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POSITION PAPER

Diagnosis and management of mantle cell lymphoma: a consensus practice statement from the Australasian Lymphoma Alliance

Allison Barraclough [1], Catherine Tang,[2,3] Masa Lasica [4], Elizabeth Smyth,[5] Melita Cirillo [6,7], Howard Mutsando,[8,9] Chan Y. Cheah[5,7] and Matthew Ku [4,10]

[1]Department of Haematology, Fiona Stanley Hospital, [5]Department of Haematology, Sir Charles Gairdner Hospital, [6]Department of Haematology, Royal Perth Hospital, and [7]Medical School, University of Western Australia, Perth, Western Australia, [2]Department of Haematology, Gosford Hospital, Gosford, [3]School of Medicine and Public Health, The University of Newcastle, Newcastle, New South Wales, [4]Department of Haematology, St Vincent's Hospital Melbourne, and [10]University of Melbourne, Melbourne, Victoria, and [8]Cancer Services, Toowoomba Hospital, and [9]Toowoomba Rural Clinical School, University of Queensland, Toowoomba, Queensland, Australia

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Correspondence
Allison Barraclough, Department of Haematology, Fiona Stanley Hospital, Perth, WA, Australia.
Email: allison.barraclough@health.wa.gov.au

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Abstract

Mantle cell lymphoma (MCL) is a clinically heterogeneous B-cell neoplasm with unique clinicopathological features, accounting for 5% of all non-Hodgkin lymphoma. Although for many chemoimmunotherapy can lead to durable remissions, those with poor baseline prognostic factors, namely blastoid morphology, *TP53* aberrancy and Ki67 >30%, will have less durable responses to conventional therapies. With this in mind, clinical trials have focused on novel targeted therapies to improve outcomes. This review details the recent advances in the understanding of MCL biology and outlines the recommended diagnostic strategies and evidence-based approaches to treatment.

Introduction

Mantle cell lymphoma (MCL) is a rare B-cell lymphoproliferative neoplasm, comprising approximately 5% of all non-Hodgkin lymphoma (NHL).[1] It has unique clinical and pathological features but significant biological heterogeneity. With the intensification of chemoimmunotherapy regimens and the recent introduction of novel therapies, long-term remissions occur; however, relapses are common. This practice statement provides an evidence-based approach to the diagnosis and treatment of this rare entity in the Australasian context.

Methodology

This consensus practice statement was undertaken by a panel of lymphoma experts with particular interest in MCL under the auspices of the Australasian Lymphoma Alliance (ALA) in accordance with the ALA policy for consensus practice statement development. The authors performed a systematic review of all available literature pertaining to MCL as of January 2024. Relevant literature was selected by the expert authors following a survey of current literature and international guidelines. The statement was drafted by the authors, and guidance was developed through an iterative consensus approach to both the opinions provided and the grading of certainty. This practice statement does not represent the treatment policies of the individual institutions where the authors are employed. A summary of recommendations is shown after each section. Levels of evidence and

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grades of recommendation have been applied using the NHMRC levels of evidence[2] and are mentioned at the end of each section. Statements without grading were considered an acceptable standard clinical practice by the experts, ALA members and key stakeholders.

This guideline aims to provide an evidence base to support therapeutic decision-making within the context of individual patient circumstances and treatment goals.

Clinical Presentation

The median age of presentation of MCL is 60–65 years, with a male predominance.[3] The majority of patients present with advanced-stage disease.[4] Widespread lymphadenopathy, splenomegaly, bone marrow infiltration and circulating lymphoma cells are common at presentation.[5] Extra-nodal disease occurs frequently, particularly in the gastrointestinal (GI) tract (GIT).[6] Central nervous system (CNS) involvement is rare but recognised and typically presents later in the disease course.[5]

MCL is clinically heterogeneous, with many patients having an indolent course, where treatment can be deferred until progression to symptomatic phase, and others presenting with rapidly progressive and symptomatic disease that can be chemo-refractory.[5,7]

The indolent MCL subtype, classified as 'leukaemic non-nodal mantle cell lymphoma' (nnMCL), is characterised by peripheral blood, bone marrow and splenic involvement without significant adenopathy.[8] Typically SOX-11 negative, this entity displays IgVH hypermutation and genetic stability.[9] Unlike classical MCL, the initial management for most patients with nnMCL is observation, and time to first treatment can be exceptionally long, although a subset of patients will have a rapid disease trajectory and require early treatment.[8,10,11]

Diagnosis

The pathological diagnosis of MCL depends on excisional biopsy of the involved lymph nodes, with core biopsy less desirable but acceptable in patients with tumours anatomically inaccessible to surgical biopsy. Fine needle aspiration is insufficient to confirm a MCL diagnosis. In cases with no nodal involvement but evidence of circulating lymphoma, bone marrow biopsy or peripheral blood can be used for diagnostic purposes.

MCL is a mature B-cell neoplasm, usually composed of monomorphic small- to medium-sized lymphoid cells with irregular nuclear contours. A spectrum of morphological variants does exist, however, with small-cell, marginal zone-like, blastoid and pleomorphic patterns recognised, with the latter two displaying a more aggressive clinical phenotype.[8]

Typically, flow cytometry is positive for CD19, CD20, CD22, CD79b, CD5 and FMC and negative for CD10, CD23 and CD200. Demonstration of either t(11;14)(q13;q32) by fluorescent in situ hybridisation (FISH) and/or cyclin D1 expression by immunohistochemistry (IHC) is generally required to diagnose MCL. The t(11;14)(q13;q32) rearranges *CCND1* and *IgH*, which leads to abnormal expression of the cyclin D1 protein and contributes to the dysregulation of cell cycling. Nonetheless, a small proportion will be negative for t(11;14). Most of these cases will have *CCND2* or *CCND3* rearrangements; and in this situation, immunohistochemical SOX11 positivity can aid in diagnosis.[8,12] Assessment of proliferation rate with Ki67 is essential for prognostication, with ≥30% associated with adverse outcomes.[13]

Staging

The diagnostic work-up and staging should be done according to the Lugano classification[14] and include baseline clinical evaluation, organ function assessment and Ann Arbor staging by fluorodeoxyglucose positron emission tomography and computed tomography (PET/CT). If GI symptoms are present, endoscopic evaluation is recommended as PET/CT may not identify bowel involvement.[15,16] Cerebrospinal fluid (CSF) assessment for cytology and flow cytometry and magnetic resonance imaging (MRI) of the brain with gadolinium should be included in symptomatic patients (Table 1).

Prognostic Factors

Several prognostic factors predict outcomes in MCL. The Mantle Cell Lymphoma International Prognostic Index (MIPI) was first devised in 2008 and is a weighted summation of age, Eastern Cooperative Oncology Group performance status, lactate dehydrogenase (LDH) and white cell count.[17] Integration of the MIPI risk score with Ki67 index levels (MIPI-c) has been shown to have robust prognostic power and separates patients into four groups: low, low-intermediate, high-intermediate and high-risk with 5-year OS rates of 85%, 72%, 43% and 17% ($P < 0.001$).[13]

Pleomorphic and blastoid histology, as well as a Ki67 index ≥30%, is associated with clinically more aggressive disease and inferior overall survival (OS).[18,19] Molecular *TP53* aberrancy has a profound impact on prognosis,[21] and high P53 expression by IHC (>50%) was strongly prognostic for both inferior time-to-treatment failure and OS compared with low P53 expression (<10%).[22] Of note, *TP53* mutation carries a significantly stronger adverse prognostic impact than *del17p/TP53* deletion[21,23,24] and is associated with Ki67 >30%, blastoid

Table 1 Recommended diagnostic evaluation of mantle cell lymphoma

Baseline information	Tests required
Histological diagnosis through excisional biopsy (preferred) and bone marrow biopsy/peripheral blood if no nodal involvement	According to WHO criteria,[8] including cyclin D1 and FISH for t (11:14); Ki67 and *TP53* for prognostication
Clinical assessment	Detailed history and physical exam, age, B symptoms, ECOG and comorbidities
Staging	FDG-PET/CT, endoscopy if GI symptoms, MRI and lumbar puncture if CNS symptoms
Organ function	Laboratory tests: FBE, LDH, UEC, LFT, urate, CMP, coagulation profile, hepatitis B and C serology, HIV serology, pregnancy test in women of child-bearing potential, ECG, echocardiogram or gated cardiac blood pool scan

CMP, calcium, magnesium, phosphate; CNS, central nervous system; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; FBE, full blood examination; FDG-PET/CT, fluorodeoxyglucose positron emission tomography and computed tomography; FISH, fluorescence in situ hybridisation; GI, gastrointestinal; HIV, human immunodeficiency virus; LDH lactate dehydrogenase; LFT, liver function test; MRI, magnetic resonance imaging; UEC, urea, electrolytes, creatinine; WHO, World Health Organization.

morphology, high MIPI score and suboptimal responses to intensive immunochemotherapy.[21] An analysis of the Nordic MCL2 and MCL3 trials (upfront cytarabine-based induction followed by autologous stem cell transplant) demonstrated a median OS, PFS and time to relapse for *TP53*-mutated patients of 1.8 years, 0.9 years and 1.0 year respectively, compared with not reached, 10.2 years and 12.3 years for the *TP53*-unmutated patients ($P < 0.0001$).[21]

There is also emerging evidence that patients with MCL who experience disease progression within 24 months of frontline treatment (POD24) have poor outcomes. A recently published large dataset of patients included in clinical trials demonstrated that POD24 could be used as a surrogate for inferior OS in MCL.[25]

Additionally, although testing is not available in routine practice, several genetic aberrations, such as *SWI/SNF, NOTCH1, NOTCH2, BIRC3 and CARD11*, predict an aggressive clinical course and poor response to therapy and may guide a more targeted approach to treatment in the future.[26,27]

Minimal residual disease (MRD) monitoring is of prognostic relevance in MCL,[28–30] with evidence that MRD negativity predicts improved PFS.[31,32] Quantitative PCR (qPCR) is the main method for MRD assessment currently. Although the role for next-generation sequencing (NGS) at diagnosis is established, availability of circulating tumour DNA (ctDNA) monitoring will likely be incorporated into response assessment and MRD surveillance in the future. Testing availability is mostly limited to the research setting. Additionally, the application of MRD technology, including how best to modulate therapy in response to treatment is unclear; as such, we would recommend enrolment in clinical trials with risk-adapted MRD monitoring where available.

CNS involvement confers a dismal prognosis with a median OS from the time of CNS involvement of 3.7 (range 0.2–69.3) months.[33]

Recommendations

1 An excisional or adequate core tissue biopsy is recommended for diagnosis. Fine needle aspiration is inadequate. If there is no nodal involvement, a bone marrow biopsy or peripheral blood sample can be used. (I,A)
2 All biopsies should be reviewed by an anatomical pathologist with lymphoma expertise. (I,A)
3 For diagnostic purposes, the tumour biopsy should be sent for t(11;14) FISH analysis. (I,A)
4 Fluorodeoxyglucose positron emission tomography and computed tomography (FDG-PET/CT) is the staging modality of choice, with stage assigned by the Lugano classification.[15] (I,A)
5 Where possible, cases should be discussed in a lymphoma multidisciplinary meeting. (IV, A)
6 Endoscopic evaluation and MRI/CSF analysis are recommended for patients with GI and CNS symptoms respectively. (III,C)
7 Assessment of the Ki67 index, P53 status by IHC, *17p* deletion by FISH and *TP53* mutational status is recommended for prognostication and predicting response to conventional chemoimmunotherapy. (II,A)

Management

First-line therapy of MCL

General principles

Although the majority of patients diagnosed with MCL follow an aggressive trajectory, it is increasingly recognised that a small proportion follows an indolent course and can be safely observed. These include asymptomatic patients with low-bulk disease, absence of high-risk factors (refer to 'Prognostic factors' section) and those with the 'leukaemic nnMCL' subtype.[34] It is important to educate these patients regarding the potential benefits and risks of active surveillance. Identifying

such patients at outset remains challenging, thereby warranting close follow-up.

For patients who require treatment, clinical trials should always be considered. This is especially relevant for patients with biologically aggressive disease, in particular those with mutated *TP53* disease, as they generally have poor outcomes with conventional chemoimmunotherapy.

Early stage

Localised (Stages I–II) MCL is a rare entity with limited evidence to guide optimal management. Complete staging, including bone marrow biopsy and endoscopic evaluation for occult GI involvement, is warranted primarily if it would influence treatment decisions. Patient age, fitness, anticipated toxicity and disease bulk are important factors when determining treatment. Given the exquisite radiosensitivity of MCL, radiotherapy alone for early stage, contiguous and non-bulky disease should be considered, acknowledging this is not curative and early relapses are noted.[35–37] A large multicentre retrospective analysis from the International Lymphoma Radiation Oncology Group (ILROG) group suggests OS rates of this cohort are similar whether chemotherapy alone, chemoradiation or radiation alone are utilised.[35]

Advanced stage: suitable for intensive therapy

For patients suitable for intensive therapy, rituximab- and cytarabine-containing chemoimmunotherapy induction followed by autologous stem cell transplantation (ASCT) remains the current standard of care.[1,38] Incorporation of high-dose cytarabine to induction has been shown to increase rates of MRD negativity, which may in part explain improved progression-free survival (PFS) demonstrated in the MCL Younger study (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) $\times 6$ vs R-CHOP alternating with rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP), followed by ASCT – median PFS 9.1 vs 3.9 years, hazard ratio (HR) 0.56, $P = 0.038$).[39] Other cytarabine-containing induction approaches include rituximab, dexamethasone, cytarabine and cisplatin or oxaliplatin (R-DHAP or R-DHAOx) alone (with the addition of R-CHOP for suboptimal responses)[40] and alternating cycles of R-high-dose cytarabine with R-maxi-CHOP.[20] In a subgroup analysis of the LyMa trial, the type of platinum administered has been shown to be important, with oxaliplatin in 'R-DHAOx' demonstrating superior OS and PFS compared with cisplatin and carboplatin.[41] Although ASCT consolidation is practised commonly, there is a paucity of randomised data to support its use. One prospective study, led by the European MCL Network, demonstrated superior outcomes with ASCT over interferon maintenance following intensive induction therapy,[42] with better outcomes seen in those who attain a complete response (CR) prior to ASCT.[43] Additionally, a pooled analysis of advanced-stage MCL trials (180 patients) showed an additive effect of ASCT (and rituximab) after induction chemotherapy on response duration.[44] Unfortunately, even with intensive therapy, there appears to be a continuous pattern of relapse in the majority.[20]

Given the poor outcomes of high-risk MCL patients treated with upfront conventional chemoimmunotherapy, recent and forthcoming trials have incorporated novel agents, such as Bruton tyrosine kinase inhibitors (BTKi) and BCL-2 inhibitors, into the frontline. Strategic use of novel agents in the upfront setting and MRD-adapted risk stratification, may challenge the future role of ASCT.[45–48] In particular, outcomes following ASCT in patients with *TP53* deletion/mutation are disappointing, and the optimal management of such patients remains unclear. Multiagent biologic approaches incorporating agents such as BTKi, BCL-2 inhibitors and CD20 monoclonal antibodies[49,50] and early consideration of T-cell engaging immunotherapies[51] should be considered where available.

Maintenance rituximab (MR) has been shown to improve PFS and event-free survival (EFS) in transplant-eligible patients. In the Phase 3 LyMA trial, 240 untreated MCL patients received four cycles of R-DHAP followed by ASCT, then MR 8 weekly for 3 years. Although MR initially prolonged both PFS (82.2% vs 64.6%) and OS (88.7% vs 81.4%),[40] the extended 7-year follow-up failed to demonstrate the persistence of the OS benefit; however, the PFS/EFS advantage remained.[52]

Advanced stage: not suitable for intensive therapy

For older patients or those who are transplant ineligible, bendamustine and rituximab (BR) has been shown to be non-inferior to R-CHOP and R-cyclophosphamide, vincristine, prednisone (CVP) in the prospective BRIGHT and STiL-NHL trials with 5-year follow-up demonstrating an improved PFS for BR in a secondary end-point analysis.[53,54] Furthermore, the addition of intermediate-dose cytarabine (500 mg/m^2) to BR in the R-BAC regimen has demonstrated promising efficacy in patients over 60 years unfit for transplant. All responding patients achieved a CR (91%) with 7-year PFS and OS rates of 55% and 63% respectively. The 7-year duration of response of the 52 responding patients was 59%.[55,56] Given the increased risk of infection with bendamustine and haematological toxicity observed with the addition of cytarabine, assessment of

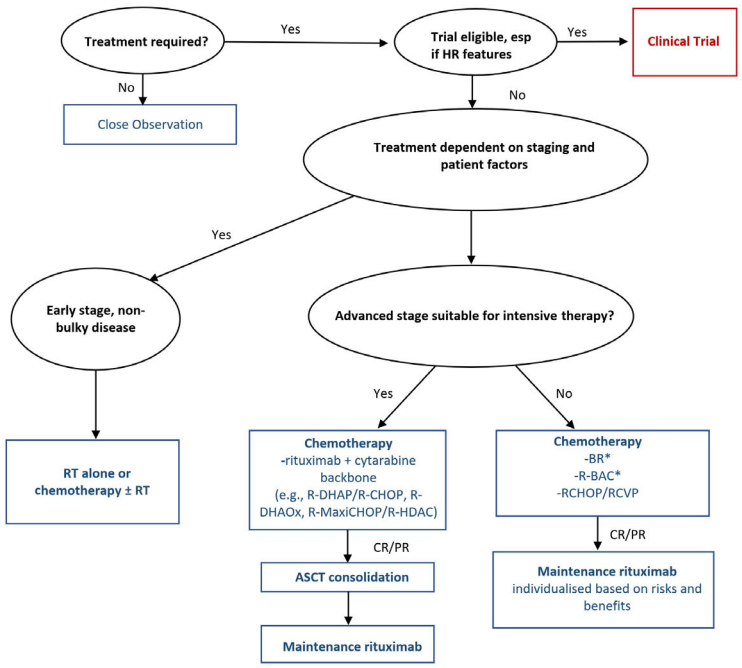
patient fitness is essential to guide treatment decisions in this cohort. Supportive medications such as antimicrobial prophylaxis and granulocyte colony-stimulating factor should also be considered in this group. Although bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisone (VR-CAP) has demonstrated an OS advantage compared with R-CHOP, use in Australia and New Zealand is hindered by lack of reimbursed bortezomib access.[57]

In the transplant-ineligible group, the MR data have been less clear. Although MR after R-CHOP significantly improved PFS and OS versus IFN[58] and PFS in a systematic meta-analysis,[59] the results after BR have been conflicting.[20,60] The Phase 2 randomised MAINTAIN trial demonstrated no improvement in the PFS or OS of 120 patients (responsive to frontline BR) with MR compared with observation only.[60] Conversely, in a retrospective analysis of MCL patients treated with BR induction therapy in the BRIGHT study, MR demonstrated improved PFS; however, maintenance treatment was not assigned on a randomised basis but was at the discretion of the investigator. Supporting this, the Flatiron US registry data showed MR after BR versus BR alone was associated with a longer time to the next treatment and OS.[61] The decision for MR in this group should be individualised and must weigh the risk of toxicity against the potential benefit.

The efficacy of incorporating targeted agents such as BTKi and BCL-2 inhibitors into frontline therapy in the transplant-ineligible population is being actively explored. The Phase 3 SHINE study examined the addition of ibrutinib to six cycles of BR followed by R-maintenance until progression/intolerability. No OS benefit was derived, but PFS improved to 80.6 versus 52.9 months (HR 0.75, $P = 0.01$), though with expected additional adverse effects from BTKi incorporation.[62] Ongoing research into the risks and benefits of novel agents is critical to inform their incorporation into the frontline management algorithm for transplant-ineligible MCL patients.[63,64]

Frail elderly patients may be offered less intensive regimens such as reduced-dose BR (50–70 mg/m^2), dose reduced R-CHOP or R-CVP, with consideration given to reducing cycles if tolerance is an issue.[65] Responses to single-agent rituximab and radioimmunotherapy are poor and therefore not recommended.[66,67]

Figure 1 depicts a suggested treatment algorithm for newly diagnosed MCL.



*For those with biologically high-risk disease, with shorter times to progression, avoidance of bendamustine-containing induction should be considered, as it may impact on T cell function for future CART therapy.

Figure 1 Treatment algorithm for newly diagnosed mantle cell lymphoma. ASCT, autologous stem cell transplant; esp, especially; HR, high risk; R-BAC rituximab bendamustine, cytarabine; R-CHOP rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CVP rituximab, cyclophosphamide, vincristine, prednisolone; R-DHAOx rituximab, dexamethasone, cytarabine, oxaliplatin; R-DHAP rituximab, dexamethasone, cytarabine, carboplatin; R-HDAC rituximab, cytarabine; RT, radiotherapy.

Recommendations

1 For patients presenting with clinically indolent disease, close observation is appropriate. (II,B)
2 For patients with confirmed early-stage MCL (Stage 1A or 2A), involved field radiotherapy, chemo-immunotherapy and combined modality treatment are all appropriate options and treatment choice should take into account patients' fitness and preference. (I,B)
3 In younger, fit patients requiring treatment, therapy with rituximab and a regimen containing high-dose cytarabine with a view to consolidative ASCT in first remission is recommended. (II,B)
4 For patients unsuitable for ASCT, R-chemotherapy is recommended, with the choice of regimen dependent on patient tolerability. (I,B)
5 For ASCT-eligible patients, MR should be considered, taking into account individual patient characteristics and preferences. (II,A)
6 For ASCT-ineligible patients, the decision to proceed with MR is recommended if R-CHOP is used as induction. After BR, the use should be based on individual patient characteristics and preferences. (II,A)

Relapsed mantle cell lymphoma

General principles

Patients should be re-biopsied at relapse to confirm histology and identify prognostic factors.[68–71] BTKi has become the cornerstone of managing relapsed and refractory MCL[72,73]; however, for those with refractory disease or early relapse, enrolment into clinical trial or utilisation of novel agents or T cell engaging cellular therapies is recommended (Fig. 2).

Covalent BTKi

With overall response rates of 77–84%, covalent BTKi, such as ibrutinib, acalabrutinib and zanubrutinib, have improved prognosis in relapsed/refractory (R/R) MCL and should be considered at first relapse.[68,72,74–78] When used in the second line, compared to subsequent lines, the median PFS and OS of ibrutinib is superior at 25.4 months versus 10.3 months and not reached versus 22.5 months respectively.[68] The choice of agent should be based on patient comorbidities and predicted toxicity. The second-generation BTKi, acalabrutinib and zanubrutinib, are notably more tolerable with fewer off-target effects such as atrial fibrillation and bleeding.[68,79–81] In addition, the recent Phase 3 SYMPATICO trial of ibrutinib and the BCL-2 inhibitor venetoclax versus ibrutinib plus placebo demonstrated improved PFS in the combination arm.[82]

Patients with high-risk features

Fit patients with high-risk features may be considered for a potentially curative allogeneic stem cell transplant (alloSCT),[24,83–87] utilising BTKi as bridging therapy if not previously exposed.

Although alloSCT is a potentially curative modality for MCL, with a 6-year PFS/OS of 46% and 53% in the relapsed setting[88] and 56% and 76% when used as frontline consolidation,[89] the non-relapse mortality (NRM) can be as high as 20%, with chronic graft versus host disease occurring in 30–60%.[87,88,90] A small series showed outcomes of alloSCT were not impacted by *TP53* status in MCL.

Relapse after BTKi

The anti-CD19 chimeric antigen receptor (CAR-T) therapy brexucabtagene autoleucel has recently been approved by the Australian Medical Services Advisory Committee (MSAC) for those with R/R MCL who have received at least two lines of therapy, including an anthracycline-, bendamustine- or cytarabine-based chemoimmunotherapy regimen that includes an anti-CD20 monoclonal antibody and a BTKi, unless the patient is considered unsuitable for treatment with a BTKi based on predicted intolerance. With a median follow-up of 3 years, this treatment has demonstrated excellent activity in R/R MCL with an objective response rate of 93%, CR rate of 67% and medians for duration of response, PFS and OS of 28.2, 25.8 and 46.6 months, respectively, in the pivotal ZUMA-2 trial,[51,91,92] 37% of evaluable patients had an ongoing response to treatment, with responses seen irrespective of high-risk features. There has been no plateau noted in the survival curves to date. Of note, in an exploratory analysis of ZUMA-2, patients with prior bendamustine exposure showed a trend towards attenuated T-cell function, with higher impact noted when bendamustine was given within 6 versus 12 months of leukapheresis.[93] For those with biologically high-risk disease, with shorter times to progression, avoidance of bendamustine-containing induction should be considered.

Although there are no clinical data to support CAR-T therapy over alloSCT, our recommendation is preferentially to utilise CAR-T post-BTKi failure, where available, due to high response rates, including those with high-risk disease and low NRM.

For patients that have relapsed after BTKi exposure and CAR-T therapy (or CAR-T ineligible), treatment options are limited and outcomes are poor, with a median OS of 4 months.[94,95] Enrolment in a clinical trial is recommended as access to novel therapies in Australia and New Zealand is limited. For those not previously

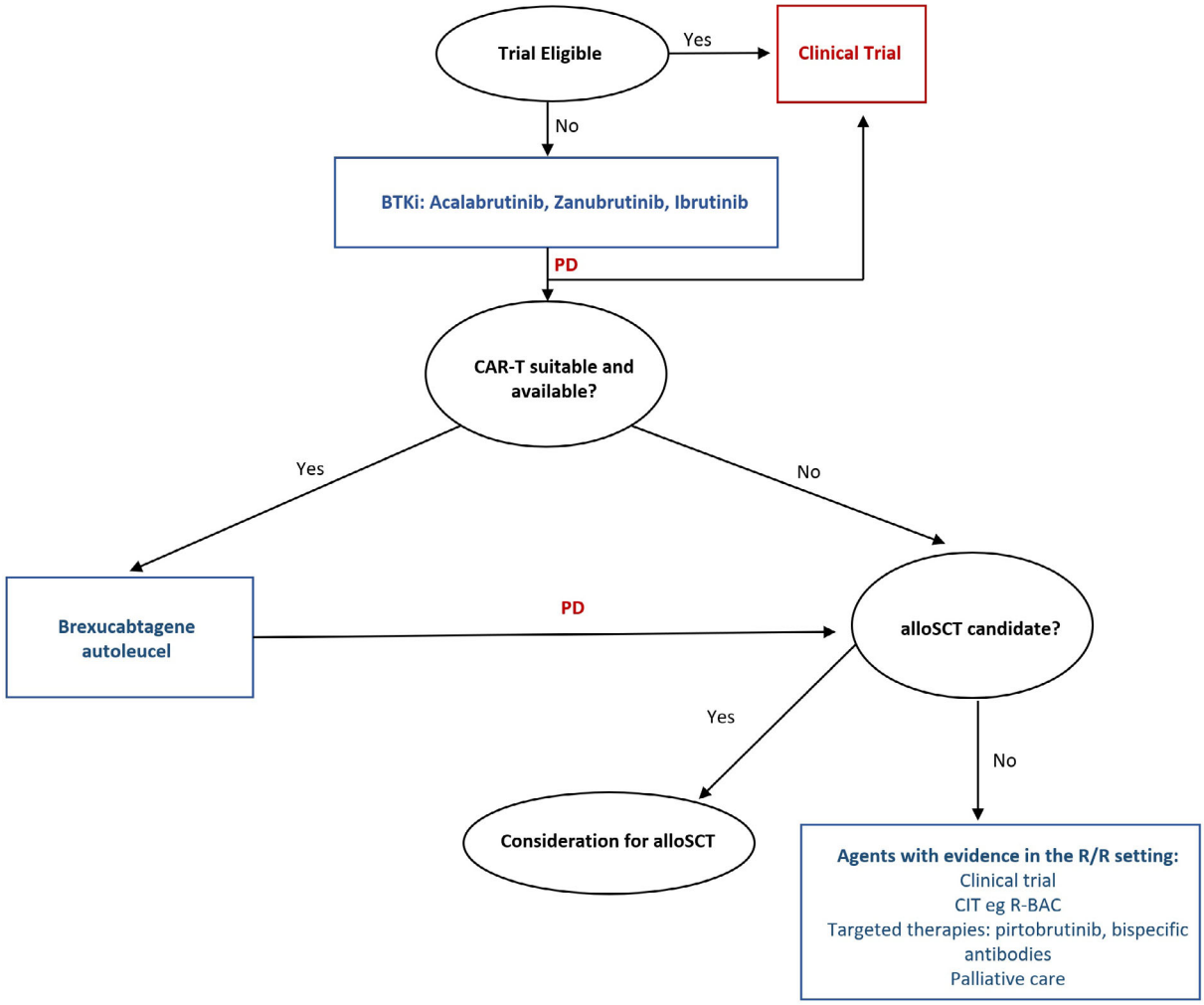


Figure 2 Treatment algorithm for relapsed/refractory (R/R) mantle cell lymphoma. alloSCT, allogeneic stem cell transplant; BTKi, Bruton tyrosine kinase inhibitors; CAR-T, chimeric antigen receptor T cell; CIT, chemoimmunotherapy; R-BAC rituximab bendamustine, cytarabine.

exposed, R-BAC is the most active chemoimmunotherapy regimen in covalent BTKi-resistant MCL.[96] Early phase trials have demonstrated impressive efficacy with the non-covalent BTKi, pirtobrutinib, as well as bispecific antibodies (glofitamab, odronextamab, mosunetuzumab, epcoritamab), and these novel agents should be accessed if possible.[97–100] Based on recent Phase 2 data, pirtobrutinib has been granted FDA approval for patients relapsing after prior BTKi therapy.[100] Newer agents, such as zilovertamab vedotin, a ROR1-targeting antibody–drug conjugate, and the BTK protein degrader BGB-16673 show promise in early-phase clinical trials.[101,102] Figure 2 depicts a suggested treatment algorithm for R/R MCL.

Recommendations

- For R/R MCL clinical trial options should be pursued where available and appropriate.
- BTKi should be considered for first relapse of MCL. (III-2,B)
- Consider consolidative AlloSCT in second remission for young, fit individuals with high-risk disease and an appropriate donor. (III-2,C)
- CAR-T therapy should be considered for eligible patients with R/R MCL. (III-2,B)
- Pirtobrutinib and bispecific antibodies have efficacy post BTKi failure. (III-2,B)

CNS disease

In those presenting with *de novo* CNS MCL (which almost exclusively occurs with concurrent systemic MCL), treatment with high-dose methotrexate therapy (≥3 g/m^2 under 60 years, ≥2 g/m^2 if over 60 years) and/or high-dose cytarabine (≥3 g/m^2) is most frequently reported.[33,103,104] Therapy is often given in combination with other agents,

including rituximab and as part of multiagent chemotherapy (e.g. hyper-CVAD), with long-term remissions mostly seen in patients who were suitable to proceed to a consolidative ASCT.[33] However, in modern treatment algorithms, ASCT is often performed in first remission, and hence, the role of ASCT in CNS relapse is less certain.

Ibrutinib, an oral BTKi, has efficacy in R/R MCL with CNS involvement, including as monotherapy in those unfit for intensive chemoimmunotherapy and after allograft.[104–106] In a large retrospective multicentre analysis, ibrutinib therapy was associated with superior OS and PFS relative to CNS-penetrating chemoimmunotherapy and, given the favourable safety profile, should be considered the therapy of choice in CNS MCL occurring in BTK inhibitor naïve patients.[105]

In those with prior BTKi exposure, the optimal treatment is unknown, but CAR-T responses with brexucabtagene autoleucel are promising[107,108] and should be prioritised if suitable and available.

The role of radiotherapy is not well studied, but whole-brain radiotherapy (alone or in combination with chemotherapy) is reported.[33,109] Palliative care, including steroids, should be considered for patients unfit for intensive therapy or where access to novel oral agents is limited.

Recommendations

- In patients with CNS MCL presenting at diagnosis, a chemoimmunotherapy regimen containing high-dose antimetabolites is preferred. (Level III-2, C)
- In patients with CNS relapse of MCL, BTKi-naïve patients should receive a BTKi. (Level III-3, C)
- In patients with CNS MCL presenting in BTKi-exposed patients, brexucabtagene autoleucel should be considered if available and clinically appropriate. (Level IV, D)

Response Assessment and Follow-Up

Following completion of induction chemo-immunotherapy, patients should be re-evaluated to confirm disease response. The end-of-treatment imaging modality of choice for response assessment is FDG-PET/CT.[110] Although interim imaging is often performed, its prognostic impact is not clear[111,112] and therefore is only recommended in the setting of concern of progression during treatment. There is no role for routine post-treatment imaging surveillance[14] and, due to the incurable nature of MCL, indefinite clinical follow-up, generally every 3–4 months initially then every 6 months, with appropriate blood tests is recommended. If there is clinical evidence of relapse, then appropriate restaging investigations, including a re-biopsy, should be performed and decisions regarding further treatment discussed with the patient.

Conclusion

MCL is a rare B-cell neoplasm that for many is incurable. Despite that, the majority of MCL patients receiving upfront combination chemoimmunotherapy have excellent long-term remissions, with consolidative autograft and MR further improving outcomes for fit individuals. Prospective clinical trials are focussing efforts to improve the duration of remission and overall outcomes, especially for those with R/R or high-risk disease, while simultaneously reducing the toxicity of subsequent treatments. The data from these trials will inform the future management direction in the foreseeable future.

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