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BSH GUIDELINES

Guideline for the treatment of chronic lymphocytic leukaemia

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SCOPE

Recent changes to the commissioned regimens and the COVID-19 pandemic necessitate an update of the 2018 British Society of Haematology guidance on chronic lymphocytic leukaemia (CLL).[1] Here we discuss: (1) considerations prior to treatment; (2) front-line treatment recommendations; (3) management of relapsed or refractory disease; (4) management of intolerance to Bruton tyrosine kinase inhibitors (BTKi); and (5) guidance for vaccinations and prophylaxis. We focus particularly on therapies approved for use in the UK at the time of writing. Guidance on initial approach to patient management, indications for treatment, molecular assessment prior to treatment, assessment of response to treatment, supportive care, and autoimmune cytopenia remain unchanged. In addition to this CLL treatment update, we have published recent guidance on management of cardiovascular complications secondary to treatment with BTKi[2] and Good Practice Guidance on the management of Richter transformation (RT) of CLL.[3]

METHODOLOGY

These guidelines were compiled according to the BSH process (https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf). The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org.

Recommendations are based on a review of the literature using Medline/Pubmed. Search terms included; CLL treatment, randomised, clinical trial, FCR, TP53 disruption, Bruton tyrosine kinase inhibitor, BCL2 inhibitor, rituximab, obinutuzumab, vaccination, Covid19. The search was limited to English-language publications and conference abstracts from the date of publication of the previous CLL guideline in 2018 to July 2021. Titles/abstracts obtained were curated and manually reviewed by the writing group who conducted additional searches, using subsection heading terms.

Review of the manuscript was performed by the BSH Guidelines Committee Haemato-Oncology Task Force, the BSH Guidelines Committee and the Haemato-Oncology sounding board of the BSH. It was also posted on the members section of the BSH website for comment. This guideline has also been reviewed by patient representatives from the UK CLL Support Association (https://www.cllsupport.org.uk) and Leukaemia Care (https://www.leukaemiacare.org.uk).

CONSIDERATIONS PRIOR TO STARTING TREATMENT

Choosing the optimal therapy for a patient with CLL requires consideration of both patient-related factors (such as comorbidities, concomitant medication, patient preference) and disease-related factors (prognostic and predictive). In addition, previous responses and toxicities from prior therapies and the impact of treatment on cellular and humoral immunity will also influence therapy choices.

The availability of targeted agents provides effective therapy for older patients for whom palliative chemoimmunotherapy was previously the only option. However, differences in the side effect profiles of first- and second-generation BTKi and B-cell lymphoma-2 inhibitors (BCL2i), phosphoinositide 3-kinase inhibitors (PI3Ki), and the option of fixed-duration venetoclax-including regimens *versus* continuous BTKi therapy all impact on the choice of therapy for individual patients.

Screening for *TP53* disruption (i.e. del 17p13.1 and/or *TP53* mutation) prior to each line of treatment is recommended as patients with these genetic abnormalities remain a high-risk group, even in the era of targeted therapy. *IGHV* gene mutation analysis should be performed to identify a subgroup of patients who often fare particularly well and may be functionally cured with fludarabine, cyclophosphamide and rituximab (FCR) (fit, younger patients) and have excellent, durable responses with 12 months' fixed-duration venetoclax–obinutuzumab (VenO) (older patients).

FRONT-LINE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKAEMIA

Since the last BSH CLL guidelines were published in 2018, targeted pathway inhibitors have challenged the role of chemoimmunotherapy (CIT) and represent a paradigm shift in front-line treatment. Criteria for initiating treatment remain as defined by the iwCLL.[4]

Front-line treatment of less fit (or unsuitable for CIT) patients with CLL and intact TP53

Given the natural CLL age distribution, the majority of patients fall into the category of 'less fit', with almost 90% having comorbidities.[5] Prior to the approval of targeted agents, the German CLL Study Group (DCLLSG) CLL11 trial established chlorambucil with obinutuzumab (CO) as an international standard of care for this patient cohort.[6] Three major randomised clinical trials in unfit patients[7–9] have since shown an improved progression-free survival (PFS) with targeted inhibitors using either a BTKi or BCL2i in combination with obinutuzumab, compared to CO (Table 1), but no overall survival benefit to date.

Ibrutinib

Ibrutinib was the first-in-class BTKi to be licensed in CLL. The phase 3 RESONATE-2 study compared indefinite ibrutinib with ≤12 cycles of chlorambucil in untreated patients over 65 years old without del17p13.1.[10] After seven years of follow-up, the ibrutinib arm displayed superior survival: PFS 61% vs 9%, and overall survival (OS) at five years of 83% vs 68% (78% of ibrutinib-treated patients were estimated to be alive at 6.5 years). Ibrutinib was well tolerated in this older population with 47% of patients remaining on treatment at this timepoint. Continued ibrutinib also improved depth of response with complete remission/complete remission with incomplete count recovery (CR/CRi) increasing from 11% at 18 months to 34% after a median follow-up of seven years.[11,12] The ALLIANCE A041707 study demonstrated an improved two-year PFS for ibrutinib with or without rituximab, compared to bendamustine–rituximab (87% vs 88% vs 74%, hazard ratio [HR] 0.38; 95% confidence interval [CI] 0.25–0.59).[13] Notably, there was no additional benefit in adding rituximab to ibrutinib. Most common/clinically relevant adverse events (AEs) are included in Table 1.

Acalabrutinib

In the ELEVATE-TN study, acalabrutinib, the second-generation BTKi, in combination with obinutuzumab or as monotherapy improved the four-year PFS compared to chlorambucil–obinutuzumab (87% vs 78% vs 25%). An ad hoc analysis showed the addition of obinutuzumab to acalabrutinib improved PFS, but at the expense of an increased rate of ≥grade 3 infection (23.6% vs 16.2%, compared with 8.3% with chlorambucil–obinutuzumab), neutropenia rate (30.9% vs 11.2% vs 41.4%), and infusion-related reactions (2.8% vs 0 vs 5.9%)[14] (see Table 1 for more information on AEs).

Venetoclax–obinutuzumab

The DCLLSG CLL14 study, which compared venetoclax in combination with obinutuzumab (VenO) to CO, showed improved four-year PFS (74% vs 35%).[15] The improved PFS of CO, compared to that in the CLL11 study,[6] is possibly explained by longer chlorambucil treatment (12 vs 6 cycles).

TABLE 1 Key front-line phase 3 trials of BTK & BCL2 inhibitors in CLL

Study name/ reference	Treatment arms	Median age/ population type	*N*	Follow-up	ORR/ CR (%)	Median PFS (months)	HR (95% CI)	Median OS (months)	HR (95% CI)	uMRD%	AE of interest
RESONATE-2	Ibrutinib Chlorambucil	73 72	136 133	78 m	92/30 37	NR 15 m	0.167 (0.117–0.238)	NR (78% 6.5 years) NR (68% 5 years)	0.450 (0.266–0.761)	– –	Ibrutinib: Hypertension (26%) AF (16%) Major haemorrhage (11%)
Alliance 2018	Ibrutinib Ibrutinib-Rituximab Bendamustine-Rituximab	71 71 70	182 183 183	24 m	93 94 81	NR (87% 2 years) NR (88% 2 years) NR (74% 2 years)	0.38 (0.250–0.59) IR vs BR 1.00 (0.62–1.62) I vs IR	NR (90% 2 years) NR (94% 2 years) NR (95% 2 years)	– – –	1 4 8	≥G3 neutropenia-I (15%), IR (21%), BR (40%) AF-I (9%), IR (6%), BR (3%) Hypertension >G3-I (29%), IR (34%), BR (15%)
iLLUMINATE	Ibrutinib-obinutuzumab Chlorambucil-obinutuzumab	70 72	113 116	40 m	88 73	NR (76% 36 m) 22 m	0.251 (0.160–0.395)	NR (86% 40 m) NR (85% 30 m)	– –	35 25	Neutropenia ≥G3 8%, AF ≥G3 1.4%
ELEVATE-TN	Acalabrutinib Acalabrutinib-obinutuzumab Chlorambucil-obinutuzumab	70 70 71	179 179 177	48 m	86 94 79	NR (78% 4 years) NR (87% 4 years) 27.8 m	– – –	NR (88% 4 years) NR (93% 4 years) NR (88% 4 years)	– – –	– – –	AF-A (4%), AO (3%), CO (1%) Hypertension ≥G3 A (2%), AO (3%), CO (3%) Bleeding >G3 A & AO (2%)
CLL14	Venetoclax-obinutuzumab Chlorambucil-obinutuzumab	72 72	216 216	52.4 m	85 71	NR (74% 4 years) 36.4 m	0.33 (0.25–0.45)	NR (85.3% 4 years) NR (83.1% 4 years)	0.85 (0.54–1.35)	76 35	Neutropenia ≥G3 VO (52.8 5), CO (48.1%)
ECOG-ACRIN E1912	Ibrutinib-rituximab FCR	56.7 56.7	354 175	36 m	96 81	NR (89% 3 years) NR (73% 3 years)	0.35 (0.22–0.56)	NR (99% 3 years) NR (92% 3 years)	0.17 (0.05–0.54)	8 59	Neutropenia ≥G3 IR (25.6), FCR (44.9%) AF-IR (7.4%), FCR (3.2%)

Abbreviations: AE, adverse event; BTK, Bruton tyrosine kinase; BCL2, B-cell lymphoma-2; CI, confidence interval; CLL, chronic leucocytic leukemia; CR, complete response; FCR, fludarabine, cyclophosphamide and rituximab; HR, hazard ratio; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; uMRD, undetectable minimal residual disease. [Correction added on 13 April 2022, after first online publication: The data in the fifth and seventh columns of Table 1 were corrected in this version.]

VenO has some potential advantages over BTKi combinations, offering a fixed-duration treatment of one year, and high rates of minimal residual disease (MRD)-negative ($<10^{-4}$) response (75.5% MRD-negative in peripheral blood and 56.9% in bone marrow). Additionally, there was a significantly lower incidence of subsequent clonal evolution than in the CO arm. Specific mutations associated with venetoclax resistance were not detected, such as mutations in *BCL2*, *BIM*, *BAX*, *BCL-XL* and *MCL1*). Grade ≥3 neutropenia occurred in 52.8% of VenO-treated patients, but precautions (use of adequate prophylaxis, initial debulking with obinutuzumab, and the well-established weekly venetoclax ramp-up dosing schedule) resulted in significant reduction of tumour lysis syndrome (TLS).

Front-line treatment of fit patients with chronic lymphocytic leukaemia and intact *TP53*

Chemoimmunotherapy

FCR was previously the standard of care for front-line treatment of fit patients with CLL and intact *TP53*. The phase 3 ECOG-ACRIN 1912 trial randomised patients to receive either ibrutinib and rituximab (IR) for six cycles, followed by ibrutinib until disease progression or unacceptable toxicity, or six cycles of FCR.[16] The IR cohort had a superior survival compared to FCR (three-year PFS 89.4% vs 72.9%, HR 0.35; 95% CI 0.22–0.56, with three-year OS 98.8% vs 91.5% HR 0.17; 95% CI 0.05–0.54). A subgroup analysis of patients with unmutated *IGHV* showed a PFS of 90.7% vs 62.5% at three years in favour of IR; whereas among those with mutated *IGHV*, PFS was comparable (87.7% vs 88.0%). The overall incidence of grade ≥3 AEs was similar; however, grade ≥3 infections were less common (10.5% vs 20.3%) in the IR group.

Among patients with mutated *IGHV* who receive front-line FCR and obtain a MRD-negative remission, extremely durable responses can be achieved leading to 'functional cure' in about 50% of patients with mutated *IGHV*,[17] while the very long-term durability of responses to targeted inhibitors is as yet unknown. FCR therefore remains a viable option for fit, younger patients with mutated *IGHV* and intact *TP53*. However, this indication for FCR may change once longer-term follow-up data exist for the targeted inhibitors.

BTKi and BCL2i

Currently, front-line BTKi with ibrutinib or acalabrutinib does not have NICE approval for use in fit, younger patients without *TP53* disruption, although the E1912 study showed an OS advantage of ibrutinib compared to FCR in this patient group. Prospective data from a phase 1b study of 32 patients indicates that VenO may be equally effective in fit patients.[18] NICE TA633 permits use, via the Cancer Drugs Fund (CDF) in England and Northern Ireland, and through a different funding stream in Wales, of up-front VenO for fit patients lacking *TP53* disruption, while more data are collected in this group.

Patients with *TP53* disruption

BTKi and BCL2i

NICE-approved front-line treatment options for all patients with CLL and *TP53* disruption include VenO, ibrutinib, acalabrutinib and venetoclax monotherapy where BTKi is contra-indicated (Figure 1).

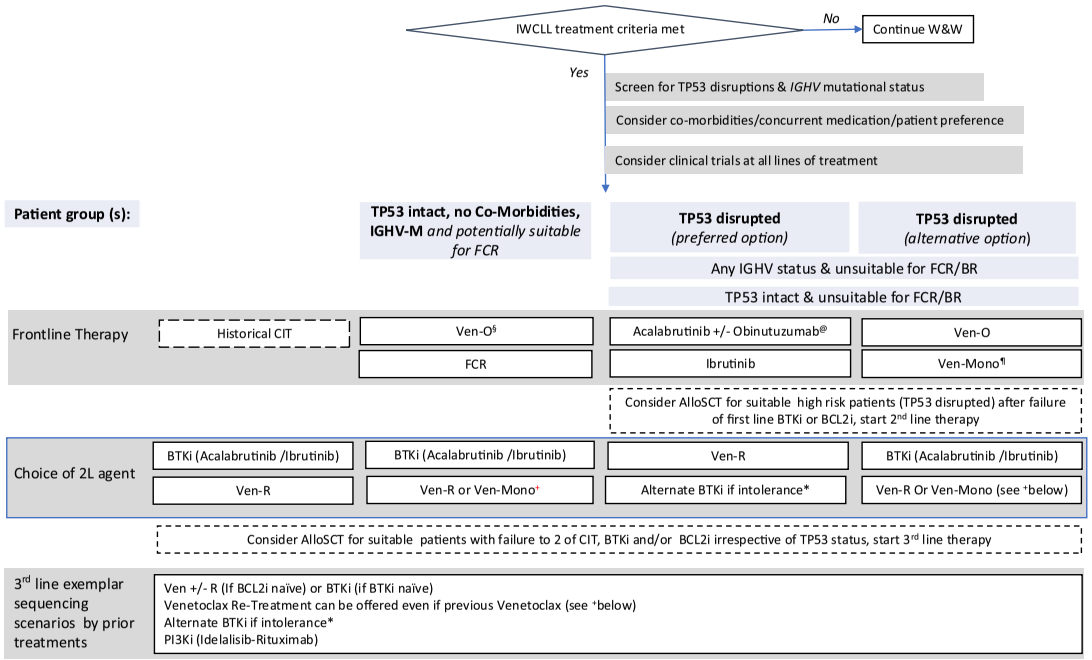
Treatment with doublet or triplet therapy

A growing body of evidence suggests that BTKi and BCL2i with or without anti-CD20 antibodies are highly effective front-line combination treatment. The phase 2 CAPTIVATE[19] trial of venetoclax combined with ibrutinib (VI) in previously untreated CLL, included patients who were fit, under 65 years, but had at least one of: del(17p), *TP53* mutation, del(11q) or unmutated *IGHV*. After 12 cycles of combined treatment, 88% of patients had CR/CRi, and 61% were MRD-negative in bone marrow, leading to FDA approval. The most common grade 3/4 AE across cohorts was neutropenia.[20]

In the less fit populations (over 65 years old or younger patients with a cumulative illness rating scale (CIRS) score of >6 or creatinine clearance <70 ml/min) efficacy and safety of fixed-duration VI is being evaluated in a phase 3 trial, GLOW. Improved PFS with VI (76% at 27.7 months) compared with CO (29%) (HR for progression or death 0.216; 95% CI 0.131–0.357) was consistent across predefined subgroups, including patients with unmutated *IGHV*. High-risk patients with known *TP53* disruption were excluded. Undetectable bone-marrow (BM) MRD rates by next-generation sequencing (NGS) were significantly higher for VI at three months after the end of treatment compared with CO (51.9% vs 17.1% respectively, $p = 0.0259$). The most common grade 3/4 AE in both treatment groups was neutropenia (VI 34.9% vs CO 49.5%), infections (17% vs 11.4%), and diarrhoea (10.4% vs 1%); 22.6% participants discontinued VI.[21] The relatively high incidence of early treatment-related mortality in VI patients compared with the control arm and VI patients in the CAPTIVATE trial suggests this combination should be used with caution in older/more comorbid patients and should be limited to fit patients with high-risk CLL.

Choosing the optimal front-line therapy

The pivotal studies described above have demonstrated superior long-term efficacy and tolerability of targeted therapy over CIT in the front-line setting for patients over 65 or with CIRS scores of >6. As result, both continuous therapy with acalabrutinib monotherapy and 12 months' fixed-duration VenO are now NICE-approved in the UK. The decision on which regimen to choose has to be based on a number of



R/R: Relapsed/refractory; TP53mut: TP53 gene mutation; 2L: Second line; 3L: Third line; CIT: Chemoimmunotherapy; BTKi: Bruton tyrosine kinase inhibitors; FCR: Fludarabine Cyclophosphamide Rituximab; Ven O: Venetoclax Obinutuzumab 12 months; Ven-R: Venetoclax-Rituximab 24 months; Ven-Mono: Single agent continuous venetoclax, ; PI3Ki: Phosphatidylinositol-3 kinase inhibitor; AlloSCT: allogeneic Stem Cell Transplantation
§ Venetoclax-Obinutuzumab is available for NHSE patients for this patient population and is preferred; ®Combination with Obinutuzumab is not licensed in the UK; *Alternate BTKi can be offered as an option if intolerant to initial BTKi choice and, when feasible, it is preferred over PI3Ki. ¶Only a first line option for TP53 disrupted patients who are ineligible for BTKi; +Venetoclax monotherapy can be offered to patients relapsing after fixed duration Venetoclax-based regimens, see text in addition.

FIGURE 1 Treatment algorithm

different factors including CLL-specific risk factors, past medical history, concomitant medication and patients' choice. Front-line ibrutinib monotherapy is NICE-approved and funded in the UK for patients with *TP53* disruption but not routinely for all other front-line patients at the time of writing.

Chronic lymphocytic leukaemia-specific risk factors

There is no evidence directly comparing targeted agents in *TP53* aberrant to recommend one over the other. Long-term follow-up of CLL14 shows that the small proportion of patients with *TP53* disruption have a shorter PFS compared to those with wild-type (WT) *TP53* following fixed-duration VenO. A similar patient population receiving continuous ibrutinib plus obinutuzumab in the Illuminate trial had a PFS of 72% at 36 months (HR 0.162; 95% CI 0.096–0.275).[22] There is long-term benefit with ibrutinib monotherapy despite lack of undetectable MRD: Ahn *et al*. reported a six-year PFS in CLL patients with *TP53* aberrations of 61% (95% CI 46–80) and an OS of 79% (95% CI 67–94).[23] Zanubrutinib, a selective, second-generation covalent BTK inhibitor, had been tested in 109 *TP53*-deleted naïve patients with overall response rates of 94.5%, 18-months PFS of 88.6% (95% CI, 79.0–94.0) and an OS of 95.1% (95% CI, 88.4–98).[24]

With respect to *IGHV* mutational status, ibrutinib and acalabrutinib with or without anti-CD20 showed broadly equal responses for *IGHV*-mutated and unmutated patients,[7,13,16] whereas *IGHV*-unmutated patients have an inferior PFS compared to those with mutated *IGHV* following VenO in CLL14.[9] Whether *IGHV* status should be used to determine use of BTKi- or BCL2i-based treatment remains unclear. Longer-term sequencing studies may provide further guidance in this area in the future.

Impact of past medical history such as cardiovascular comorbidities, use of anticoagulation, and bleeding risk on choice of front-line therapy is covered by related guidance.[2] Here, the use of a more selective BTKi, such as acalabrutinib, with fewer cardiovascular side effects may be preferable.[25] Alternatively, a venetoclax-based combination is a reasonable alternative for this patient group. Patients with a history of cardiac disease should be monitored closely during obinutuzumab infusion, also treatment with BCL2 inhibitors requires adequate renal function and patients with severe renal impairment (creatinine clearance [CrCl] ≥15 and <30 ml/min) should only be considered for venetoclax if benefit outweighs risk, with close monitoring for the increased risk of TLS.[26] Therefore, for patients with high tumour burden and/or chronic renal impairment, BTKi may be a preferred option.

Concomitant medication

Before deciding on the type of treatment, current medication should be carefully reviewed, with particular attention given to strong CYP3A inducers or inhibitors which should be stopped or replaced by other medication. Careful adjustment of dose for all targeted inhibitors is required if they are taken concomitantly with moderate CYP3A and P-GP inhibitors. Please refer to the *Summary of Product Characteristics* (SMPC) for details. For guidance on management of anticoagulation/antiplatelet therapy please refer to the BSH good practice paper on management of cardiovascular complications of Bruton tyrosine kinase inhibitors.[2]

Patient choice

A discussion of the nature, delivery and theoretical benefits of fixed-duration therapy and continuous therapy should take place. Individual patient compliance, age (for young patients, fixed-duration treatment may be preferable), and the effect of treatment on quality of life should be considered. In addition, the long-term risks of secondary myeloid cancers should be discussed with younger fitter patients with mutated *IGHV*, *TP53*-intact CLL where FCR is being considered.

Identifying and addressing side effects is important throughout treatment but is particularly relevant in the first 6–12 months following initiation of a BTKi. Early data demonstrated a 41% discontinuation rate of ibrutinib therapy,[11] with subsequent 'real world data' also showing a discontinuation rate of 42% at 17 months.[27] Acalabrutinib discontinuation rates were 25% for acalabrutinib with obinutuzumab and 30% for acalabrutinib monotherapy[28] Most side effects decrease with time with the exception of hypertension and cardiac arrhythmias.

Recommendations (NICE-approved)

- Venetoclax–obinutuzumab (VenO) or acalabrutinib are recommended options as initial therapy in patients unsuitable for CIT irrespective of *TP53* status (GRADE IB).
- Bendamustine or chlorambucil-based CIT are no longer recommended (GRADE IB).
- NICE-approved treatment options for fit patients with *TP53* disruption include acalabrutinib, ibrutinib, or venetoclax monotherapy for those with a contra-indication to a B-cell receptor inhibitor (GRADE IB).
- For fit patients with intact *TP53*, VenO may be obtained via CDF.
- For fit patients with intact *TP53* and with mutated *IGHV*, chemoimmunotherapy with FCR remains an acceptable initial therapy (bendamustine–rituximab [BR] or CO are no longer recommended) (GRADE IB).

Recommendations (not NICE-approved)

- Acalabrutinib–obinutuzumab is a front-line treatment option (GRADE IB) for all patients with or without *TP53* disruption (GRADE IB).
- Ibrutinib monotherapy is a front-line treatment option for all patients with or without *TP53* disruption (GRADE IB).
- There is currently no role for BTKi/BCL2i combinations for treatment of standard-risk CLL in the front-line setting outside or clinical trials.

MANAGEMENT OF RELAPSED OR REFRACTORY (R/R) CHRONIC LYMPHOCYTIC LEUKAEMIA

The current licensed therapies in relapsed CLL are BTKi (ibrutinib and acalabrutinib), BCL2i (venetoclax monotherapy or in combination with rituximab) and phosphoinositide 3-kinase inhibitors (PI3Ki) (idelalisib and rituximab).[29–36] After one or several cycles of CIT, BTK, PI3K and BCL2 inhibitors, alone or in combination with anti-CD20 antibodies, constitute standard treatment options for relapsed CLL, regardless of presence or absence of *TP53* disruption. No randomised evidence has compared BTKi *versus* venetoclax-based combinations in R/R CLL after chemoimmunotherapy. Individualised decisions are recommended, taking into account patient preference and toxicity profile. There are also little data on the ideal sequencing strategy when patients relapse following targeted agents (Table 2).

If a patient is relapsing on a targeted agent, treatment should be continued for as long as the patient derives clinical benefit until the subsequent targeted therapy is available, as there is a risk of rapid progression once therapy is discontinued.

Acalabrutinib

Acalabrutinib monotherapy demonstrated benefit in relapsed CLL over investigator's choice (BR or idelalisib–rituximab [IdelaR]), in the ASCEND trial.[32] With a median follow-up of 16.1 months, patients treated with acalabrutinib showed an overall response rate (ORR) of 81% and a 12-month PFS of 88% compared to 68% on the investigator´s choice. Acalabrutinib also improved PFS in *TP53*-disrupted and unmutated *IGHV* subgroups. There were no new safety signals for acalabrutinib and the rate of discontinuation due to AEs was 11%.

Venetoclax–rituximab

Twenty-four-month fixed-duration venetoclax and rituximab (VenR) for R/R CLL recently demonstrated PFS and OS benefit compared to BR in MURANO with a four-year PFS of 57.3% and 4.6%, respectively (HR 0.19; 95% CI 0.14–0.25). A greater proportion of VenR-treated patients attained peripheral blood MRD negativity at the end of treatment (62.4% vs 7.6%).[35,37] Only 5/389 patients enrolled had previously been exposed to BCRi. VenR was active in unmutated *IGHV* patients and in those with *TP53* disruption.

Ibrutinib

Ibrutinib showed superior efficacy in R/R CLL compared to single-agent ofatumumab in RESONATE.[29] Six-year follow-up demonstrated an ORR of 91% and a CR rate of 11%.[38] Median duration of therapy was 41 months with 22% still on ibrutinib at study closure. Median PFS was 44.1 months for the ibrutinib arm and 8.1 months for the ofatumumab arm. Atrial fibrillation and hypertension were seen in 12% and 21% respectively.[38]

Idelalisib–rituximab

In a phase 3 trial of R/R patients unfit for standard chemoimmunotherapy, IdelaR demonstrated an ORR of 83.6%,[31] a PFS of 19.4 months and an OS of 40.6 months compared to rituximab monotherapy. The IdelaR subgroup of ASCEND showed a similar median PFS of 15.8 months.[32] However, IdelaR remains a less used treatment option due to immune-mediated and infectious complications.

SEQUENCING OF TARGETED INHIBITORS

Few prospective data exist to guide the sequencing of targeted therapy, with pivotal randomised controlled trials (RCTs), primarily performed in targeted inhibitor-naïve patients relapsing after CIT. A prospective phase 2 trial[29,33,35] of venetoclax monotherapy in 91 ibrutinib-exposed patients noted an ORR of 65% and a modified progression-free survival (mPFS) of 24.7 months. Thirty-six patients who received prior idelalisib showed an ORR of 67% and a 12-month estimated PFS of 79%.[39] Sixteen dual PI3Ki/BTKi-exposed patients demonstrated an ORR of 50% and a mPFS of 16.4 months.[40] Venetoclax monotherapy post BCRi is further supported by retrospective data.[41–43]

No prospective studies provide evidence for sequencing with BCRi post venetoclax. Recent retrospective evidence suggests however that BTKi provide high ORR in heavily pretreated patients including those previously exposed to venetoclax[44,45] and produce more favourable results than PI3Ki in this setting. Venetoclax monotherapy is licensed for relapsed CLL patients who have failed or are unsuitable for BCRi.[33,42,46,47] Venetoclax monotherapy remains a theoretical option for retreatment following fixed-duration-including venetoclax regimens; however evidence for this approach remains limited.[34,48] (Box 1). The non-covalent BTKi pirtobrutinib has efficacy in patients exposed to both covalent BTKi and venetoclax,[49] but is not yet approved in Europe.

BTKi INTOLERANCE

The majority of data on BTKi intolerance comes from experience of treating with ibrutinib and represents small numbers. Two clinical trials[50,51] demonstrated that acalabrutinib is effective in patients stopping ibrutinib due to intolerance. A phase 2 trial of 60 patients[51] found an ORR of 73% (CR 5%)

TABLE 2 Key relapsed phase 3 trials of BTK & BCL2 inhibitors in CLL

Study name/ reference	Treatment arms	Median age/ population type	*N*	Follow-up	ORR/CR (%)	PFS (months)	HR (95% CI)	OS (months)	HR (95% CI)	uMRD%	AE of interest (≥Grade 3)
ASCEND (Ghia *et al.*[32])	Acalabrutinib Investigator's choice (BR/ IdelaR)	68 67	155 155	16 m	81/0 76/2	NR (88% 1 year) 16.5 (68% 1 year)	0.31 (0.2 0– 0.49)	NR (90% 1 year) NR (88% 1 year)	0.84 (0.42–1.66)	N/A N/A	Acalabrutinib: neutropenia (15%), infections (15%), anaemia (11%), hypertension (2%) Afib (1%), major bleeding (1%),
MURANO (Seymour *et al.*[35]) (Kater *et al.*[37])	VenR BR	64 66	194 195	59 m	92.3/26.8[a] 72.3/8.2[a]	53.6 17	0.19 (0.15–0.26)	NR (82% 5 years) NR (62% 5 years)	0.40 (0.26–0.62)	X°62.4 13.3	VenR: neutropenia (57.7%), infections (18%), anaemia (11%), febrile neutropenia (3.6%), TLS (3.1%).
RESONATE (Byrd *et al.*[29]) (Munir *et al.*[38])	Ibrutinib Ofatumumab	67 71	195 196	6 years	91/11	44.1 8.1	0.15 (0.11–0.19)	67.7 65.2	0.81 (0.6 0–1.09)	N/A N/A	Ibrutinib: neutropenia (25%), infections (45%), hypertension (9%) major bleeding (10%), Afib (6%).
GS-US-312-0116 (Furman *et al.*[31]) (Sharman *et al.*[82])	IdelaR Rituximab	71 71	110 110	18 m	85.5/0 17/0	19.4 6.5	N/A	40.6 34.6	0.8 (0.5–1.1)	N/A N/A	IdelaR: Neutropenia (46%), Infections (33%), Diarrhoea (16%), Transaminitis (15%), Penumonitis (6%)

Notes. Median Age: Expressed in years; Follow-up: Denotes median follow-up in months;

Abbreviations: AE, adverse events; Afib, atrial fibrillation; BR, bendamustine and rituximab; CR, complete response rate; G3, Grade 3; HR, hazard ratio; IdelaR, idelalisib and rituximab; m, months; N/A, not available; NR, not reached; ORR, overall response rate; OS, median overall survival at longest available/published follow-up; PFS, median progression-free survival at longest available/published follow-up; TLS, tumour lysis syndrome; uMRD, undetectable minimal residual disease; VenR, venetoclax and rituximab.

[a]uMRD rates for VenR arm: 83% vs 23.1% for BR arm.

RELAPSED THERAPY	SUGGESTED SEQUENCE
BTKi relapse	→BCL2i* or PI3Ki***
PI3Ki relapse	→BTKi or BCL2i
BCL2i/BTKi relapse	→PI3Ki or AlloSCT or clinical trial
BCL2i/BTKi/PI3Ki relapse	→ AlloSCT or clinical trial
Venetoclax Obinutuzumab	→BTKi or Venetoclax Rituximab**or PI3Ki***
Venetoclax mono relapse	→BTKi or PI3Ki***
Venetoclax Rituximab relapse**	→BTKi or Venetoclax monotherapy or PI3Ki***

*the only sequence with phase 3 clinical trial evidence
**as long as the patient have not relapsed whilst on Venetoclax combination treatment and had at least 12 months remission
*** BTKi or BCL2 are the preferred options in those naive to those classes
BTKi: Bruton tyrosine kinase inhibitors; Ven O: Venetoclax Obinutuzumab;
VenR: Venetoclax-Rituximab regimen; PI3K: Phosphatidylinositol-3 kinase inhibitor
AlloSCT, allogeneic Stem Cell Transplantation

BOX 1 Sequencing options for targeted agents

and a two-year PFS of 72%. Frequent AEs were diarrhoea (53%), headache (42%), and contusion (40%). Prospective trial data indicate that long-term outcomes are better for patients who discontinue a BTKi for intolerance rather than resistance, but there are no available data on responses to subsequent therapies.[52–54] In exploratory post-hoc subgroup analyses, 19 (63%, 95% CI 44–80) of 30 patients who had discontinued ibrutinib therapy because of AEs had an overall response with venetoclax, compared with 27 (54%, 95% CI 39–68) of 50 patients who had discontinued ibrutinib because of disease progression.[33] Direct comparison of acalabrutinib and ibrutinib showed that acalabrutinib is better tolerated with similar efficacy to ibrutinib in previously treated patients, but has lower frequencies of common AEs, severe AEs and AE-related treatment discontinuation. In particular, cardiovascular events were less common.[25]

A prospective phase 2 trial has demonstrated that the selective PI3K-delta inhibitor umbralisib is safe and effective in BTKi and PI3Ki intolerant patients.[55]

Recommendations

- Targeted inhibitors (BTKi or BCL2i alone or in combination with rituximab) are the treatment of choice for relapsed CLL. In England and Wales, ibrutinib, acalabrutinib, and venetoclax with or without rituximab are currently approved and commissioned for this indication (GRADE IB).
- For patients relapsing after BTKi offer venetoclax-based regimens, irrespective of *TP53* status (GRADE IIB).
- For patients relapsing following fixed-duration venetoclax-based therapy consider either a BTKi (GRADE III) or venetoclax retreatment depending on duration of PFS1 (GRADE III).
- For relapsed patients who are intolerant to ibrutinib, offer either venetoclax-based therapy or acalabrutinib depending on the reason for intolerance (GRADE IIB).
- For patients relapsing on BTKi, continue treatment until alternative therapy is initiated (GRADE III).
- Idelalisib–rituximab remains an option for relapsed patients who are unsuitable for or who are refractory to BTKi- and BCL2i-based treatment. (GRADE IIB).
- Patients with double refractory CLL after BTKi and BCL2i should be considered for clinical trials (GRADE III).

ROLE OF ALLOGENEIC STEM CELL TRANSPLANTATION AND CHIMAERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY

British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT) indications for allogeneic transplantation in CLL remain as defined in 2013 (https://bsbmtct.org/). This therapy continues to be an option for patients with high-risk features such as *TP53* disruption and treatment failure. The decision to transplant patients with high-risk disease should be based on remission status, patient age, performance status, comorbidity and patient preference, donor status and availability of alternative treatments. Given the rapid evolution of targeted treatment options available, the definition of treatment failure that indicates allogeneic transplantation remains unclear. At the time of writing, patients who are transplant-eligible, refractory to CIT and/or carry *TP53* disruption, and relapse following at least one targeted agent should be considered. Of note, targeted inhibitors do not appear to impact the safety of allogeneic transplantation, and survival outcomes are similar regardless of number of agents received, prior chemoimmunotherapy exposure, or targeted inhibitors immediately prior to transplant.[56]

Alternative immune effector-cell therapies to allogeneic transplantation are emerging, including CD19-directed chimaeric antigen receptor therapy (CAR-T)

which has been evaluated in clinical trials throughout the last 10 years following initial success reported in 2011.[57] A variety of constructs, effector-cell ratios and administration with concurrent ibrutinib have been or are undergoing evaluation in phase 1 and 2 trials.[58–62] Overall response rates of up to 95% of patients have been reported, with CR rates of 25% to 60%–65% in heavily pretreated patients. These disappointing results may be due to CLL-associated exhaustion of autologous T cells. Toxicity has also limited the use of CAR-T to the minority of patients with CLL who do not have underlying comorbidities. Long-term follow-up data are lacking and currently such treatment remains an option only through clinical trials. It is of note that a number of trials of cellular products licensed for other B-cell malignancies have either been terminated (e.g. NCT02640209 using tisagenlecleucel) or are not progressing (e.g. NCT03624036 using brexucabtagene autoleucel). RT remains a very challenging complication of CLL for which CAR-T cell therapy may have a role. For the management of RT please refer to the recent BSH good practice paper.[3]

Recommendations

- Allogeneic stem cell transplantation (AlloSCT) is a treatment option for suitable patients with high-risk CLL defined by either:
  (i) failed two out of chemoimmunotherapy, BCRi and/or BCL2i irrespective of *TP53* status (GRADE IV), or
  (ii) failed either BCRi and/or BCL2i therapy and harbour a *TP53* disruption (GRADE III).
- AlloSCT should be considered for suitable patients with RT (GRADE III).
- CAR-T therapy is currently only an option in clinical trials.

VACCINATIONS, PROPHYLAXIS, AND COVID-19

Vaccinations

A hallmark of CLL is progressive immunodeficiency[63] characterised by impaired responses to vaccination, including influenza, pneumococcal, hepatitis B and Varicella zoster virus (VZV).[64–66] We strongly advise patients to keep a vaccination log book (see Appendix).

At diagnosis, the conjugate pneumococcal vaccine Prevenar13 is recommended, followed at least two months later by the polysaccharide vaccine Pneumovax23 (https://www.gov.uk/government/publications/pneumococcal-the-green-book-chapter-25). Serum antibody response to vaccination should be checked in those with a history of recurrent or severe bacterial infections. The annual seasonal 'flu vaccine' is advised.

Live vaccines (measles/mumps/rubella, live polio, yellow fever and varicella vaccine [Zostavax]) should not be given. Patients should avoid contact with children who have received the live nasal influenza vaccine for seven days (https://www.cdc.gov/flu/prevent/nasalspray.htm.)

The recombinant varicella vaccine (Shingrix) is safe for patients with CLL,[67] and is available in the UK for those aged 70–79 years of age (https://www.gov.uk/government/publications/shingles-immunisation-programme-introduction-of-shingrix-letter).

Anti-microbial prophylaxis with targeted agents

Anti-bacterial prophylaxis should be considered for all patients with a history of recurrent or serious bacterial infections. Most patients with relapsed/refractory disease suffer from secondary immunodeficiency. For patients taking BTKi continuously *Pneumocystis jirovecii* (PJP) prophylaxis is recommended either throughout therapy or for at least the first 12 months when the risk of atypical infection appears to be highest.[68] For relapsed/refractory patients on fixed-duration regimen (Ven-R), prophylaxis may be considered for at least six months after the end of treatment or until CD4 T-cell recovery. Reports from the Medicines and Healthcare products Regulatory Agency [MHRA] on PJP pneumonia in patients treated with BTKi in a front-line setting vary and use of PJP prophylaxis here is poorly defined.[68,69] We recommend PJP prophylaxis for the first year of BTKi therapy in those on combination therapy or for patients with significant comorbidities and a history of recurrent or serious infections. For BCL2i, reports of PJP infection are rare[70] and limited to those heavily pretreated.

Prophylaxis with azoles is not routinely recommended with BTKi or BCL2i due to potential drug interactions. There are however several reports of invasive fungal infections on patients receiving BTKi therapy,[71] and the risks and benefits of combining azoles with targeted therapy should be weighed against each other depending on the individual patient's risk profile.

Immunoglobulin replacement therapy

Hypogammaglobulinaemia is a common finding in patients with CLL.[72] Immunoglobulin (Ig) replacement therapy is advised for patients who: (1) suffer recurrent or severe bacterial infections despite six months of continuous oral antibiotic therapy; (2) have a total IgG <4 g/l; and (3) have documented failure to respond to polysaccharide vaccine challenge (https://igd.mdsas.com/clinical-info/).

Subcutaneous preparations of immunoglobulin replacement therapy (scIg) that can be self-administered may be more convenient for patients and can be used as an alternative to intravenous preparations. A starting dose of 0.4–0.6 g/kg/month is recommended with adjustment according to the trough IgG (https://igd.mdsas.com/clinical-info/). In a small cohort, the scIg formulation resulted in higher IgG trough levels and patient quality of life

improved in comparison to intravenous formulations. In addition, a reduction in the number of AEs were seen with scIg.[73]

COVID-19

This recommendation represents information available on 15/01/2022. Please refer to online updates for the latest information found here: https://b-s-h.org.uk/about-us/news/covid-19-updates/

The COVID-19 pandemic has presented particular challenges for patients with CLL and their physicians. It is likely that the secondary immunodeficiency associated with CLL confers a higher risk of severe COVID-19 disease requiring hospitalisation, but no reliable data exist to estimate the true relative risk compared with age/sex-matched controls.

An early report suggested the prevalence of COVID-19 in patients with CLL was similar to that in the general population but associated with a high mortality rate in those with symptomatic infection (reported to be between 30.4% and 33%).[74,75] Survival rates were similar amongst treatment-naïve patients and those on therapy, including those on BTKi.[75]

In a single-centre cohort, where CLL patients were screened for COVID-19 infection during clinic attendance, the all-cause mortality was lower (13%), but this included a number of asymptomatic patients.[76] Patients who have recovered from COVID-19 infection have lower seroconversion rates (67% vs. 98% IgG positivity in individuals without CLL), and this is most notable in those with hypogammaglobulinaemia.[76]

The degree of protection afforded to patients with CLL by the available COVID-19 vaccines is lower than that of healthy age-matched controls.[77] An initial study from Israel found serological responses to the mRNA BNT162b2 COVID-19 vaccination of 52% compared with 100% for age-matched controls. The response rate for untreated patients was 55.2% compared with 16% in those on BTKi therapy. No patient within 12 months of anti-CD20 therapy mounted a serological response to vaccination.[77] The UK CLL-VR study recruited 500 patients who had received either the BTN162b2 and ChAdOx1 vaccination, with an extended interval between the two doses. Here, an antibody response rate of 67% was observed compared to 100% in healthy donors. This increased to 79% amongst those on watch and wait. Reduced response rates were seen in those on BTKi therapy or with hypogammaglobulinaemia. Notably, amongst antibody responders, reduced neutralisation titres against the Delta variant, which was dominant in the UK at the time of study, were observed compared to healthy controls, suggesting a further functional deficit in those with detectable antibody responses.[78] The immune correlates of protection from severe COVID-19 disease with specific antibody levels remains unknown. Immune response to COVID-19 vaccination is complex and includes cellular responses, which are difficult to measure in routine diagnostics. However, recent reports suggest that cellular responses to vaccination are also reduced in CLL compared to healthy controls (between 32% and 38% compared to 90%).

Encouragingly, reponse rates and antibody titres do appear to improve with subsequent doses of vaccination.[79] Vaccination should be recommended to all patients and ideally completed before commencing therapy, particularly for those starting BTKi.[66] Due to the inferior response rates observed amongst patients with CLL, a third primary dose, followed at least three months later by a fourth dose, is now recommended.

For patients who develop COVID-19 infection, treatment options have been extended and are available now for patients with CLL in the community. Sotrovimab (a monoclonal antibody against SARS-CoV-2 spike protein) has been shown to reduce the risk of hospitalisation and death in unvaccinated, high-risk patients by up to 85%.[80] Currently it is restricted to patients who test positive for infection and have developed symptoms within the last five days. Trials are ongoing for its use as a prophylactic treatment option. Similarly, molnupiravir, an antiviral, is associated with a 30% reduction in the risk of hospitalisation or death[81] and is available with the same eligibility criteria and where administration of monoclonal antibody therapy is not possible or contra-indicated (https://www.england.nhs.uk/coronavirus/publication/interim-clinical-commissioning-policy-neutralising-monoclonal-antibodies-or-antivirals-for-non-hospitalised-patients-with-covid-19/).

Recommendations

- All patients should be offered vaccination at diagnosis, keep a vaccine logbook and avoid live vaccines (GRADE IV, UK DoH guidance).
- Vaccination against pneumococcal infections include: Prevnar13 followed two months later by Pneumovax23. Functional antibodies should be checked six weeks later in those with a history of recurrent or serious infection, to accelerate access to IVIg (UK DoH guidance; GRADE IV). Vaccination should be repeated every five years.
- Patients with recurrent or serious infections should be recommended prophylactic antibiotics (GRADE IV).
- PJP prophylaxis should be considered in patients at risk (GRADE IV).
- Patients with a low IgG (<4 g/l), recurrent or serious infection despite six months of prophylactic antibiotics and a documented failure to respond to vaccination should be offered immunoglobulin replacement therapy (NHSE guidance).
- The annual flu vaccination is recommended for patients and household members.
- COVID-19 vaccination is recommended in all patients and household members (UK DoH guidance).
- Routine testing for COVID-19 antibody is currently not recommended.
- Monoclonal antibody therapy against the spike protein (or anti-viral therapy if administration of monoclonal is

not available) is recommended for patients who develop COVID-19 infection and are within five days of symptom onset.

PATIENT SUPPORT, INFORMATION AND CONSENT TO TREATMENT

CLL Support Association (https://www.cllsupport.org.uk), Leukaemia Care (https://www.leukaemiacare.org.uk) and other groups provide valuable support to CLL patients. After confirmation of diagnosis and initial counselling, we recommend that patients are directed to these charities, and also during later points of the patient's journey where they can receive help on a personal basis. When embarking upon treatment patients should be consented using the dedicated Systemic Anticancer Therapy (SACT) consent forms (https://www.cancerresearchuk.org/health-professional/treatment-and-other-post-diagnosis-issues/consent-forms-for-sact-systemic-anti-cancer-therapy#sact_consent5) or equivalent local documents if available.

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CONFLICT OF INTEREST

The BSH paid the expenses incurred during the writing of this guideline. All authors have made a declaration of interest to the BSH and Task Force Chairs which may be viewed on request.

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SUPPORTING INFORMATION

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