Diagnosis and Management of Mantle Cell Lymphoma: A British Society for Haematology Guideline

Writing group: on behalf of the Haemato-Oncology Task Force of the British Society for Haematology

Toby A. Eyre[1], Mark J. Bishton[2], Rory McCulloch[3], Maeve O'Reilly[4], Robin Sanderson[5], Geetha Menon[6], Sunil Iyengar[7], David Lewis[8], Jonathan Lambert[4], Kim M. Linton[9], Pamela McKay[10]

1. Department of Haematology, Cancer and Haematology Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom.
2. Department of Haematology, Nottingham University Hospitals NHS Foundation Trust, Oxford, United Kingdom.
3. Department of Haematology, Gloucestershire Hospitals NHS Foundation Trust, Gloucester, United Kingdom
4. Department of Haematology, University College London Hospitals, London United Kingdom.
5. Department of Haematology, King's College Hospital, London, United Kingdom
6. Department of Cellular Pathology, Liverpool University Hospitals NHS Foundation Trust, Liverpool, United Kingdom
7. Department of Haematology, The Royal Marsden Hospital, London, United Kingdom.
8. Department of Haematology, Derriford Hospital, Plymouth, United Kingdom
9. Department of Medical Oncology, the Christie NHS Foundation Trust, Manchester, UK
10. Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom

Correspondence: BSH Administrator, British Society for Haematology, 100 White Lion Street, London, N1 9PF, UK. E-mail: bshguidelines@b-s-h.org.uk

Scope

The objective of this guideline is to provide healthcare professionals with clear guidance on the diagnosis and management of patients with Mantle Cell Lymphoma.

Methodology

This Guideline was compiled according to the BSH process at https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf and represents best practice in both teaching and district hospitals in the UK. 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.

Literature review details

Recommendations included a systematic review of published English language literature from publication of previous British Society for Haematology (BSH) Management of Mantle Cell lymphoma Guidelines 2018 up to 02/2023. The search was limited to English language publications and conference abstracts. Titles/abstracts obtained were curated and manually reviewed by the writing group who conducted additional searches, using sub-section heading terms. In addition, there are some further pertinent references and a consensus of expert opinion where no published data are available. PubMed, MEDLINE, EMBASE, Cochrane databases and Web of Science were searched using the preliminary search terms; MCL OR Mantle Cell lymphoma OR aggressive Mantle Cell lymphoma OR indolent Mantle Cell lymphoma. Systematic reviews, meta-analysis including guidelines from other countries, prospective clinical trials, observational studies i.e., cohort or case–control studies, expert reviews and opinions and case series of >10 patients were considered and reviewed as appropriate.

Review of the manuscript

Review of the manuscript was performed by the BSH Guidelines Committee, Haemato-oncology Task Force, Haemato-oncology sounding board of BSH.

WORD COUNT 5350 *(excluding Recommendations and Tables)*

Pre-treatment evaluation

Histopathological Assessment

Mantle cell lymphoma (MCL) has a heterogenous cellular origin, corresponding to subsets of mature B-cells in the primary lymphoid follicle and mantle area of secondary lymphoid follicles. Most cases are pre-germinal in origin, characterised by few/no immunoglobulin heavy chain variable region gene (IGHV) somatic mutations. ~15-20% are post-germinal centre in origin and associated with a higher somatic IGHV mutational burden (1–3). Classical MCL involves nodal and extra-nodal sites, including the liver, spleen and the gastrointestinal (GI) tract. A non-nodal leukaemic form with indolent and aggressive variants are described (4).

Nodal architectural features include classic, blastoid, pleomorphic, marginal zone-like and small cell types (5). Blastoid and pleomorphic types are associated with poorer survival (6). TP53 genetic aberrations are the strongest predictors of poor responses to chemoimmunotherapy, early disease progression and mortality (7,8).

Nodal and bone marrow tissue should undergo histomorphological, immuno-phenotypic and genetic analysis (Table 1). In cases with an immunophenotypic profile for MCL which are cyclinD1-negative by immunohistochemistry, fluorescence in situ hybridization (FISH) should be undertaken for CCND1 rearrangement and if this is negative, further studies for CCND2 and CCND3 should be undertaken (9). Routine karyotyping is of unclear clinical value and should be confined to clinical trials.

Peripheral blood morphology	**Flow cytometry** *Standard panel should include CD19, CD20, CD79b, CD5, FMC7, CD200, CD10, CD23, surface immunoglobulin*	**Histology**	**Immunohistochemistry** *Standard panel should include CD20, PAX5, CD10, BCL6, CD5, CD23, cyclinD1, SOX 11, Ki-67*	**Cytogenetics**	**Mutations**
- Small to medium sized lymphocytes, mature nuclei with a cleft. - Larger atypical lymphoid cells are seen in blastoid and pleomorphic variants. - Occasionally prolymphocytic morphology is observed	- CD5, CD19, CD20, CD79b, CD22, FMC7 and ROR1 expression is typical with expression of surface light chains; more often lambda. - A lack of CD23 and CD200 expression distinguishes from CLL.	-Classic phenotype: monotonous proliferation of small to intermediate lymphoid cells with cleaved nuclei. -Pleomorphic and blastoid forms show larger cells with a higher mitotic index (10). -Small cell variant is composed of cells like small lymphocytes -MZ-like variant has cells with abundant cytoplasm -All variants are associated with 'pink' histiocytes and hyalinised vessels. -A 'starry sky' pattern seen in blastoid and pleomorphic variants (5)	-Pan-B cell markers are expressed, including CD19, CD20, CD22, PAX5 and CD79a. - Surface immunoglobulins is expressed moderately/strongly including co-expression of IgM and IgD. -CD5 is commonly expressed, but CD5 negativity can be seen in small cell variant. - CyclinD1 expression is a constant and specific feature. -Expression of SOX11 is common, except in small cell and non-nodal leukaemic variants (11) -Usually CD23 negative, but a small % show weak expression (12) -Usually CD10 and BCL6 negative. -Usually CD200 negative; a small % of non-nodal leukaemic SOX11-negative cases can express CD200 (13) and have an indolent course. -intracellular LEF1 is usually expressed in CLL but rarely in MCL, mostly in blastoid/pleomorphic variants (14). -MUM1 (15) and plasma cell transcription factors BLIMP-1 and XBP1 can be expressed (16). - p27 expression is more frequent and stronger in blastoid and pleomorphic variants (17) -Although P53 IHC has been used as a surrogate marker for TP53 mutations, this can be unreliable and NGS remains gold standard (18,19)	-t(11;14)(q13;q32) is characteristic and results in cyclin D1 overexpression. -Rare cases that are both cyclin D1 and SOX11 negative need further evaluation for *CCND2* and *CCND3* mutation -Secondary alterations include losses of chromosomes 1p, 6q, 8p, 9p, 10p, 11q, 13 and 17p and gains 7p, 3q, 8q,12q and 18 q. -CK is seen in blastoid and pleomorphic variants. -8q24 alterations indicate a very aggressive clinical course in blastoid and pleomorphic variants.	-*ATM* is most frequently mutated (43.5%), followed by *TP53* (26.8%), *CDKN2A* (23.9%), *CCND1* (20.2%), *NSD2* (15.0%), *KMT2A* (8.9%), *S1PR1* (8.6%), and *CARD11* (8.5%). (20) -*TP53* mutations rather than deletions are associated with poor outcomes. (7,8). This may be explained by the frequent biallelic disruption in *TP53* mutated MCL in contrast to monoallelic deletions. (19,21). *NOTCH1* (22), *KMT2D* (23) and *CDKN2A* (24) mutations individually confer a worse prognosis, with *TP53* aberrations remaining an adverse prognostic predictor.

Table 1 – Diagnostic features of MCL

Abbreviations: IHC immunohistochemistry, NGS next generation sequencing, MCL, mantle cell lymphoma, CK complex karyotype, MZ marginal zone, CLL chronic lymphocytic leukaemia,

Initial clinical assessment

Patients should be assessed for B-symptoms, hepato-splenomegaly and lymphadenopathy, including Waldeyer's ring, and for neurological and GI symptoms. Eastern Co-operative Oncology Group performance status (ECOG PS) and fitness for immunochemotherapy should also be assessed and frailty identified. Blood tests should include a full blood count with blood film, biochemistry including urate and lactate dehydrogenase (LDH), and human immunodeficiency virus (HIV) and hepatitis B/C virology. Echocardiography should be considered, and fertility counselling/preservation offered.

Frailty assessments

There are no specific MCL-based assessments in MCL, and recommendations are typically extrapolated for frail diffuse large B-cell lymphoma (DLBCL) patients. Frail patients have poor outcomes if treated with intensive chemotherapy (25), making it important to identify frailty to optimise reversible problems and facilitate discussions about treatment intensity and prognosis. Formal frailty assessment tools are preferred over informal methods as they are more sensitive (25). The Geriatric 8 screening tool is a 3-5 minute screening tool for frailty (26,27). The Cumulative Illness Rating Scale for Geriatrics and the Geriatric Assessment in Haematology, a 10-15 minute tool specifically developed for haematological malignancies (28) can be considered on a case-by-case basis and within clinical trials.

Staging

Current international guidelines recommend fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography (^{18}F-FDG PET/CT) to stage FDG-avid lymphomas, including MCL (29,30) on the basis that the higher accuracy of PET/CT vs. conventional CT changes staging in ~20% (31,32). PET/CT is most accurate for detecting nodal and splenic involvement (33,34) and higher standardised uptake value (SUV) rates correspond with more aggressive variants (34,35). Although specificity remains high, PET/CT has lower and variable sensitivity for detecting extranodal involvement; a recent meta-analysis reported an average sensitivity of 36% compared to bone marrow (BM) biopsy and an average sensitivity of 39% compared to endoscopy +/- biopsy (32). The prognostic role of baseline and interim PET/CT remain uncertain (33). End of induction PET/CT assessment is associated

with improved survival outcomes for patients achieving complete metabolic response (36), including those undergoing autologous stem cell transplantation (ASCT) consolidation (33,37,38).

The BM is the most commonly involved extranodal site (50-90%) and as PET/CT has low detection rates (29), a routine BM biopsy +/- aspirate should be considered in all cases for histologic and immunohistochemical examination. This is usually sufficient to identify infiltration (39) with ancillary multi-parameter flow cytometry in cases of uncertainty (40,41). BM evaluation for minimal residual disease (MRD) assessment is evolving (42) but not yet standard practice.

Approximately 15-30% of patients have symptomatic GI involvement (43) but routine endoscopy rarely changes management (44) and should only be considered for symptomatic patients or when radiotherapy is planned pending confirmation of early-stage disease (see later section on early stage MCL). In these cases, only upper GI endoscopy should be considered on the basis that PET/CT has low concordance with endoscopy for gastric involvement but sufficiently high concordance for colorectal disease to obviate colonoscopy in asymptomatic patients (45).

CNS involvement at diagnosis is uncommon (46). Lumbar puncture with cerebrospinal fluid (CSF) analysis (cytospin and immunophenotyping) and cranio-spinal magnetic resonance imaging (MRI) are only recommended when there are concerning neurological signs or symptoms. CSF cellular morphology and immunophenotypic features are similar to peripheral tissue (Table 1). False positive results can occur from peripheral blood contamination in leukaemic MCL.

Prognostic models

Several prognostic models are described (Table 2). These models are typically validated in patients receiving first line treatment in clinical trials and should not be used clinically to influence when frontline therapy is initiated. The independently validated MCL international prognostic index (MIPI) can be readily applied. MIPI was predictive of overall survival (OS) and progression-free survival (PFS) for patients treated in the MCL2 trial (47).

A simplified version, s-MIPI, has also been described, as has a biological MIPI (MIPI-B) score which incorporates Ki-67, and the combined MIPI (MIPI-C) (48) which allocates equal weighting to MIPI and Ki67 scores. The discriminatory precision of MIPI-C appears better than the MIPI but requires validation.

Table 2 – Prognostication models in MCL

		MIPI (49)	s-MIPI (49)	MIPI-B (49)	MIPI-C (48)
Variable	Age (years)	X	X	X	X
	PS (ECOG)	X	X	X	X
	WBC (10^9/L)	X	X	X	X
	LDH (ratio to ULN)	X	X	X	X
	Ki67 (%)			X	X
Calculation		Weighted sum of 4 variables: 0.03535 x age (years) + 0.6978 (if ECOG >1) + 1.367 x $\log_{10}$ (LDH/ULN) + 0.9393 x log10 (WBC per 10^{-6})	Sum of points: Age: <50 years = 0pt; 50-59 = 1pt; 60-69 = 2pt; 70+ = 3pt) PS ECOG: 0-1 = 0pt; 2-4 = 2pt LDH (/ULN): <0.67 = 0pt; 0.67-0.99 = 1pt; 1-1.49 = 2pt; >1.50 = 3pt WBC: <6.7 = 0pt; 6.7-9.9 = 1pt; 10-14.9 = 2pt; >15.0 = 3pt	Weighted sum of 5 variables: 0.03535 x age (years) + 0.6978 (if ECOG >1) + 0.02142 x Ki67 + 1.367 x $\log_{10}$ (LDH/ULN) + 0.9393 x log10 (WBC per 10^{-6})	Calculate MIPI risk group, then stratify based on MIPI risk group and Ki67 value as shown below
Risk groups (*percentage of patients in each group in original datasets*)		Low risk = score ≤5.70 (*44%*) Intermediate risk = score 5.70-6.19 (*35%*) High risk = score ≥ 6.20 (*21%*)	Low risk = score 0-3 (*NR*) Intermediate risk = score 4-5 (*NR*) High risk = score 6-11 (*NR*)	Low risk = score <5.70 (*28%*) Intermediate risk = score 5.70-6.49 (*47%*) High risk = score ≥6.5 (*25%*)	Low risk = low-risk MIPI and Ki67 <30% (*36%*) Low intermediate risk = either low-risk MIPI and Ki67 ≥30%, or intermediate-risk MIPI and Ki67<30% (*34%*) High intermediate risk = either intermediate-risk MIPI and Ki67 ≥30%, or high-risk MIPI and Ki67<30% (*21%)* High risk = high risk MIPI and Ki67 ≥30% (*9%*)

OS	Median OS: Low risk = NR (5-year OS = 60%) Intermediate risk = 51 months High risk = 29 months	5-year OS Low risk = 81% Intermediate risk = 63% High risk = 35%	Median OS: Low risk = NR Intermediate risk = 58 months High risk = 37 months	Median OS: *European MCL Younger and Elderly cohorts:* Low risk = NR Low intermediate risk = NR High intermediate risk = 52 months High risk = 18 months *GLSG1996/GLSG2000 cohorts:* Low risk = 113 months Low intermediate risk = 59 months High intermediate risk = 38 months High risk = 22 months
Comments			Low and intermediate groups do not separate well (and nearly half of patients were in intermediate-risk group) Need to calculate Ki67 precisely by counting 200 cells at high power in 2 separate areas, not estimation (https://link.springer.com/article/10.1007/s12308-009-0036-x)	Better separation of curves than either MIPI or MIPI-B but requires validation with independent dataset

Abbreviations: MIPI Mantle cell lymphoma international prognostic index, s-MIPI simplified MIPI, MIPI-B biological MIPI, MIPI-C combined MIPI, OS overall survival, MCL, mantle cell lymphoma, LDH lactate dehydrogenase, WBC white blood count, NR not reached, ULN upper limit of normal, GLSG German low grade study group

RECOMMENDATIONS

- **Patients should undergo clinical assessment, blood tests including a FBC, blood film, routine biochemistry (including urate and LDH), Hepatitis B/C, and HIV serology (1C)**
- **Histological reporting should include formal morphological subtyping and flow cytometric/immunohistochemical phenotyping (1C)**
- **Ki67% (or equivalent) should be reported in all MCL biopsies wherever possible and reported as <30% vs ≥30% as a minimum (1B)**
- **Perform *TP53* mutational analysis in all patients at diagnosis (in preference to FISH analysis for 17p deletions) (1B)**
- **Consider *CCND2* and *CCND3* testing for Cyclin D1 negative, t11:14-negative, SOX11-positive cases which are otherwise clinico-pathologically in keeping with MCL (2B)**
- **Consider formal frailty assessment in potentially frail patients (2C)**
- **Patients should be offered fertility counselling or preservation if appropriate (1B)**

- **We recommend that patients are staged with either ^{18F}-FDG-PET/CT or CT as both are valid initial staging modalities for MCL (1B)**
- **Perform a bone marrow biopsy +/- aspirate if required for formal staging, or to investigate cytopenias pre-treatment as PET/CT has low sensitivity to detect bone marrow involvement (2B)**
- **Perform a lumbar puncture and CSF analysis with immunophenotyping in patients with clinical features suspicious for CNS involvement. Craniospinal MRI is recommended in these patients (1B)**
- **Patients should undergo pre-treatment baseline risk stratification using the MIPI or MIPI-C (1A)**

Early-stage MCL

Limited stage disease represents approximately 5% of MCL and evidence to guide practice remains limited. Localised radiotherapy (RT) is associated with high response rates and some responses appear durable (50,51). Late relapses, often at distant sites to original disease, are reported in case series where patients did not have comprehensive staging investigations, and undetected advanced stage disease at diagnosis was likely (52). If RT is considered on this basis, diagnostic gastroscopy alongside PET-CT and bone marrow biopsy should be considered prior to treatment to exclude stage IV disease.

Studies have described small cohorts of early stage MCL managed with initial observation (53,54). The numbers are too small to make definitive conclusions, but outcomes appear similar to those receiving initial therapy. For asymptomatic patients keen to avoid the potential toxicities associated with RT, adopting initial observation appears a valid option.

RECOMMENDATIONS

- **Patients with CT-based early stage MCL who are candidates for localised RT, consider more extensive staging including a PET-CT, bone marrow biopsy and gastroscopy (2B)**

- **Consider local RT (4-24 Gy) or active observation for early stage MCL (2B)**

Frontline ASCT-fit patients

For younger patients who require treatment, are deemed fit and typically <65 years of age, intensive chemotherapy induction and ASCT consolidation remains the current standard of care. Several induction regimens have been examined including alternating augmented cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) and high dose cytarabine (HDAC) (55), 3 cycles of CHOP followed by 3 cycles of DHAP (56), 6 cycles of alternating CHOP/DHAP (57) and DHAP x 4 +/- CHOP x 4 (58). No specific induction regimen is clearly superior with overall response rates (ORR) of >90% and CT-based complete response (CR) rates of >50% reported. Incorporating high dose cytarabine (HDAC) in the rituximab-containing induction has resulted in a long-term adjusted OS benefit in the MCL Younger Trial of R-CHOP (rituximab-CHOP) vs R-CHOP/R-DHAP (dexamethasone, HDAC, cisplatin) (59).

It is challenging to separate the beneficial effects of intensive induction from those of consolidation. Several phase II single arm studies evaluated ASCT consolidation after intensive induction with 4–5-year PFS rates of 56-73% and OS rates of 64-81% (55,56,60,61). In the MCL Younger trial (57), consolidation with ASCT increased the MRD-negativity rate, a validated predictor of improved survival. Although responses are durable following ASCT there is little evidence that this procedure is ‘curative’ for most patients although a small percentage of low risk (low Ki67%, low-risk MIPI) patients obtain remissions beyond 10 years and may obtain a functional cure (59). A continuing pattern of relapse with no clear survival plateau was seen in the MCL2 trial (47,62) although in low and intermediate MIPI risk groups, 40% remained in first CR at 12 years follow up. Rituximab maintenance (R-M) for 3 years post-ASCT improves PFS and OS (58). Four-year PFS and OS were 83% and 89% respectively for those receiving rituximab versus 64% and 80% in the control group (observation only) and R-M remains a recommended standard of care.

Only one prospective randomised study has compared ASCT to interferon-alpha maintenance as front-line consolidation following CHOP-based induction with or without rituximab (63). The median PFS was 39 months in the ASCT arm versus 17 months with interferon-alpha consolidation with no OS advantage demonstrated. With 14 years follow-up, there was significantly superior PFS and OS in the ASCT group, however this benefit was restricted to rituximab-naïve patients (64). Only 7% of patients had high-risk MIPI with no detail provided on patients with blastoid morphology or on *TP53* status.

There is no clearly established optimal ASCT conditioning regime with BEAM (carmustine, etoposide, cytarabine, melphalan) or BEAC (carmustine, etoposide, cytarabine, cyclophosphamide) commonly used.

The TRIANGLE study (NCT02858258) assessed whether ASCT consolidation can be safely omitted following intensive induction by including the covalent Bruton tyrosine kinase inhibitor (cBTKi) ibrutinib. Patients were randomised to ibrutinib-R-CHOP/R-DHAP followed by ASCT (arm A), ibrutinib-R-CHOP/R-DHAP followed by ASCT and ibrutinib maintenance (arm A+I) or ibrutinib-R-CHOP/R-DHAP followed by ibrutinib maintenance alone (arm I). Preliminary results (65) reported non-inferiority of arm I compared to arm A (failure-free survival 86% vs 72%, p=0.9979), suggesting that ASCT is not required when ibrutinib is used with R-CHOP during induction and for 2-years maintenance.

Patients with blastoid MCL were included in the above studies and were associated with worse outcomes, with the exception of MCL2 (47). A pooled analysis of the MCL2 and MCL3 trials demonstrated dismal outcomes for patients with *TP53* mutations receiving intensive chemo-immunotherapy induction and ASCT (7). The median PFS was only 11 months and, as such, these patients should be considered for clinical trials evaluating novel agents. International joint practice recommendations for transplantation and cellular therapies in the first line setting (66) recommend consideration of ASCT in patients with a *TP53* mutation who achieve CR or PR after induction despite recognized poor outcomes as no specific proven alternative strategy is available. They also recommend alternative consolidation strategies such as chimeric antigen receptor (CAR) T cell therapy or

allogeneic transplantation, preferably in the context of a clinical trial. The optimal approach for *TP53*-mutated disease in this setting is currently unclear.

RECOMMENDATIONS

- **Younger fit patients should receive a first-line induction regimen containing high dose cytarabine (1A)**
- **Patients obtaining an objective response to induction therapy should be offered consolidation ASCT (1B)**
- **Patients should be offered maintenance rituximab (subcutaneous or intravenous) post ASCT (1A)**
- **Consider patients with a *TP53* mutation for alternative consolidation strategies, preferably in the context of a clinical trial (2C)**
- **Offer ibrutinib during the R-CHOP component of R-CHOP/R-DHAP induction and for 2 years maintenance in place of ASCT if licensed and reimbursed in this setting (1A)**

First line treatment of MCL - unfit for transplant

The European MCL Elderly study compared R-FC (rituximab, fludarabine, cyclophosphamide) with R-CHOP in 560 previously untreated MCL over 65 years and demonstrated superiority of R-CHOP induction (median OS 6.4 years vs 3.9 years). R-M after R-FC was associated with a non-relapse mortality (NRM) of 22%, but following R-CHOP R-M delivered to progression improved the PFS from 1.9 to 5.4 years compared to interferon maintenance (67,68).

Randomised studies in indolent non-Hodgkin lymphoma (NHL) including MCL demonstrated a PFS advantage for bendamustine-rituximab (BR) compared to R-CHOP (69,70). Both studies were conducted without R-M. No PFS advantage for R-M following BR was demonstrated in a randomised study (71). However subsequent large real-world evidence supports a role for R-M following BR, with substantial improvements in OS and time-to-next-treatment in patients receiving R-M following an initial response to BR (72).

In a randomised study comparing R-M to rituximab-lenalidomide (R2) maintenance after initial R-CHOP/cytarabine-based induction, R2 resulted in a significant 2-year PFS advantage (76.6% vs 60.8%). No OS difference was observed at a median follow-up of 25.2 months and R2 was associated with increased toxicity (73). R2 is not currently licensed or reimbursed in this setting in the UK.

VRCAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisolone) improves PFS compared to R-CHOP (24.7 vs 14.4 months) but is associated with greater haematological toxicity (74). An OS benefit was subsequently reported: 90.7 vs 55.7 months (75). However, this study was conducted in a pre-R-M and pre-cBTKi era and is difficult to compare to results achieved with R-CHOP/B-R followed by R-M. VRCAP is National Institute for Health and Care Excellence (NICE) approved and represents a possible option for non-ASCT fit patients although there is currently no evidence regarding the delivery of R-M following VRCAP induction.

The addition of cytarabine to BR (R-BAC500, bendamustine 70 mg/m^2 on days 2-3, cytarabine 500 mg/m^2 on days 2-4) leads to high response rates in the first-line setting (76). Long-term follow-up demonstrated an impressive 7-year PFS of 56% and 7-year OS of 63% (77). The regimen is associated with significant infective and haematological toxicity and as such should be considered in patients either fit for ASCT but considered borderline in age e.g., 65-70 years or those aged 60-65 years and considered ineligible for ASCT. Venetoclax is being studied in combination with R-BAC in the national Italian FIL_VR-BAC study, testing the value of venetoclax consolidation and maintenance after abbreviated R-BAC in high-risk older patients with MCL, with the trial fully recruited and results currently awaited (NCT03567876).

The SHINE trial compared continuous ibrutinib (I) with placebo alongside BR and R-M. At a median follow-up of 84.7 months, BR-I demonstrated an improvement in median PFS in the ibrutinib-BR arm (80.6 vs 52.9 months) (78). No OS benefit was demonstrated (7-year OS 55% (I) vs 56.8% (placebo)). There was no clear PFS advantage seen in *TP53*-mutated or high risk MIPI subgroups. Although SHINE was designed for Ibrutinib to be delivered continuously to progression, despite long follow-up the median time on ibrutinib was only 2 years. More patients stopped Ibrutinib due to an adverse event compared to placebo (39.5% vs 24%) and more infective toxicity

was demonstrated during I-R maintenance. BR-I was also associated with more cardiac events, particularly atrial fibrillation (13.9% vs 6.5%). The combination is not currently licensed or reimbursed in the UK. Large, randomized trials comparing cBTKi combinations with immunochemotherapy are ongoing. The UK/NORDIC ENRICH trial of ibrutinib-rituximab followed by R-M and continuous ibrutinib versus RCHOP or BR followed by R-M is fully recruited and currently awaiting results. BR plus R-M with and without continuous acalabrutinib (ECHO, NCT02972840) and BR without R-M versus zanubrutinib-rituximab (MANGROVE, NCT04002297) are assessing second generation cBTKi in first-line ASCT-unfit MCL patients.

RECOMMENDATIONS

- **In patients unsuitable for high dose cytarabine-based induction and ASCT, offer R-chemotherapy combinations as current standard of care (1A)**
- **Offer R-CHOP, R-Bendamustine, R-BAC, and VR-CAP as options for previously untreated patients unsuitable for ASCT (1A)**
- **Offer rituximab maintenance post RCHOP induction (1A)**
- **Consider rituximab maintenance post R-Bendamustine induction (2B)**
- **Do not offer rituximab maintenance following R-BAC outside of a clinical trial (2A).**

Initial treatment of frail patients with MCL

Frail patients with lymphoma, including MCL, experience more treatment-related toxicity and have worse outcomes than non-frail patients. In many cases, patients may prioritise quality of life and symptom-relief over prolonging life. For patients planned to receive systemic therapy, consideration should be given to pre-phase steroids where disease burden is driving impaired performance status, as well as involving a geriatrician to optimise co-morbidities (79,80)

Cytotoxic treatment options include chlorambucil, CVP (cyclophosphamide, vincristine, prednisolone) and attenuated CHOP or bendamustine, in combination

with rituximab. Fourteen patients treated with R-chlorambucil for up to 8 months reported an ORR of 64%, CR rate of 36%, and median PFS of 15 months (81), whilst another study of 20 patients who received R-chlorambucil for a year followed by 12-months of rituximab maintenance reported a 3-year PFS of 89% (82). Both series included mainly younger patients (median 64 years) with relatively low-risk MCL.

Rampotas *et al* (83) retrospectively evaluated 95 UK MCL patients considered unfit for full-dose R-CHOP or R-bendamustine (median 79 years), who instead received R-CVP, R-Chlorambucil, attenuated R-CHOP or R-bendamustine. The median PFS was between 7.4-21.9 months, depending on the regimen used. On multivariable analysis of composite groups, patients receiving attenuated R-CHOP/R-Bendamustine experienced significantly longer PFS than those on R-CVP/R-Chlorambucil but experienced more toxicity-related hospitalisations. There was no OS difference between the treatment groups.

Non-cytotoxic approaches include ibrutinib, lenalidomide, bortezomib and rituximab monotherapy (84). Modest sized first-line phase II trials demonstrate clear efficacy of ibrutinib-rituximab (3-year PFS and OS rates of 87% and 94% respectively) (85) and lenalidomide-rituximab (5-year PFS and OS rates of 64% and 77% respectively) with durable disease control seen (86). Although these regimens may be appropriate in selected older patients with comorbidities, the trials performed were not specifically in this cohort and neither option is currently licensed nor reimbursed in the UK.

Finally, in some cases best supportive/palliative care (including radiotherapy) may be appropriate, either alongside or instead of systemic anti-cancer therapy.

RECOMMENDATIONS

- **Considered for review by a geriatrician and pre-phase steroids for frail patients with MCL (2B)**
- **Consider R-Chlorambucil, R-CVP, attenuated R-Bendamustine or attenuated R-CHOP for frail patients appropriate for cytotoxic therapy (2B)**

- **Consider best supportive/palliative care (including radiotherapy) in selected patients. (2B)**
- **Consider enrolment into prospective trials of targeted novel therapies (2C)**

Management of Indolent MCL

Indolent MCL can be defined clinically and pathologically and accounts for 10-15% of all MCL cases. Several studies suggest that these patients can initially be safely observed or receive non-intensive treatment. Non-nodal MCL typically presents with bone marrow, peripheral blood and splenic involvement, and develops from IGHV-mutated, SOX11-negative B cells. Nodal MCL can also present with small nodal volume disease with a low Ki67 proliferation index, classical histology (i.e., non-blastoid or pleomorphic) and can follow an indolent, asymptomatic course. This selected group of newly-diagnosed MCL patients may have excellent outcomes with initial observation.

The UK MCL Biobank Observational Study (87) demonstrated that 27.6% were initially observed: women more than men (40% versus 22%). ~75% continued observation at 1 year and >50% at 2 years follow up from diagnosis. Raised LDH and a high Ki-67 were more common in patients requiring upfront therapy. Numerous other studies conclude that for a carefully selected nodal and non-nodal MCL, initial observation is safe and can have excellent outcomes (88). More data are required regarding the impact of adverse genetic features such as *TP53* mutation or deletion on time-to-first-treatment.

Alternatively, recent small prospective frontline trials of ibrutinib-rituximab (89,90)and immunomodulatory agents (91) have demonstrated durable disease control in low burden disease. IMCL-2015 GELTAMO trial (90) tested the concept of MRD-driven cessation of ibrutinib-rituximab (70% stopped after 2 years treatment), and the MD Anderson examined ibrutinib to progression and observed high atrial fibrillation rate (~1/3) and discontinuation rates due toxicity (42%) (89). These therapeutic classes could be considered if available for appropriate patients, ideally in the context of a

clinical trial. In the future, MRD-based stopping rules or fixed duration therapy may be reasonably assessed in this specific patient group.

RECOMMENDATIONS

- **Consider active observation in untreated, asymptomatic MCL patients with low volume nodal disease (2B)**
- **Consider active observation in untreated, asymptomatic MCL patients presenting with isolated splenic and marrow/peripheral blood involvement (2B)**
- **Consider early intervention with non-toxic targeted therapy in the context of clinical trials (2B)**

Management at first relapse

For patients relapsing after first-line immunochemotherapy, routine use of a cBTKi is established in clinical practice and real-world data has linked this development with improved outcomes, particularly in older patients (92,93).

When patients are considered candidates for future cellular therapies, it is recommended that risk profile is assessed before starting second-line treatment. This should include a re-biopsy for histopathological subtyping, assessment of TP53 mutation status and Ki67%. Around a third of patients do not respond to second-line cBTKi and prognosis for this group is very poor (94,95). High-risk patients should be discussed with a CAR-T centre and early response assessment is recommended to minimise delay to next therapy (full details in BSH Addendum (96)). Where possible, high-risk patients should be prioritised for clinical trials. Early progression of disease (POD) following first line treatment is associated with worse outcomes on second line cBTKi as a continuum i.e., POD within 6 months < POD within 24 months < no POD24 (97). This recent data suggests survival outcomes for patients on a 2nd line cBTKi can be modelled according to a simple clinical model incorporating POD, Ki67% and MIPI at diagnosis (the ‘2L BTKi MIPI’).

The 2L BTKi MIPI identifies 3 groups with distinct 2-year PFS2, including high risk (14%), intermediate risk (50%), and low risk (64%). Time to POD, Ki67, and MIPI are associated with survival outcomes in patients with R/R MCL receiving 2L BTKis. Simple clinical models incorporating these variables may assist in planning for alternative therapies such as chimeric antigen receptor T-cell therapy, allogeneic stem cell transplantation, or novel agents with alternative mechanisms of action.

The oral cBTKis ibrutinib, acalabrutinib and zanubrutinib all have U.S. Food and Drug Administration (FDA) approval for use in relapsed, refractory (R/R) MCL (98) (Table 3). First-in-class ibrutinib demonstrated high response rates in a multiply relapsed cohort in a phase 2 study (ORR 68%, CR 21%) (99), and in a randomised controlled trial, displayed superior PFS compared to temsirolimus (median PFS 14.6 months versus 6.2 months; HR 0.43; $p<0.0001$) (100). A pooled trial analysis observed improved median PFS in patients receiving ibrutinib at first relapse, compared to later relapse (median PFS 25.4 months versus 10.3 months), supporting earlier use in the treatment algorithm (101,102). The addition of rituximab to ibrutinib has also been assessed in a small phase 2 study (103). Response rates appear improved (ORR 88%, CR 44%), but findings are limited by the small proportion of high-risk patients included.

Approval in R/R MCL for the second generation cBTKis acalabrutinib and zanubrutinib are based on phase 2 studies. Acalabrutinib achieved ORR 81% and CR 40%, and median PFS 22 months (104). Zanubrutinib achieved ORR 84% and CR 68.6% with median PFS 33 months (105). No randomised studies to date have compared efficacy and tolerability of the cBTKis in R/R MCL. Given the differences in patient characteristics and methods of response assessment across studies, it is unclear whether differences observed in ORR and CR rates are significant. Although not directly comparable with MCL, randomised studies in chronic lymphocytic leukaemia and Waldenström macroglobulinaemia comparing outcomes of ibrutinib to acalabrutinib or zanubrutinib observed improved toxicity profile for the second-generation cBTKis, with reduced rates of atrial fibrillation, hypertension, and bleeding (106–108). At present, ibrutinib is the only cBTKi approved by the European Medicines Agency (EMA).

In recent years, clinical trials and early access schemes have provided access to first-line cBTKi therapy. Management of first relapse in this setting is not established but options include use of standard immunochemotherapy. Rituximab plus bendamustine (R-B) and R-BAC have both demonstrated high response rates in phase 2 studies in non-cBTKi exposed R/R MCL patients (109,110), and bortezomib-CHOP demonstrated superiority over CHOP in cBTKi naive MCL patients at first relapse. In a phase 2 study, lenalidomide-rituximab demonstrated median PFS 11.1 months in a cBTKi-naive R/R MCL cohort and appears superior to lenalidomide monotherapy (111,112). Neither bortezomib-CHOP or lenalidomide-rituximab are reimbursed in the UK at present.

RECOMMENDATIONS

- **Patients relapsing after first line immunochemotherapy should be offered a covalent BTKi (1A).**
- **Offer ibrutinib monotherapy as an approved and reimbursed standard of care option in the UK at first relapse (1B)**
- **Where the choice of ibrutinib, acalabrutinib or zanubrutinib is available, treatment should be individualised based on the specific toxicity profile of each agent (1B).**
- **Where a covalent BTKi has been used in first line as continuous therapy, consider clinical trials or immunochemotherapy at first relapse (2B).**

Table 3. Prospective studies evaluating covalent BTKi monotherapy in R/R MCL

Treatment	Reference	Study	N	Median age, years	Median prior lines (range)	High risk MIPI	Response	Median PFS (months; 95% CI)	Key grade 3/4 adverse events >=10%
Ibrutinib	Wang et al, 2013 (99)	Phase 2	111	68	3 (1-5)	49%	ORR 68%; CR 21%	13.9 (7.0-NE)	Neutropenia 16%; thrombocytopenia 11%

Ibrutinib	Dreyling et al, 2016 (113)	Phase 3	139	67	2 (1-9)	22%	ORR 72%; CR 19%	14.6 (10.4-NE)	Neutropenia 13%
Ibrutinib	Rule et al, 2017 (101)	Pooled analysis	370	68	2 (1-9)	32%	ORR 70%; CR 27%	12.5 (9.8-16.6)	Neutropenia 17%; thrombocytopenia 12.4%; pneumonia 12.7%; anaemia 10.0%
Acalabrutinib	Wang et al, 2018 (104)	Phase 2	124	68	2 (1-2)	17%	ORR 81%, CR 40%	22 (16.6-33.3)	Neutropenia 12%; anaemia 12%
Zanubrutinib	Song et al, 2020 (105)	Phase 2	86	60.5	2 (1-4)	38.4%	ORR 83.7%; CR 77.9%	33 (19.4-NE)	Neutropenia 18.6%; infection 18.6%; pneumonia 12.8%
Zanubrutinib	Tam et al, 2021 (114)	Phase 1/2	32	70.5	1 (1-4)	31.3%	ORR 90.6%; CR 31.3%	21.1 (13.2-NE)	Infections 18.8%; anaemia 12.5%

Abbreviations: ORR overall response rate, CR complete response, NE not-evaluable, MIPI mantle cell lymphoma international prognostic index, PFS progression-free survival

Chimeric Antigen Receptor (CAR) T-cell Therapy

Brexucabtagene autoleucel (Brexu-cel), an autologous CD19-targeting CAR T-cell therapy, has been granted conditional marketing authorisation by the EMA for R/R MCL after ≥2 lines of therapy, including a cBTKi. The ZUMA-2 study reported impressive initial responses (ORR 93%, CR 67%) with 37% of evaluable patients in ongoing response at a median follow-up of 35.6 months (115,116). Significant ≥ grade 3 adverse events included cytokine release syndrome (15%), neurological events (31%) and infection (32%).

After approval by NICE in February 2021, each application for treatment in England and Wales is reviewed by the National CAR T Clinical Panel (NCCP) using uniform

eligibility criteria (Table 4). A similar system exists in Scotland. Early real-world UK experience of Brexu-cel at 3rd line suggests that efficacy and safety outcomes for those reaching infusion are comparable with ZUMA-2. However, prospective intention-to-treat (ITT) analysis highlights the challenge of disease control at cBTKi failure with a significant drop-out between NCCP approval and T-cell harvest and/or infusion (117). Our guidance proposes a risk-based surveillance strategy for potential CAR T candidates at first relapse, with the goal of identifying those at high risk of early ibrutinib failure (94,100,101,118) and capturing early refractory or progressive disease (PD) in such patients (Figure 1) (96).

High-risk patients should be discussed with a CAR T centre at first relapse and followed closely; at least 4-weekly face-to-face appointments in the first 3 months. Patients with significant constitutional symptoms showing no improvement after 4 weeks of ibrutinib should be considered for early re-imaging. All high-risk patients should have first imaging response assessment as early as 8 weeks but no later than 12 weeks. Best response of stable disease after 8 weeks of ibrutinib or any PD should prompt an urgent referral to a CAR T-cell centre (Figure 1). Earlier referral at the first sign of ibrutinib failure may mitigate some risk of drop-out, improving the accessibility of CAR T-cell therapy to such patients. Abrupt cessation of ibrutinib at this stage should be avoided due to risk of tumour flare (119). Stabilisation of disease may be required prior to T-cell harvest and where possible, bendamustine should be avoided due to its potential impact on T-cell fitness (120).

Bridging therapy (BT) is defined as any lymphoma-directed treatment delivered between T-cell harvest and lymphodepletion and may consist of chemoimmunotherapy such as R-BAC (121), radiotherapy or other targeted therapies such as non-covalent BTKis and venetoclax (alone or in combination) although these are unlicensed targeted agents in the UK. BT practice varies widely, reflective of heterogeneous patient groups, lack of published data, physician preference and geographical variation in cell turn-around times and access to novel therapies. Some retrospective analyses suggest inferior CAR T outcomes in high-grade B-NHL patients receiving BT but also demonstrate an association between the use of BT and high-risk disease features (122,123). With the goal of achieving disease control and maintaining ECOG PS prior to cell infusion, UK practice favours

BT, administered to 87% of patients with high-grade B-NHL after T-cell harvest, where a CR/PR to BT conferred a 42% reduction in PD and death following infusion (124). Likewise, markers of high-grade B-NHL activity, 3+ extra-nodal sites and inferior ECOG PS correlate with inferior survival and immediate CAR T-related toxicity post-infusion (124–128).

Extrapolating this experience to MCL, adequate disease control may be critical to improve the drop-out rate but also to optimise the chances of durable remission and improve tolerability of Brexu-cel. In real-world practice, the vast majority of MCL patients are receiving BT with poor ORRs of 22-33% (117,129,130), highlighting the need for more effective bridging strategies.

Strong predictors of long-term durable remission post CAR T-cell therapy in MCL are incompletely explored. Overall initial responses in high-risk disease appeared comparable in ZUMA-2 but small numbers preclude valid conclusions. Real-world reporting, enriched for patients with poor prognostic features, has demonstrated inferior PFS for those with high-risk disease such as high-risk sMIPI score, Ki-67 ≥50%, *TP53* aberrations, complex karyotype, and blastoid/pleomorphic morphology (117,129,130).

The largest reported real-world dataset (n=168) found age ≥65 years, ECOG PS ≥2 high-risk sMIPI, blastoid/pleomorphic morphology, bulky disease and bridging were associated with grade ≥3 ICANS (130) which remains the most significant immediate risk. Further, 20% of patients required intensive care for a median of 3 days (range 1-12), 11% required vasopressors, 3% mechanical ventilation and 2% dialysis. Of note, NRM was 9.1% at 1 year, primarily because of infections. Consideration of tolerance of such toxicities are important in selecting an appropriate patient. Nonetheless, the 12-month duration of response (DOR) and PFS of 65% and 59% respectively appear comparable to ZUMA-2 (115,116,130). Clinical studies exploring CAR T products with a more favourable toxicity profile may also be considered.

Monitoring for late effects after CAR T-cell therapy should be in accordance with EBMT guidance (131), with a particular focus on delayed cytopenia and infection. At

month 3 post Brexu-cel, persistent anaemia, thrombocytopenia and neutropenia was noted in 5%, 11% and 18%, respectively (129). Infection prophylaxis (anti-viral, anti-pneumocystis) is recommended for at least 1 year and until CD4 count >0.2 x 10^9/L (130). Immunoglobin replacement therapy is considered in select patients with secondary hypogammaglobulinaemia and repeated bacterial infections. Despite the lack of evidence and the high likelihood of lower responses, vaccination post CAR T may reduce the risk and severity of late infection (130).

RECOMMENDATIONS

- **Eligible MCL patients who are relapsed or refractory (including stable disease) after anti-CD20 antibody-containing immunochemotherapy and BTKi should be offered Brexu-cel (1A).**
- **Potential candidates for future CAR T treatment should be risk assessed at first relapse prior to initiation of a BTKi. All high-risk cases should be discussed with a CAR T-cell centre. High risk includes: blastoid/pleomorphic morphology, Ki67% >50, *TP53* mutation, high risk sMIPI, bulk >5 cm or POD24. (1B).**
- **Assessment pre-BTKi in potential candidates should include CT re-staging, sMIPI score with blood/tissue biopsy to establish morphology, Ki67% and *TP53* mutation status (if feasible) (1B).**
- **High-risk patients starting ibrutinib should have CT or PET-CT re-staging within 8-12 weeks (earlier if concern). Lack of early response with stable or progressive disease on ibrutinib should prompt an urgent referral to a CAR T-cell centre (1B).**

Table 4: NCCP eligibility criteria for Brexu-cel and organ function parameters for real-world use

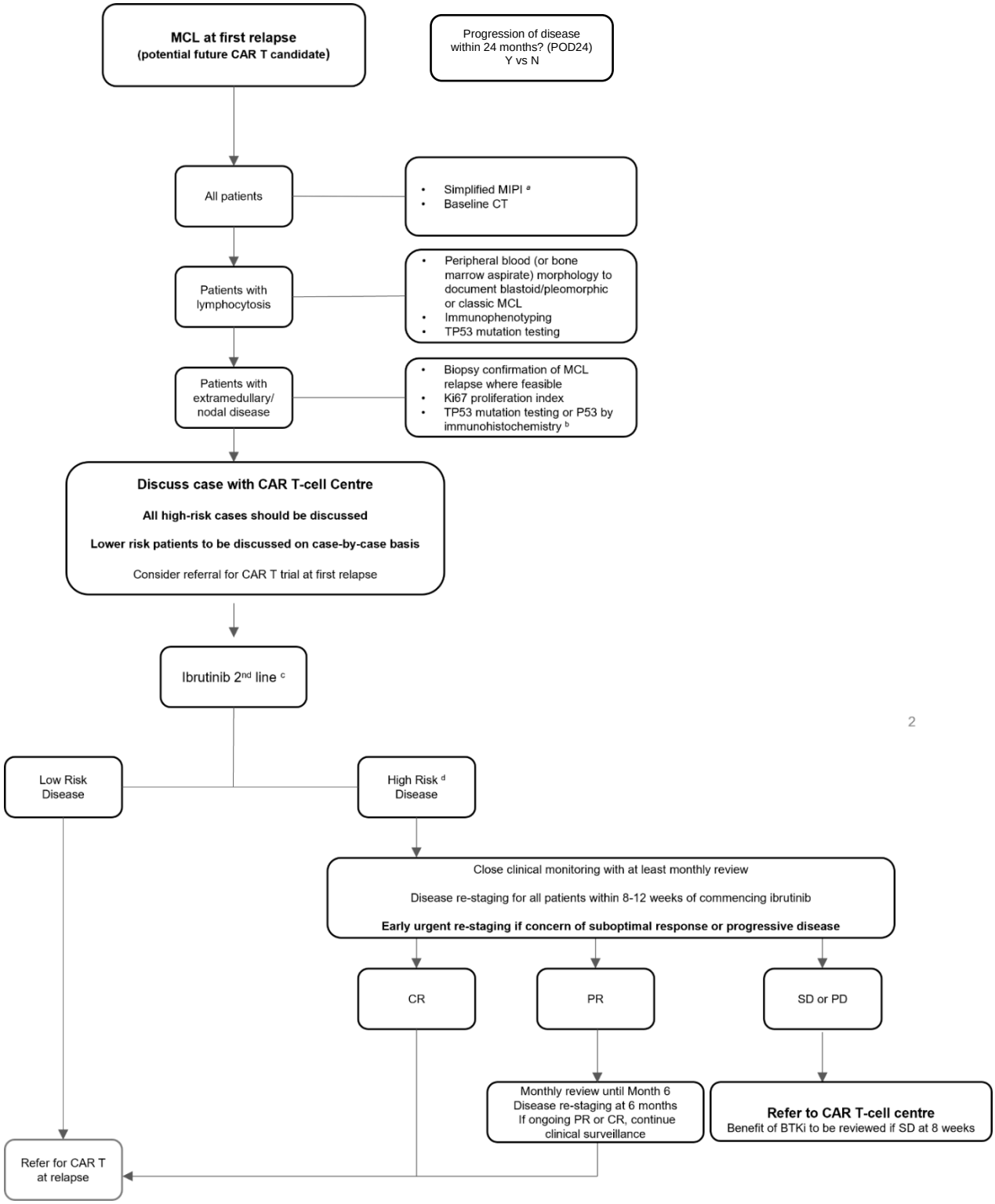
NHS England NCCP eligibility criteria		Comments
Diagnosis	MCL with t(11;14) or cyclin D1 overexpression	
Age	No upper age limit	Suitability at discretion of CAR T-cell centre
Previous Treatment	• Anthracycline or bendamustine or high-dose cytarabine-containing regimen	

	and • Anti-CD20 monoclonal antibody *and* • BTKi (ibrutinib/acalabrutinib/other BTKi)	Prior allograft is not an exclusion
Patient	• ECOG PS 0-1 at assessment (ECOG PS 2 at infusion is acceptable) • No active CNS disease • HIV/Hepatitis B/Hepatitis C negative or undetectable viral load	A prior history of MCL in the CNS is not an exclusion Medical co-morbidities at discretion of CAR T-cell centre
Organ function requirements [a]		
ZUMA-2 eligibility	**Real-world practice**	
CrCL ≥60 ml/min	>30-40 ml/min considered	Dependent on aetiology, fitness and other risk factors
EF ≥50%	EF<50% considered	Dependent on aetiology, fitness and other risk factors
Oxygen saturations >92%, no pleural effusion	Pleural effusion and ascites not an exclusion	
Bone marrow function: Platelets ≥75 $x10^9$/L Neutrophils ≥1$x10^9$/L Lymphocytes ≥0.1 $x10^9$/L	Lower acceptable, particularly if confirmed bone marrow involvement with MCL	

Abbreviations: CrCL Creatinine clearance, CNS central nervous system, MCL mantle cell lymphoma, EF Ejection fraction, ECOG PS, Eastern Cooperative Oncology Group Performance Status, CAR chimeric antigen receptor, BTKi Bruton Tyrosine Kinase inhibitor

[a] Supported by real-world Axicel CIBMTR data.

Figure 1: Proposed surveillance strategy for high-risk MCL patients commencing ibrutinib at second-line.



[a] The Simplified Mantle Cell Lymphoma International Prognostic Index (MIPI) is used to assess risk based on age, ECOG PS score, LDH level and white cell count

[b] IHC for p53 is a feasible alternative to *TP53* mutation testing where the latter is not accessible or fails. Overexpression of p53 in tumour biopsies has a high predictive accuracy for missense mutations in *TP53*.

[c] Allogeneic haematopoietic stem cell transplantation may be considered in select patients responding to 2nd line therapy. ASTCT, CIBMTR, EBMT have published clinical practice recommendations on the sequencing of cellular therapies in MCL.

[d] high risk disease is defined by blastoid/pleomorphic morphology, Ki67%>50, *TP53* mutation (including high expression by immunohistochemistry), high risk sMIPI score, bulk >5 cm or progression of disease within 24 months of 1st line (POD24)

Management options for patients who are failed by a covalent BTK inhibitor and are unfit for, or have already received CAR-T

Outcomes for patients failed by a cBTKi and following or unfit for CAR-T are dismal (132–134). Patients with poor ECOG PS may require best supportive care as real-world data suggests less than half receive further systemic therapies (135). A multitude of ongoing trials are evaluating novel therapies in this context, but no standard of care is currently recognised.

Data for immunochemotherapy is limited to small retrospective studies, the largest comprising 36 patients receiving R-BAC. ORR (83%) and CR rates (60%) were high with a modest median PFS and OS of 10.1 and 12.5 months respectively. Dose reductions related to toxicity occurred in nearly all patients over 70 years, with hospitalisation seen in 50% of the whole cohort (121).

Non-covalent BTKi (ncBTKi) target wild-type and C481-mutated B-cell malignancies following cBTKi resistance. Pirtobrutinib is the most clinically advanced ncBTKi (136). To date, 90 MCL patients with prior cBTKi exposure have been treated, with ORR of 58% and CR rate 20%. At 12 months follow-up, the median DOR among 52 responders was 22 months. Toxicities appear limited and primarily haematological, while rates of atrial fibrillation and hypertension were very low (137). An ongoing randomised phase 3 superiority study is comparing investigator choice cBTKi with pirtobrutinib at first or later relapse (138). Several other ncBTKi are under clinical development but only nemtabrutinib is actively advancing in phase 2 studies in MCL, although patient numbers are small (139).

Venetoclax is a BH3-mimetic targeting BCL2. Phase I study results reported high ORR and a PFS of 14 months in cBTKi-naïve patients (140). Retrospective studies of monotherapy in cBTKi-resistant MCL patients report PFS of 3-8 months despite most showing initial responses (141,142) . BCL2-inhibitor combinations are being applied earlier in the disease course and a new highly selective BCL2-inhibitor, BGB-11417, has moved directly to a zanubrutinib combination in phase I development (143)

Zilovertamab vedotin is an immuno-conjugate targeting ROR1, carrying the toxin monomethyl auristatin E. Of 17 patients enrolled following cBTKi, there were nine responses with a median DOR of 10.0 (0-20.3) months. Neutropenia and peripheral neuropathy were the most significant adverse events recorded (144)

Bispecific antibodies recruit T cells to tumour cells and show great promise in B-cell lymphomas (145–147). Glofitamab is under investigation specifically in MCL, using standardised step-up dosing and obinutuzumab priming. In a phase I-II study, 37 heavily pre-treated patients, 24 with prior cBTKi exposure, have been treated. At a median follow-up of 8 months, the ORR was 83.8%, CR rate was 73.0%, and median DOR 12.6 months. No patients discontinued treatment due to adverse events despite significant rates of high-grade cytokine release syndrome (148). There are limited data in MCL patients treated with the CD3-CD20 bispecifics odronextamab, mosunetuzumab and epcoritamab to date.

A retrospective study of 58 patients using lenalidomide following cBTKi report an ORR of 29% with a median DOR of 20 weeks. The safety profile was favourable, but the limited number and durability of responses means lenalidomide is uncommonly used (149). Bortezomib and temsirolimus are licensed for relapsed MCL but, due to a combination of low responses and lack of data following cBTKi failure, cannot be recommended (149,150).

RECOMMENDATIONS

- **Suggest patients relapsing on a covalent BTKi continue this until the initiation of subsequent therapy to avoid the risk of disease flare (2C).**
- **There is no standard therapeutic approach at relapse post-covalent BTKi in those ineligible or post-CAR-T. Clinical trials should be considered wherever possible. Consider an individualised approach based on co-morbidities, performance status, and available options (2B).**
- **If immunochemotherapy is considered, then R-BAC may be preferred (2B).**
- **Consider a non-covalent BTK inhibitor such as pirtobrutinib if available as an option (2B).**

The current role of allogeneic stem-cell transplantation (alloSCT)

Limited data for alloSCT in first response is available in registry and prospective trial data, and whilst low relapse rates are reported, benefits were negated by high NRM rates and graft-versus-host-disease (GVHD) (151,152). Prior to effective options for relapsed MCL becoming available, alloSCT was widely used in fit patients with a significant number achieving extended PFS, again with the caveat of high NRM and GVHD (152–157). Clinical data to support CAR T-cell therapy over alloSCT following cBTKi is not available; but international consensus is to preferentially offer CAR T-cell therapy where available, based on high response rates with CAR T-cell therapy following multiple lines of contemporary therapy, demonstrable efficacy in high-risk MCL including *TP53*-mutated, and an ability to deliver CAR T-cell therapy with active disease (158).

Data for alloSCT post-cBTKi is confined to retrospective studies of 22 patients describing a 1-year PFS of 76% and 5% NRM (159), and another of 11 patients who received alloSCT following R-BAC, also with a 1-year PFS of 76% (121). There are no published studies considering alloSCT post-CAR T-cell therapy at present. Although alloSCT is a potential option for patients failing current contemporary therapies including cBTKi and CAR-T, the numbers of eligible patients will be small due to a combination of the age of patients receiving multiple lines of therapy, cumulative treatment-related toxicities, adequate disease control and the need for a well-matched donor.

Consideration can be given to alloSCT in select eligible patients responding to BTKi, where the feasibility of CAR T is in question. Drop-out between NCCP approval and cell harvest/infusion, primarily due to progressive disease, may render CAR T inaccessible to certain high-risk candidates. However, there is insufficient data to make any recommendations on which patients may be considered. Accumulating real-world experience of CAR T and timely access to novel bridging strategies may further inform the sequencing of cell therapy in MCL.

RECOMMENDATIONS

Consider alloSCT for fit patients with an appropriate donor following immunochemotherapy, cBTKi and CAR-T failure. (2B)

Management of CNS MCL

Central nervous system (CNS) relapse of MCL is uncommon and remains incompletely studied. It typically occurs at a crude incidence of ~4% (including ~1% at diagnosis) with a median time to presentation of 15 months (46). The incidence of leptomeningeal involvement is greater than parenchymal disease (160–162). A higher risk is noted in patients with high Ki67%, blastoid histology, raised LDH, worse ECOG PS and high MIPI score (161–163). It is unclear whether CNS-penetrating agents used in systemic treatment algorithms such as high-dose cytarabine or cBTKi influence this risk. CNS MCL involvement is a common exclusion criterion within prospective clinical trials, and as such the evidence base for management is primary limited to retrospective case series. Ibrutinib is known to penetrate the CNS and a recent relatively large retrospective international series suggests that response rates and survival are superior to blood-brain-barrier penetrating immunochemotherapy (164). Little is known about the efficacy of 2nd generation cBTKi acalabrutinib, zanubrutinib or the ncBTK inhibitor pirtobrutinib in this setting.

Scant data of treatment approaches exists in patients developing CNS disease following a cBTKi. Although CAR T cells are measurable within the CNS and there are small retrospective series (165) and pilot studies (166)suggesting clear efficacy in relapsed DLBCL with CNS involvement, there is only a single case of a MCL patient with CNS disease treated with lisocel within the TRANSCEND trial to date (167). Further data with CAR T-cell therapy is needed before recommendations can be made.

RECOMMENDATIONS

- **Primary CNS prophylaxis with CNS penetrating agents in front line MCL treatment algorithms is not recommended (2C)**

- **Suggest ibrutinib for CNS relapse in patients who are previously cBTKi naïve (2C)**

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Conflict of Interest

The BSH paid the expenses incurred during the writing of this guidance. All authors have made a declaration of interests to the BSH and Task Force Chairs which may be viewed on request. None of the authors have conflicts of interest to declare.

Review Process

Members of the writing group will inform the writing group Chair if any new pertinent evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website (**https://b-s-h.org.uk/guidelines/**).

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