease progression or intolerance, or six cycles of FCR.³⁰ After a median follow-up of 6 years, IR was superior to FCR for PFS (78% vs 51%; $P < 0.0001$) and OS (95% vs 89%; $P = 0.018$). The PFS for IR was superior to FCR in both IGHV-unmutated CLL (75% vs 33%; $P < 0.0001$) and IGHV-mutated CLL (83% vs 68%; $P = 0.001$). The NCRI FLAIR trial phase I, in a 1:1 randomisation of

771 patients ≤75 years of age (median 62), compared six cycles of FCR with IR with ibrutinib given for up to 6 years. At a median follow-up of 53 months, IR had a superior PFS compared to FCR (median PFS not reached for IR vs 67 months for FCR; $P < 0.001$) but identical OS.⁴⁹ In contrast to E1912, PFS was significantly superior with IR for IGHV-unmutated CLL but not significantly different for IGHV-mutated CLL.⁵¹

BCL2-inhibitor (BCL2i, e.g. venetoclax)

The GAIA/CLL13 trial randomised treatment-naïve fit patients with CLL without *TP53* aberrations to CIT or one of three venetoclax-based combinations. Patients were randomised to six cycles of CIT (FCR ≤ 65 years; BR > 65 years), venetoclax and rituximab (RV), venetoclax and obinutuzumab (GV), or venetoclax, obinutuzumab and ibrutinib (GIV), where ibrutinib could be continued for 36 months in those who did not achieve uMRD.^{50,52} At a median follow-up of 38 months, the median PFS was not reached for GIV and GV compared with 52 months for CIT. GIV significantly reduced the relative risk of disease progression by 68% and GV by 58% compared with CIT. The 3-year PFS rates were 90.5% (GIV), 87.7% (GV) and 75.5% (CIT). The median PFS of RV was inferior to GV/GIV combinations yet similar to CIT, suggesting the choice of CD20 antibody is important. Adverse events with BCL2i included tumour lysis syndrome (TLS) and cytopenia; TLS requires dose ramp-up and active prophylaxis according to regimen protocol and published guidelines.

Combination, fixed duration BTKi + BCL2i

The CAPTIVATE FD study examined untreated patients with CLL ≤70 years (median 60 years) with ibrutinib for 3 months, followed by combination of ibrutinib with venetoclax for 12 months. Patients received treatment in either fixed-duration or MRD-guided cohorts. For fixed-duration cohort patients, the ORR was 96%, CR was 55%, and the best uMRD rate in blood was 77% after a median follow-up of 27 months. Investigator-assessed 24-month PFS and OS rates were 95% and 98% respectively. Adverse events of grade 3 or more were most commonly neutropenia in 33% and hypertension in 6%, with one sudden death.⁵³ Longest follow-up is available for the confirmed MRD patients from the MRD cohort who received subsequent double-blind placebo or ibrutinib, for whom 4-year PFS rates were 88% and 95% respectively.⁵⁴

CLL with del(17p) or *TP53* mutation

Outcomes with CIT for this subgroup of patients are very poor.⁴⁵ Ibrutinib demonstrates similar PFS for patients with *TP53* aberrant CLL in pooled data from

non-randomised studies^{55,56} to that reported in large studies for CLL without *TP53* aberrancy.^{30,57} Ibrutinib, acalabrutinib and zanubrutinib demonstrate improved PFS compared with CIT in subgroup analyses of patients with *TP53* aberrant CLL from randomised studies in older, unfit patients.^{28,29,35,38} Studies of zanubrutinib in treatment-naïve patients have revealed similar outcomes to CLL without del(17p).⁵⁸ Venetoclax is active against *TP53* aberrant disease as continuous monotherapy or fixed-duration therapy in combination with obinutuzumab (VenO).^{59,60} While *TP53* aberrancy is associated with inferior PFS among patients receiving VenO in the CLL14, PFS following VenO remained superior compared to ChO for this patient subgroup.⁶¹

Recommendations. Novel agent therapy is increasingly preferred over CIT internationally wherever possible^{10,62} because of equivalent outcomes among non-high-risk genetic patients and improved safety (level II).

For patients with IGHV unmutated disease, BTKi or venetoclax combination therapies are superior to CIT^{30,31,51,52} (level II). For patients with *TP53* dysfunction, BTKi or venetoclax-based therapy should be used wherever possible. Targeted therapy agents (either BTKi or BCL2i-based regimens) should be considered the standard of care for patients with *TP53* dysfunction (level II).

Management of relapsed/refractory CLL

BTKIs and venetoclax consistently give significantly superior results in patients relapsing after prior CIT compared to retreatment with CIT.^{63–65}

Venetoclax-based regimens

The phase-III MURANO trial demonstrated significantly superior response rates, PB and BM uMRD, PFS and OS for patients with relapsed/refractory (R/R) CLL following 24 months of fixed-duration venetoclax plus six doses of rituximab (VenR) compared with six cycles of BR. The median PFS with VenR was 54 months, with an estimated 5-year OS rate of 82%. End-of-treatment (EOT) PB uMRD (62%) was associated with significantly prolonged PFS and OS, with 18-month post-treatment PFS of 90%, 64% and 8% among patients with undetectable, low-positive (10^{-4} to 10^{-2}) and high-positive ($>10^{-2}$) EOT MRD respectively.⁶⁶

BTKi therapy

The phase 1b/II PCYC-1102 study confirmed the safety and efficacy of ibrutinib 420 mg daily with ORR 89%, 7-year PFS 34% and 7-year OS 55%, the longest follow-up for any BTKi to date in the R/R setting.⁶⁷ The RESONATE study⁶⁸ confirmed the superiority of ibrutinib over ofatumumab in all genomic high-risk subgroups, with an improved median PFS (44.1 vs 8.1 months, hazard ratio (HR) 0.148, $P < 0.001$).

The ASCEND study randomised patients to idelalisib or BR (physician choice) or acalabrutinib, a second-generation covalent BTKi.⁶⁶ Acalabrutinib demonstrated a significant PFS benefit (median PFS not reached vs 16.8 months; 36-month PFS 63% vs 21%, $P < 0.001$) and maintained in high-risk del(17p) (median PFS not reached vs 13.8 months, 36-month PFS 66% vs 5%).⁶⁹ There was no difference in OS rates, likely confounded by the 23% crossover to acalabrutinib. Acalabrutinib has non-inferior PFS to ibrutinib and has been associated with a small but significant reduction in number of cardiovascular adverse events.⁷⁰

Zanubrutinib is another second-generation BTKi, currently only available for CLL in Australasia through clinical trials or compassionate access. The phase III ALPINE study randomised patients to zanubrutinib or ibrutinib. Zanubrutinib demonstrated higher ORR when PR with lymphocytosis was excluded (78.3% vs 62.5%, $P = 0.0006$).⁷¹ After median 29.6 months of follow-up, zanubrutinib was associated with superior PFS compared with ibrutinib (HR 0.65; 95% confidence interval (CI) 0.49–0.86, $P = 0.002$). Superiority was retained in patients with CLL harbouring del(17p) (HR 0.53; 95% CI 0.31–0.88) and other major patient subgroups.⁷²

Managing patients with BTKi resistance (commonly mediated by *BTK* C481 mutations) or intolerance remains an area of unmet need, resulting in up to 40% discontinuation rates on long-term follow-up.^{73–76} Pirtobrutinib (LOXO-305) is a non-covalent BTKi with a 300-fold higher selectivity for BTK.⁷⁷ The phase 1/2 BRUIN study⁷⁸ for BTKi pretreated CLL/SLL patients demonstrated ORR 68%, PR 54% with 74% of patients remaining on pirtobrutinib over a median follow-up of 9.4 months.

PI3k inhibitors

Selective inhibitors of the phosphatidylinositol 3-kinase (PI3K) are another treatment option and are PBS-funded in Australia. Idelalisib is inferior to BTKi and venetoclax in R/R CLL.^{66,79} PI3Ki are frequently associated with immune-mediated toxicities (e.g. colitis, pneumonitis and hepatitis) and opportunistic infections, therefore usually reserved for patients without other therapeutic options.^{80–83} In patients relapsing after BTKIs or

venetoclax-based regimens, the efficacy of PI3K inhibitors is generally poor.⁸⁴

Allogeneic stem cell transplant

The availability of BTKi and BCL2i therapies has diminished the role of allogeneic stem cell transplants. Allogeneic transplant should generally be considered in:

- Younger patients with high-risk prognostic features and a suitable donor, usually after failure of at least one targeted therapy.
- Patients with Richter transformation clonally related to CLL who are in remission after CIT.

Outcomes after transplant do not appear to be adversely impacted by the use of one versus two targeted therapies or prior CIT exposure.⁸⁵ The optimal timing of allo-HSCT needs to be individualised and consider various competing risks.

Recommendations

BCL2i and BTKi are preferred in all patients with R/R CLL after prior CIT. The choice between BCL2i and BTKi is largely based on patient-related factors, for example,

comorbidities and desire for finite therapy. The choice among BTKi is dependent on toxicity profile and availability. PI3Ki is usually employed after failure of BTKi and BCL2i (level 2).

Sequencing of therapies for R/R CLL

An algorithm for treatment sequencing is depicted in Figure 2.

Patients who have received only CIT are candidates for venetoclax or BTKi. Venetoclax may be preferred for patients with atrial fibrillation, bleeding disorders, uncontrolled hypertension or cardiovascular risk factors or for whom fixed-duration therapy is appealing; BTKi may be preferred in those with a high risk for tumour lysis syndrome.

Data available suggest that effective bidirectional salvageability is possible after prior treatment with either BTKi or BCL2i.^{84,86} Emerging data suggest that venetoclax retreatment can be effective for relapse after time-limited therapy; however, this is not currently funded outside of clinical trials.^{87–89} PI3K inhibitors are an option for R/R CLL, which has failed both BTKi and venetoclax.⁹⁰ Clinical trials are strongly recommended in this context.

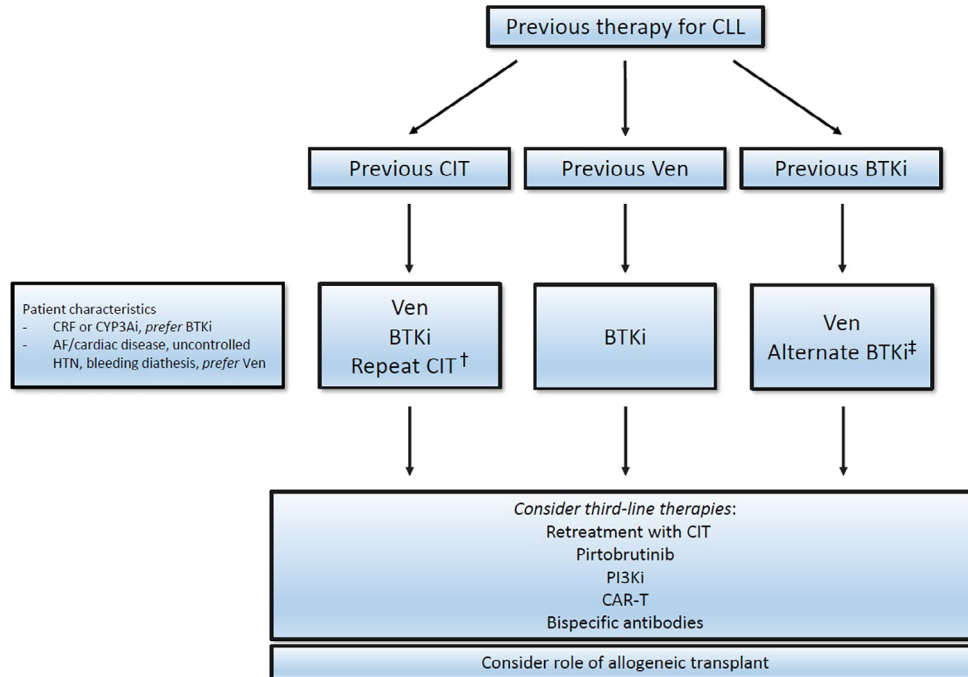


Figure 2 Sequencing of therapy in second and subsequent relapse of CLL. Note that frontline BTKi is not PBS funded at the time of publication. †Repeat CIT may be considered if relapse occurs after >3 years, if venetoclax and BTKi are contraindicated or not tolerated. ‡Alternative BTKi can be tried in event of intolerance, but are unlikely to be beneficial following covalent BTKi failure. BTKi, Bruton's tyrosine kinase inhibitor; CIT, chemo-immunotherapy; CLL, chronic lymphocytic leukaemia; PBS, Pharmaceutical Benefits Scheme.

Supportive care

Infection is the leading cause of death in people with CLL.⁹¹ Predisposition to infection in CLL is multifactorial, encompassing B-cell dysfunction (including hypogammaglobulinaemia), T-cell dysfunction, defects of complement function and impaired phagocytic function. CLL therapies add further to infection risk, exacerbating dysfunction of both adaptive and innate immunity.⁹²

Vaccination

Although humoral responses to vaccination are impaired in people with CLL, vaccination against certain pathogens is strongly recommended (see Table 2), ideally prior to CLL therapy. Most vaccines are safe, but live attenuated vaccines, such as Zostavax, the yellow fever vaccine, BCG and MMR, are contraindicated. Shingrix is safe and effective for shingles prevention in CLL but is not currently PBS-funded. If a patient has received anti-CD20 mAb therapy, some vaccines may be better deferred until 6–12 months after the last anti-CD20 mAb dose to optimise humoral responses. Deferral of SARS-CoV-2 vaccination is not recommended as patients usually develop T-cell responses to mRNA SARS-CoV-2 vaccines⁹³ and the risks of COVID-19 are high in CLL. Multiple SARS-CoV-2 vaccine doses improve rates of seroconversion, provide higher anti-spike antibody levels and improve SARS-CoV-2-specific T-cell responses.⁹⁴

Pretreatment testing

Hepatitis B serology (HBsAg and HBcAb) must be checked before commencing CLL or other immunosuppressive therapy because of the risk of life-threatening hepatitis B reactivation. Patients who are HBcAb positive but HBsAg negative may require prophylactic antiviral therapy and hepatitis B viral load monitoring throughout treatment until at least 24 months after B-cell suppression. Hepatitis

C status should be checked before immunosuppressive therapy and eradication may be recommended prior to treatment if therapy can be safely deferred.

Antimicrobial prophylaxis

Prophylactic antimicrobial treatments can be utilised in selected patients during CLL therapies. Possible regimens are summarised in Supporting Information, Table S1.

Immunoglobulin replacement

Acquired hypogammaglobulinaemia is common in CLL, with incidence rising following CLL therapy.⁹⁵ Immunoglobulin (Ig) replacement therapy (IgRT) reduces the incidence of bacterial infections, although its effect on mortality remains unproven.⁹⁶ IgRT is approved, widely used in Australia, and should be considered in patients with either IgG level < 4 g/L, or between 4 g/L and lower limit of reference range with a history of either one life-threatening bacterial infection within 12 months or two or more serious bacterial infections within 5 months requiring hospitalisation or intravenous antibiotics.⁹⁷ IgRT may be administered by either 4-weekly intravenous or weekly subcutaneous regimen.^{98,99} Acquired hypogammaglobulinaemia often persists long term, but a trial of IgRT cessation should be considered.⁹⁹

SARS-CoV-2

People with CLL are at increased risk of dismal outcome with severe COVID-19 and should be vaccinated against SARS-CoV-2, although the serological response to vaccination is substantially impaired.^{16,93,100} People with CLL who develop COVID-19 may be eligible for COVID-19-specific therapies. Primary prophylaxis against COVID-19 with long-acting monoclonal antibodies (e.g. tixagevimab/cilgavimab, Evusheld) has been useful but at the time of final submission has largely lost activity against current Omicron-strains.

Table 2 Recommended vaccines for people with CLL

Pathogen	Timing	Suggested vaccine schedule	Reference(s)
Streptococcus pneumoniae	At diagnosis	PCV13 (conjugate, Prevenar); 23PPV (polysaccharide, Pneumovax) 8 weeks later; 23PPV booster after 5 years	Svensson <i>et al.</i> ¹⁴ Schuh <i>et al.</i> ¹⁵
SARS-CoV-2	At diagnosis	mRNA vaccine: 3 primary doses followed by booster dose(s) [†]	McCaughan <i>et al.</i> ¹⁶
Influenza	At diagnosis	Annual vaccination	Schuh <i>et al.</i> ¹⁵
Varicella zoster	At diagnosis	VZV recombinant vaccine (Shingrix), two doses 8–16 weeks apart (Live attenuated vaccine such as Zostervax is contra-indicated).	Dagnew <i>et al.</i> ¹⁷

[†]These recommendations may change.
CLL, chronic lymphocytic leukaemia.

Early antiviral treatment is recommended if COVID-19 infection occurs. Potential for drug interactions between antiviral therapy and targeted agents for CLL should be considered – the ritonavir component of Paxlovid is a strong CYP3A4 inhibitor and may require short-term dose modification or interruption of venetoclax and BTK inhibitors while on antiviral therapy.

Secondary malignancy in CLL

The higher risk of secondary primary malignancy (SPM) associated with CLL has been recognised for many years.^{101–106} There is a significantly increased risk of SPM and skin cancer (SC) in CLL.¹⁰⁷ There are CLL-specific recommendations for routine skin cancer surveillance, given the high risk in this group.¹⁰⁸ Patients with CLL should follow standard guidelines for other cancer screening.

Response assessments

Response assessment in CLL follows iwCLL guidelines.⁸ Achieving uMRD is the strongest prognostic marker of response except with BTKi therapy.^{31,109,110} Whether patients who are MRD positive at the end of treatment benefit from treatment intensification, consolidation and maintenance strategies remains a research question. The European Research Initiative on CLL (ERIC) proposed a standardised approach to the detection of MRD by flow cytometry in CLL. The presence of MRD is reported as the percentage of CLL cells within the total leukocyte population. Conventionally, uMRD is defined by threshold of <0.01% or < 10⁻⁴ (i.e. <1 CLL cell per 10 000 leukocytes).^{111,112} MRD can also be measured by quantitative PCR or massively parallel sequencing,¹¹³ which has shown good concordance with flow cytometry results at the 0.010% (10⁻⁴) level.

Recommendations

- Response should be assessed by iwCLL criteria⁸ using full blood examination; clinical assessment of the lymph nodes, liver and spleen; including imaging by contrast-enhanced CT of the neck, chest, abdomen and pelvis where clinically indicated.
- Bone marrow examination is recommended for response assessment in cases where there are unexplained persistent cytopenias, where documentation of CR is desirable, or where MRD is negative in the peripheral blood, and increased sensitivity is desired.
- MRD testing may be performed for prognostication for patients on finite therapy but is not required in all circumstances.

- There is no evidence supporting routine surveillance imaging and bone marrow assessments for monitoring relapse or progression; clinical and blood assessments are usually adequate.

Special circumstances

The incidence of CLL is not specifically described in rural/regional Australia or in the Indigenous population, though the incidence of all forms of leukaemia appears not significantly different.¹¹⁴ The NZ Cancer Registry suggests that Māori are at similar risk of lymphoid leukaemia as non-Māori, although age-adjusted incidence has not been reported.¹¹⁵

Conclusion

The management of CLL has been revolutionised over the last decade. There is an improved understanding of CLL biology, and equitable access to molecular testing is desired to guide therapy. Three new classes of therapeutics have become available, and this has translated into better outcomes for patients. Further studies on optimal combinations and time-limited therapies remain the focus for future research.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Table S1. Recommended antimicrobial prophylaxis.