bjh guideline

Guideline for the management of mantle cell lymphoma

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Methodology

This guideline was compiled according to the British Society for Haematology (BSH) process at www.b-s-h.org.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.

MEDLINE, EMBASE, DYNAMED, TRIP and NHS EVIDENCE were searched systematically for publications in English from 1980 to 2017 using the Keywords 'lymphoma' and 'mantle cell'. References from relevant publications were also searched. Editorials, studies with <8 cases and letters were excluded. Conference abstracts have been included if deemed to be of particular relevance.

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 BSH. It was also placed on the members section of the BSH website for comment and has also been reviewed by patient representatives identified by the Lymphoma Association; these organisations do not necessarily approve or endorse the contents.

The aim is to provide healthcare professionals with guidance on the management of patients with mantle cell lymphoma (MCL). Individual patient circumstances may dictate an alternative approach. This is an update of the guidance published in 2012 (McKay *et al*, 2012), incorporating new therapeutic options, including transplant data. Developments in pathology, in particular molecular pathology and use of positron emission tomography/computed tomography (PET/CT) scanning in staging and response assessment are now covered in a separate Good Practice Paper (McKay *et al*, 2018).

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Introduction

Mantle cell lymphoma (MCL) is a B cell malignancy with unique biological, pathological and clinical features comprising 3–10% of all non-Hodgkin lymphomas (NHLs) (Swerdlow *et al*, 1983). It was recognised as a specific entity in the revised European-American classification of lymphoid neoplasms (REAL) classification (Harris *et al*, 1994) and is characterized by the chromosomal translocation t(11;14)(q13·3; q32·33), resulting in over-expression of the cell cycle protein cyclin D1 (Akiyama *et al*, 1994; Campo *et al*, 1999).

MCL arises mainly in older adults (median age 60–65 years) with a male predominance (Argatoff *et al*, 1997; Bosch *et al*, 1998). It often has the worst features of both high- and low-grade NHL; an aggressive clinical course, but with a pattern of resistant and relapsing disease, rendering it incurable with standard therapy. Historically, median survival was 4–5 years (Herrmann *et al*, 2009) however this is now in the order of 8–12 years in younger fitter patients who are able to tolerate modern intensive therapies (Eskelund *et al*, 2016; Hermine *et al*, 2016).

The clinical presentation of MCL is well described (Zucca *et al*, 1995; Argatoff *et al*, 1997; Bosch *et al*, 1998; Tiemann *et al*, 2005). The majority (>90%) of patients present with advanced stage disease. Lymphadenopathy is generally widespread at diagnosis. Splenomegaly, bone marrow infiltration and peripheral blood involvement are common. Bulk disease at diagnosis and B symptoms are less common. Extranodal involvement is frequent, particularly affecting the gastrointestinal (GI) tract (Romaguera *et al*, 2003) and liver, but infiltration of breast, lung, skin, soft tissue, salivary gland and orbit are also seen. Involvement of more than two extranodal sites occurs in 30–50% of patients (Jares & Campo, 2008). Spread to the central nervous system (CNS) can occur, but this is rare at diagnosis.

The clinical course is heterogeneous. Presentation can correlate with pathological sub-type; patients with blastoid histology often have an aggressive clinical course, show refractoriness to treatment and have short survival. In

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contrast, some cases present with more indolent disease (Eve *et al*, 2009a; Martin *et al*, 2009) characterized by splenomegaly, peripheral blood lymphocytosis, little or no nodal disease (Nodit *et al*, 2003; Orchard *et al*, 2003) and survival of the order of 5–12 years. The entity of MCL *in situ* is now recognized, indicating early foci of disease in otherwise reactive nodes in asymptomatic patients (Carvajal-Cuenca *et al*, 2012).

CNS disease

CNS relapse rates of 4·1–7·8% are reported, with high Ki67 and blastoid histology identified as risk factors in multivariate analysis (Conconi *et al*, 2013; Chihara *et al*, 2015; Cheah *et al*, 2016). CNS relapse tends to occur early (median 15–20 months) and survival is poor (3–8 months). A high incidence of leptomeningeal disease (91% by flow cytometry) has been reported (Cheah *et al*, 2013) with parenchymal disease being uncommon (12% of cases).

Diagnosis, Initial Investigations, Staging and Prognostic Scores – please refer to the Good Practice Paper (McKay *et al*, 2018).

Management (for therapeutic algorithm, see Fig 1)

Patients should be offered a clinical trial if available.

Assessment of performance status (PS) using the Eastern Cooperative Oncology Group (ECOG) performance status tool is recommended.

Geriatric tools, such as the Cumulative Illness Rating Scale (CIRS) and activities of daily living (ADL) assessment may be useful in elderly patients with lymphoma (Nabhan *et al*, 2012).

First-line management

Early stage MCL

A minority of patients present with localised (stage 1A and 2A) MCL. Evidence for management of this group is scarce. Involved field radiotherapy may result in good responses with 64–80% complete remission (CR) and long-term remission, with possible cure in some patients (Vandenberghe *et al*, 1997; Rosenbluth & Yahalom, 2006). If early-stage disease is suspected, staging should be confirmed with bone marrow examination and gastro-intestinal investigations. The role of (^{18}F) Fluorodeoxyglucose (FDG)-PET in early stage MCL remains unproven but may be considered if radical radiotherapy is being proposed – please refer to the Good Practice Paper (McKay *et al*, 2018).

Advanced stage MCL

The majority of patients require treatment at diagnosis but a small subgroup of patients, often with leukaemic presentation ± splenomegaly, have more indolent disease. Some patients presenting with widespread low volume lymphadenopathy may also run an indolent course. A watch and wait approach is reasonable in well patients with leukaemic presentation ± splenomegaly and in elderly, asymptomatic patients with advanced stage disease. It is not clear whether early treatment of young, asymptomatic patients with advanced stage disease alters long term outcome. A retrospective study of 97 patients demonstrated that for 30% of cases managed initially by observation, treatment was deferred for a median of 12 months (range 4–128) with acceptable outcomes (Martin *et al*, 2009). We advise careful assessment of the individual patient. Indications for treatment include:

- Bulky symptomatic lymphadenopathy
- B symptoms
- Symptomatic organomegaly
- GI symptoms, including bleeding
- Bone marrow failure

Once treatment is deemed necessary, choice of regimen will depend on age, co-morbidities, performance status and the aim of therapy. Distinction should be made between young fit patients suitable for autologous peripheral blood stem cell transplantation (ASCT), and those for whom this is not appropriate. For those where the aim is to proceed to high dose therapy (HDT) and ASCT in first remission, intensive chemotherapy should be given with the aim of obtaining a complete response.

Rituximab has less activity in MCL than in follicular or diffuse large B cell lymphoma. Rituximab monotherapy, although well tolerated, is not recommended, having been shown in several trials to have only modest activity (Foran *et al*, 2000; Ghielmini *et al*, 2005; Weigert *et al*, 2007). Addition of rituximab to chemotherapy, however, improves responses, including CR rate (Howard *et al*, 2002; Lenz *et al*, 2005; Schulz *et al*, 2007). A recently published phase III randomised trial (Rule *et al*, 2016) confirms survival benefit when rituximab is combined with chemotherapy in first line treatment.

Patients fit for autologous stem cell transplant. CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) (or CHOP + rituximab – R-CHOP) is not as efficacious as more intensive regimens for achieving maximal response prior to transplantation (Lefrere *et al*, 2002; Andersen *et al*, 2003; Dreyling *et al*, 2005). There is increasing awareness of the efficacy of cytarabine in MCL, with excellent responses, overall response rate (ORR) and CR rate, when incorporated into first line regimens. Most studies have shown an ORR of >90% and CR rate of >50%.

High-dose cytarabine was first utilized in MCL as part of the dose-intense hyperCVAD regimen (hyperfractionated cyclophosphamide, vincristine,doxorubicin, dexamentasone + methotrexate and cytarabine)with good results in single-arm,

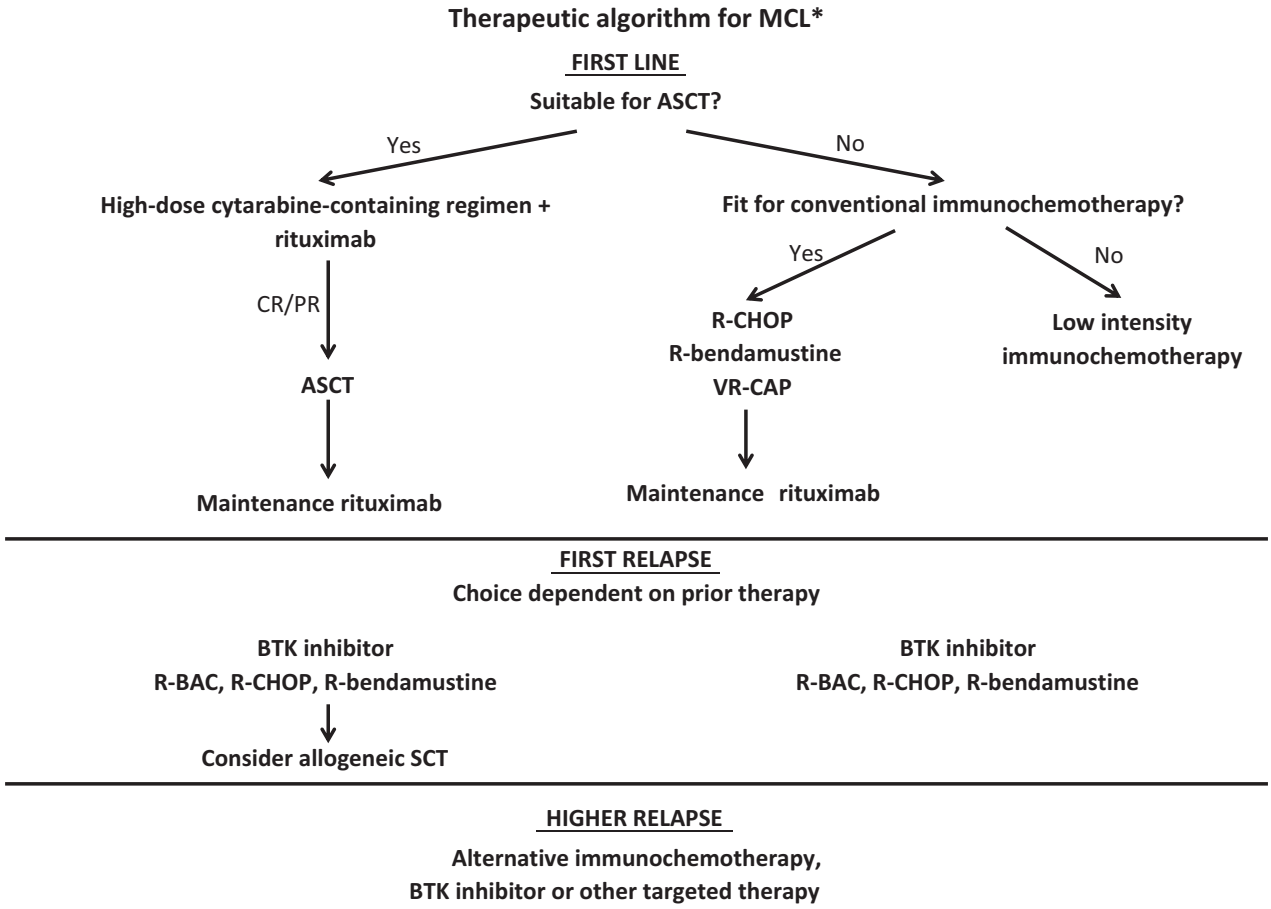

Fig 1. Therapeutic algorithm for mantle cell lymphoma. ASCT, autologous stem cell transplantation; BTK, Bruton tyrosine kinase; CR, complete response; MCL, mantle cell lymphoma; PR, partial response; R, rituximab; R-BAC, rituximab, bendamustine, cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; SCT, stem cell transplantation; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone. *Patients with Stage 1A–2A disease may be suitable for radiotherapy Asymptomatic patient with advanced stage indolent disease may have a period of observation Patients should be offered a clinical trial if available.

single-centre settings (Khouri *et al*, 1998). Addition of rituximab gave CR rates of 87–92% (Ritchie *et al*, 2007; Romaguera *et al*, 2010); remissions appeared durable, even without consolidation with ASCT. The main concern with rituximab + hyperCVAD (R-hyperCVAD) is acute marrow toxicity and infectious complications, and a long-term 5% risk of myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML). Two multi-centre studies (Merli *et al*, 2012; Bernstein *et al*, 2013) concluded that while R-hyperCVAD is an active regimen for first-line therapy in MCL, it is difficult to deliver, with almost 40% of patients unable to complete the planned treatment schedule. As a result, hyperCVAD-like regimens are not recommended as a first line approach.

High-dose cytarabine was subsequently incorporated into other combination chemotherapies. In the Nordic MCL2 study (Geisler *et al*, 2008), excellent results were achieved with a cytarabine-containing intensive induction immunochemotherapy regimen followed by ASCT: Patients received three cycles of augmented CHOP alternating with 3 cycles of high-dose cytarabine. Rituximab was given from cycle 4 onwards with an additional dose given as *in vivo* purging prior to stem-cell mobilization. Event-free survival (EFS) at 5 years was >60%, suggesting possible cure, but two updates of this study (Geisler *et al*, 2012; Eskelund *et al*, 2016) have shown a continuous pattern of relapse and no plateau in the survival curve despite very durable responses. Notably, in the low and intermediate risk groups, 40% of patients were still in first remission at 12 years.

In a phase 2 Groupe d' Etude des Lymphomes de l' Adulte (GELA, now known as the Lymphoma Study Association [LYSA]) trial (Delarue *et al*, 2013), cytarabine and rituximab were incorporated into induction before ASCT. Treatment comprised 3 cycles CHOP(21) with rituximab included in cycle 3, and 3 cycles of R-DHAP (rituximab + dexamethasone, high dose cytarabine, cisplatin). Responding patients were eligible for ASCT. ORR was 93% after R-CHOP and 95% after R-DHAP with more CRs on completion of R-DHAP (57% vs. 12%). Median EFS was 83 months and median overall survival (OS) was not reached at median follow-up 67 months. Five-year OS was 75%.

The 'MCL Younger' study evaluated use of a high-dose cytarabine- containing ASCT conditioning regimen after induction treatment with alternating courses of R-CHOP and R-DHAP (cytarabine group), compared to 6× R-CHOP and conventional, cyclophosphamide/total body irradiation (TBI), myeloablative conditioning prior to ASCT (control group). After median follow-up of 6·1 years, time to treatment failure was significantly longer in the cytarabine group (9·1 vs. 3·9 years) (Hermine *et al*, 2016).

In the phase 3 LyMa trial (Le Gouill *et al*, 2017), 299 patients received 4 cycles of R-DHAP, with 4 cycles R-CHOP if not in CR/partial remission (PR) as induction therapy prior to ASCT with R-BEAM (rituximab + carmustine, etoposide, cytarabine, melphalan) conditioning, and randomization to rituximab maintenance or not. Following induction therapy, ORR was 94% (CR/CRu 77%). At a median follow-up of 54·4 months, median PFS and OS were not reached, with a 4 years PFS and OS of 67·8% and 78% respectively.

A phase 2 study (Armand *et al*, 2016) tested induction with 3 cycles of R-bendamustine followed by 3 cycles of R-high dose cytarabine in 23 transplant-eligible patients. CR/unconfirmed CR (CRu) rate was 96%. Of 15 minimal residual disease (MRD)-evaluable patients, 93% achieved MRD negativity. PFS was 96% at median follow-up of 13 months. Toxicity was mainly haematological and was more common after R-high dose cytarabine, but overall the regimen was well tolerated.

Despite increasing response rate and response quality, duration of response with chemoimmunotherapy alone remains disappointing. There is, therefore, an increasing tendency to consolidate with high dose therapy and peripheral blood stem cell transplantation in younger patients. This has been shown to increase EFS, and possibly OS, and is discussed further in the transplant section below.

The optimal approach to therapy of blastoid variant MCL has not been determined, with no studies specifically designed for this subtype. Blastoid variant MCL patients have, however, been included in most of the studies reported above: many have identified blastoid morphology as a poor prognostic factor with early relapses and short survival (Shrestha *et al*, 2015). More durable responses in patients treated with intensive up front therapy, including R-hyperC-VAD (Romaguera *et al*, 2010), have been reported, and those consolidating primary therapy using ASCT (Damon *et al*, 2009; Gressin *et al*, 2010; Geisler *et al*, 2012).

Conventional chemotherapy for patients unfit for high-dose regimens

The majority of MCL patients are elderly and high-dose therapy is not feasible. For this group, there is no gold-standard therapy, and it is difficult to recommend a specific regimen. Historically, MCL was grouped with low grade lymphomas in clinical studies and treated with regimens including CVP (cyclophosphamide, vincristine, prednisolone) (Meusers *et al*, 1989; Teodorovic *et al*, 1995; Unterhalt *et al*, 1996), fludarabine combinations (Cohen *et al*, 2001) and CHOP (Meusers *et al*, 1989; Lenz *et al*, 2005; Nickenig *et al*, 2006). Most studies included only small numbers of patients. The general pattern was of reasonable ORR (60–88%), but short progression-free interval (PFI) (7–21 months) and poor OS (40–85% at 2 years). No particular combination appeared superior in terms of OS. In particular, the addition of anthracycline in the only randomized controlled trial (RCT) (Meusers *et al*, 1989) did not confer survival benefit. Despite this being confirmed in other studies (Bosch *et al*, 1998; Weisenburger *et al*, 2000) CHOP (+R) remains a widely used chemotherapy regimen and forms the control arm in many randomized studies.

The efficacy of purine analogues in MCL has been studied in the front-line setting, with mixed results. When used as a single agent, ORRs of around 30% are seen (Ghielmini *et al*, 2005; Grillo-Lopez, 2005). However, when used in combination with cytotoxic agents, such as idarubicin or cyclophosphamide, response rates increase to approximately 60% (Zinzani *et al*, 1999, 2000; Cohen *et al*, 2001). In addition to the significant haematological and immunological toxicity of purine analogues, their use may preclude stem-cell mobilization (Dreyling & Hiddemann, 2008; Eve *et al*, 2009b).The European MCL Consortium compared 6 cycles of R-FC (rituximab with fludarabine and cyclophosphamide) to 8 cycles of R-CHOP (Kluin-Nelemans *et al*, 2012). Responding patients underwent a second randomization to maintenance treatment with either rituximab or interferon alfa, which was continued until disease progression. Complete response rates were similar (R-FC 40%, R-CHOP 34%), but R-FC was associated with more frequent disease progression (14% vs. 5%) and shortened OS at 4 years (47% vs. 62%, $P = 0{\cdot}005$). The R-FC regimen was associated with significantly more toxicity (also demonstrated in the study by Rule *et al* (2016)) and is therefore no longer recommended as first line therapy for elderly patients with MCL.

Bendamustine has efficacy in MCL (Rummel *et al*, 2005; Herold *et al*, 2006) and having a favourable toxicity profile compared to CHOP may have an increasing role in treatment. The combination bendamustine and rituximab (BR) demonstrated an ORR of 75% (CR 50%) in the study by Rummel *et al* (2005). In the BRIGHT study, a randomized global non-inferiority phase 3 study in indolent lymphomas, including MCL (Flinn *et al*, 2014), BR was non-inferior to R-CHOP or R-CVP with ORR 97% (CR 31%) for BR and 91% (CR 25%) for R-CHOP/R-CVP. Another phase 3 non-inferiority multicentre study by the StiL group (Rummel *et al*, 2013) compared BR with R-CHOP as first line treatment for patients with indolent and mantle cell lymphomas, reporting improved PFS in the BR group (69·5 vs. 31·2 months) at a median follow-up of 45 months. BR was associated with less alopecia, haematological toxicity, infections and peripheral neuropathy, although skin reactions were more common.

In a phase 3 trial (Robak *et al*, 2015), 487 patients with untreated MCL ineligible for ASCT, were randomized to

receive 6–8 cycles of R-CHOP or VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone) where bortezomib was substituted for vincristine in the R-CHOP regimen and given at a dose of 1·3 mg/m^2 on days 1, 4, 8 and 11. VR-CAP improved PFS (24·7 vs. 14·4 months), CR rate (53% vs. 42%) and 4-year OS (64% vs. 54%) but haematological toxicity was increased. This study showed surprisingly poor PFS in the R-CHOP control arm compared to historical data and considering the tolerability of BR in the BRIGHT and StiL studies, BR appears to be an attractive option for elderly patients.

The Groupe Ouest Est d'Etude des Leucémies et Autres Maladies du Sang (GOELAMS) evaluated the RiPAD+C (rituximab, bortezomib, doxorubicin, dexamethasone and chlorambucil) regimen in a phase 2 study of 39 patients, median age 72 years (Houot *et al*, 2012). After 6 cycles, ORR was 74% with 59% CR. Median PFS was 26 months, median OS not reached. The intravenous delivery of bortezomib may have contributed to the high incidence of grade 3 neurotoxicity.

Use of cytarabine in the treatment of older MCL patients is less well established. Visco *et al* (2013) used a combination of rituximab, bendamustine and cytarabine (R-BAC) in a phase 2 study of 20 treatment-naive patients aged >65 years. At a cytarabine dose of 800 mg/m^2 (the maximum tolerated dose established in phase 1of the study), the main toxicity was transient grade 3–4 thrombocytopenia (87%) with febrile neutropenia occurring in 12%. ORR was 100% (95% complete response) with a 2-year PFS of 95%. A dose adjusted R-BAC regimen with cytarabine dose 500 mg/m^2 was better tolerated, with less haematological toxicity. Final results of the phase 2 study (Visco *et al*, 2017) showed CR of 91% with 2-year PFS and OS of 81% and 86%, respectively. The R-BAC combination therefore has considerable potential but results need to be substantiated in larger studies.

Radio-immunotherapy has been added to R-CHOP in an attempt to improve outcome. In a phase 2 study (Smith *et al*, 2012), 56 patients aged >18 years, median age 60 years, received 4 cycles of R-CHOP followed by consolidation with yttrium-90-ibritumomab tiuxetan. ORR was 82% (55% CR/CRu) and median time to treatment failure was 34·2 months (median follow-up 72 months). Estimated 5-year OS was 73%. The regimen was well tolerated with results comparing favourably with historical R-CHOP alone.

Other reported regimens for elderly patients include rituximab combined with chlorambucil (Bauwens *et al*, 2005; Sachanas *et al*, 2011) or cladribine (Spurgeon *et al*, 2011) with overall response rates of 60 to 90%.

CNS prophylaxis. The ability of CNS-penetrating therapies to reduce the incidence of CNS relapse is unclear, with conflicting results reported (Cheah *et al*, 2013; Conconi *et al*, 2013; Chihara *et al*, 2015). It is not possible to give clear recommendations on CNS prophylaxis. Empirical use of CNS-penetrating chemotherapy may be beneficial in patients with high Ki67 and/or blastoid morphology.

Maintenance rituximab. In some studies, R-chemotherapy followed by rituximab maintenance has prolonged duration of response but not OS (Forstpointner *et al*, 2006; Kahl *et al*, 2006). In others, such as the European MCL Network Study, MCL Elderly Study (Kluin-Nelemans *et al*, 2012) a survival benefit was demonstrated: Here, in addition to reducing the risk of progression or death by 45%, 58% of patients receiving maintenance rituximab were in remission after 4 years compared with 29% of patients receiving interferon alfa. Patients who responded well to R-CHOP induction had significantly improved OS after maintenance rituximab (87% in CR vs. 63% in PR patients). In a subgroup analysis of the StiLNHL7-2008 MAINTAIN trial, maintenance rituximab every 2 months for 2 years conferred no additional benefit (PFS and OS) compared to observation alone in patients treated with BR (Rummel *et al*, 2016; abstract 7503. A meta-analysis of 3 large randomized clinical trials demonstrated improved PFS but not OS with rituximab maintenance (Vidal *et al*, 2014). Maintenance rituximab is included as standard in many current clinical trials and despite the lack of definitive evidence, akin to follicular lymphoma, we recommend maintenance rituximab in patients responding (CR or PR) to R-chemotherapy and who are not proceeding to ASCT as well as in the post-ASCT setting (discussed later). It is difficult to recommend an optimum duration of maintenance therapy. In the European MCL Network Study, MCL Elderly Study (Kluin-Nelemans *et al*, 2012), treatment was continued until disease progression; however many institutions limit duration to 2 years. It is therefore advised that duration should be in accordance with local regulatory approvals. In the post-transplant setting, duration should be for 3 years (Le Gouill *et al*, 2017).

Assessment of treatment response

Treatment response in MCL is assessed using conventional CT scanning (Cheson *et al*, 2007). As mentioned in the Good Practice Paper (McKay *et al*, 2018) the role of FDG-PET imaging in MCL is not established. There is increasing evidence that end of treatment (EOT) PET/CT scan has prognostic significance (Mato *et al*, 2012; Kolstad *et al*, 2014) however as this does not affect management decisions, we do not recommend a routine EOT PET/CT scan at present unless in the context of a clinical trial.

Although minimal residual disease (MRD) monitoring (using quantitative polymerase chain reaction for the t (11;14) translocation) has been shown to have predictive value, particularly following ASCT (Hoster & Pott, 2016), the methodology is not widely available at the present time and the clinical benefit unclear.

Recommendations

- **When considering how to treat mantle cell lymphoma (MCL), clinical presentation (with recognition of the "indolent" form), proliferation index, clinical risk scores**

(simplified MCL international prognostic index [sMIPI] and combined MCL international prognostic index [MIPI-c]) and performance status, should be taken into account. (1B)

- **For patients with confirmed early-stage MCL (stage 1A or 2A), involved field radiotherapy is recommended. (1B)**
- **For patients presenting with indolent disease, a period of observation may be appropriate, prior to initiation of definitive therapy. (2B)**
- **Addition of rituximab (R) to combination chemotherapy regimens improves outcomes. Rituximab should therefore be included in the first line chemotherapy regime in the treatment of MCL. (1B)**
- **Patients who are unsuitable for autologous stem cell transplantation (ASCT) should receive R-chemotherapy. The best outcome data is for R-CHOP (rituximab + cyclophosphamide, doxorubicin, vincristine, prednisolone) followed by maintenance rituximab,however R-bendamustine is efficacious and has a more favourable side effect profile (1B)**
- **Younger, fit patients should receive rituximab with a regimen containing high dose cytarabine with a view to proceeding to ASCT in first remission. (1B)**
- **Single agent rituximab is not recommended. (1A)**
- **Maintenance rituximab therapy is recommended in patients achieving a response (complete or partial) following R-chemotherapy who are not proceeding to autograft. (1B)**
- **Treatment response should be assessed using conventional computed tomography (CT) scanning. (^{18}F) Fluorodeoxyglucose positron emission tomography (FDG-PET) imaging and assessment of minimal residual disease (MRD) status are not currently recommended outside a clinical trial. (1B)**

Management, second line and beyond

Excluding transplant-eligible patients, median survival after first relapse of MCL is 1–2 years. There is no standard second line chemotherapeutic regimen. Treatments generally produce fewer CRs and duration of response is shorter than following initial therapy, being of the order of 9 months for second and subsequent treatments. Many publications have examined therapeutic regimens in relapsed lymphoma, including patients with MCL. Most are single arm studies, containing fewer than 15 cases, thereby limiting the conclusions that can be drawn. Additionally, inclusion/exclusion criteria of the various relapse studies are different, making it impossible to comment on comparative efficacy.

Transplant

Where the patient has not received ASCT as part of first-line therapy but is considered fit for such therapy at relapse, consideration of consolidation of second response with ASCT is a clinical option. In young patients who have previously undergone ASCT, assessment of fitness for an allogeneic procedure (alloSCT) should be made. If the patient is sufficiently fit, the aim should be to obtain a response with second-line therapy and consolidate with transplantation. This usually involves use of standard salvage regimens as applied in the context of aggressive lymphomas. With the advent of the oral Bruton tyrosine kinase (BTK) inhibitor, ibrutinib, however, an alternative salvage option exists; ibrutinib is highly active in the majority of relapsed MCL patients, and the duration of response provides a window to plan and perform the allograft procedure.

The majority of relapsed MCL patients will not be eligible for ASCT or alloSCT. Choice of therapy will be influenced by age, performance status, co-morbidities and initial therapy. It is logical that, where a patient has received one prior line of treatment, a different agent be chosen at relapse.

Role of rituximab

Based on the only randomised trial demonstrating survival benefit (Forstpointner *et al*, 2004), combination chemotherapy is usually given with rituximab in relapsed MCL The role of maintenance rituximab following second line therapy is not clear, with only one published study (Forstpointner *et al*, 2006): 56 MCL patients treated with R-FCM (rituximab + fludarabine, cyclophosphamide and mitoxantrone) were randomised between rituximab maintenance and no further therapy. Median response duration was identical between arms, but a higher proportion of patients in the maintenance arm experienced remissions beyond 2 years (45% vs. 9%).

Bendamustine-based regimens

The largest relapse study of bendamustine in combination with rituximab included 45 patients (Czuczman *et al*, 2015). ORR was 82%, CR was 40%, with a median duration of response of 1·6 years, and 3-year OS of 55%. The addition of cytarabine to bendamustine and rituximab (R-BAC) seems an active regimen in relapse as well as in the front line setting (Visco *et al*, 2013); 20 relapsed or refractory patients were treated, achieving an 80% response rate (70% CR) and estimated 2-year PFS of 70%.

Purine analogues

The activity of fludarabine monotherapy (ORR 33%) (Decaudin *et al*, 1998) is enhanced by addition of cyclophosphamide (Cohen *et al*, 2001) and rituximab (Thomas *et al*, 2005) where ORR was 75%, with 57% CR and response duration 11 months. Single agent cladribine in the relapse setting leads to response rates of 46%, with 21% CR and median PFS 5·4 months (Inwards *et al*, 2008). Responses are

probably improved by the addition of cyclophosphamide and rituximab (Robak *et al*, 2006).

Gemcitabine

In a small study of 30 patients with relapsed/refractory disease, gemcitabine was given in combination with dexamethasone (12 patients) or dexamethasone together with cisplatin (18 patients) (Morschhauser *et al*, 2007). ORR was similar, at 36% and 44% respectively, but PFS was very short at 3 months.

Thalidomide

Thalidomide as a single agent is probably less active than lenalidomide. However, in a small study of 16 patients, when thalidomide was given in combination with rituximab, ORR was 81% with 31% CR (Kaufmann *et al*, 2004). Responses were durable with a PFS of 20·4 months. Rituximab and thalidomide have been added to the PEP-C regimen, a low dose continuous chemotherapy schedule incorporating prednisolone, cyclophosphamide, etoposide and procarbazine: among 22 patients ORR was 82% with 46% CR. Median duration of therapy was 17 months (Coleman *et al*, 2008). Addition of thalidomide and rituximab to this regimen did not appear to improve results (Ruan *et al*, 2010).

Licensed agents including ibrutinib

Worldwide, there are 4 drugs licensed for use in relapsed MCL, bortezomib, lenalidomide, temsirolimus and ibrutinib. The comparative efficacy of these drugs as single agents in trials involving relapsed and refractory patients is shown in Table I. These were registration trials, with broadly comparable patient populations. Ibrutinib appears the most active of these agents with best ORR, CR rate and duration of response. There has been one randomised trial involving these drugs (Dreyling *et al*, 2016), where ibrutinib was compared with temsirolimus in 280 patients after a median of two prior lines of therapy. There was a significantly better primary endpoint, PFS, with ibrutinib (14·6 vs. 6·2 months: $P < 0{\cdot}0001$), and less treatment-related toxicity, but after a median follow-up of 20 months, no survival benefit was observed.

As with chemotherapy in MCL, novel agents have been used in combination with rituximab and the results of these studies are included in Table I. Whilst there is no randomised data, there is a consistent improvement in both response rate and depth following the addition of rituximab for all agents, and a suggestion of improved PFS.

A small randomised trial of 46 patients incorporated a novel agent into standard chemotherapy in the relapsed setting: Bortezomib was added to standard CHOP in first relapse MCL (Furtado *et al*, 2015). There was improved ORR (83% vs. 48%), CR rate (35% vs. 22%) and OS (36% vs. 12%) in favour of the bortezomib combination. Of note, bortezomib was given on a weekly schedule of 1·6 mg/m^2, which did not significantly increase neurotoxicity, even when added to vincristine.

Studies of bortezomib combined with dexamethasone and rituximab (Lamm *et al*, 2011), bendamustine and rituximab (Friedberg *et al*, 2011), high dose cytarabine (William *et al*, 2014) (Weigert *et al*, 2009), gemcitabine (Kouroukis *et al*, 2011) and radioimmunotherapy (Beaven *et al*, 2012) show response rates over 50%, but numbers are very small. Morrison *et al* (2015) studied the addition of bortezomib to lenalidomide in 54 patients with ORR 39·5% (CR 15%) but a median PFS of only 7 months.

Lenalidomide is an oral immunomodulatory agent exhibiting activity in a range of haematological malignancies, and in MCL has single agent activity of around 30% (Goy *et al*, 2013). Responses may, however, be durable, on a par with those with ibrutinib. Response rates can be increased by combining with rituximab, 57% ORR (36% CR) (Wang *et al*, 2012), dexamethasone, ORR 52% (24% CR) (Zaja *et al*, 2012) or bortezomib, ORR 39·5% (15% CR) (Morrison *et al*, 2015). PFS is improved with all of these combinations but is

Table I. Comparison of the 4 drugs licensed for use in Mantle cell lymphoma: data as single agents and in combination with rituximab.

Treatment	Study	Patients (*n*)	ORR	CR	Median DOR (months)	Median PFS (months)	Median OS (months)
Ibrutinib	Wang *et al* (2013)	111	68%	21%	17·5	13·9	Not reached
Ibrutinib + rituximab	Wang *et al* (2016)	50	87%	38%	NR	15-month PFS 69%	15-month OS 83%
Bortezomib	Fisher *et al* (2006)	155	33%	8%	9·2	6·5	23·5
Bortezomib + rituximab	Agathocleous *et al* (2010)	19	58%	16%	NR	NR	NR
Lenalidomide	Goy *et al* (2013)	134	28%	8%	16·6	4	19
Lenalidomide + rituximab	Wang *et al* (2012)	44	57%	36%	19	11·1	24·3
Temsirolimus	Hess *et al* (2009)	54*	22%	2%	7·1	4·8	12·8
Temsirolimus + rituximab	Ansell *et al* (2011)	69	59%	19%	10·6	9·7	29·5

CR, complete response; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; NR, not reported.

*Results are presented for temsirolimus 175/75 mg dose group.

most durable with rituximab or dexamethasone, at around 12 months.

Temsirolimus is an mTOR inhibitor with an ORR in the registration study of 22% (2% CR) (Hess *et al*, 2009). The ORR was higher at 40% (1% CR) in the randomised study against ibrutinib (Dreyling *et al*, 2016), reflecting the fact that these patients were far less heavily pre-treated. Addition of rituximab increases response, especially the CR rate (59% ORR, 19% CR), but there are limited published data on further combination therapies. One study of temsirolimus with bortezomib (Fenske *et al*, 2015) was active, but only included 7 patients.

Ibrutinib appears the most active single agent in the treatment of relapsed refractory MCL, with response rates of 68% (21% CR) (Wang *et al*, 2013). In contrast to temsirolimus, responses were virtually identical in the licensing and randomised trials (Dreyling *et al*, 2016). Addition of rituximab increased the ORR to 87% (38% CR) and, in the only other published combination study, addition of bendamustine and rituximab in 17 patients produced an ORR of 94% with 66% CR (Maddocks *et al*, 2015). Ibrutinib can cross the blood brain barrier and is effective in CNS relapse (Tucker *et al*, 2017). The earlier ibrutinib is used the more effective it is (Rule *et al*, 2017). Trials are on-going, assessing a wide range of ibrutinib combination therapies both at relapse and front line. Alternative BTK inhibitors appear to have comparable efficacy (Walter *et al*, 2016; Wang *et al*, 2018).

Other drugs

The newer anti-CD20 monoclonal antibodies have lower activity than single agent rituximab in relapsed MCL, (Morschhauser *et al*, 2013; Furtado *et al*, 2014), but because the majority of the patients studied were exposed to prior rituximab, comparisons are difficult to interpret.

The PI3K inhibitor, idelalisib, shows activity as a single agent in relapsed MCL, with ORR 40% (CR 5%). Responses are very short, with median duration 2·7 months and PFS 3·7 months (Kahl *et al*, 2014).

The BCL2 inhibitor, venetoclax, looks extremely active. A phase I trial (Davids *et al*, 2017) included 28 patients with MCL and demonstrated an ORR of 75% (21% CR) and median PFS of 14 months, almost identical to results seen with single agent ibrutinib.

Single agent flavopiridol (Kouroukis *et al*, 2003), enzastaurin (Morschhauser *et al*, 2008), everolimus (Wang *et al*, 2014) and vorinostat (Kirschbaum *et al*, 2011) have been evaluated in MCL but the observed responses do not warrant further exploration.

Recommendations

- **There is no standard therapeutic approach at relapse. An individualised approach should be adopted based on age, co-morbidities, performance status, and response and toxicity with prior therapy (1B)**
- **Ibrutinib is the most active single agent in the relapse setting and should be considered as an option (1A).**
- **An alternative chemotherapeutic regimen should be give at relapse to that given front line (1A)**
- **Rituximab should be given in combination with chemotherapy at relapse (1A)**
- **The activity of novel agents is increased with co-administration of rituximab (1B)**
- **There is little evidence to support the role of maintenance rituximab following relapse therapy**

Stem cell transplantation in mantle cell lymphoma

Autologous stem cell transplantation (ASCT)

Only one prospective study has compared outcome of ASCT with non-SCT strategies for first-line consolidation in MCL (Dreyling *et al*, 2005). This trial compared outcome of HDT and ASCT *versus* interferon after CHOP-based induction. Whilst a PFS advantage for HDT consolidation was shown (median PFS 39 vs. 17 months) no OS advantage was demonstrated.

There have been a number of phase 2, single arm studies evaluating the role of HDT consolidation after more intensive induction regimens (Khouri *et al*, 1998; Gianni *et al*, 2003; Geisler *et al*, 2008; Damon *et al*, 2009; Delarue *et al*, 2013). Whilst it is difficult to separate the beneficial effects of intensive induction from those of consolidation, HDT results are impressive, with 4- and 5-year PFS and OS rates of 56–73% and 64–81%, respectively. Data from the recently reported MCL Younger trial, which tested induction with either R-CHOP or R-CHOP/R-DHAP prior to HDT and ASCT, showed that irrespective of induction used, consolidation HDT converted a significant percentage of patients to an MRD-negative state (Hermine *et al*, 2016). Further, achievement of MRD negativity was an important predictor of favourable outcome. Some investigators have questioned whether HDT consolidation is required after modern, intensive induction regimens, which alone may achieve similar results (Romaguera *et al*, 2010), but, given the excellent results obtained following intensive induction and HDT consolidation, this approach should be considered a standard of care for suitable patients. Whether HDT can be safely omitted from intensive first-line therapy that incorporates a BTK inhibitor will be tested in the European MCL Network TRIANGLE trial (NCT02858258): ASCT After a Rituximab/Ibrutinib/Ara-c Containing iNduction in Generalized Mantle Cell Lymphoma.

Despite such intensive first line approaches, most patients will relapse (Geisler *et al*, 2012; Eskelund *et al*, 2016). Prognostic factors predicting favourable outcome of first line consolidation HDT include a low or intermediate MIPI score

(Geisler *et al*, 2012), achievement of an MRD-negative state (Hermine *et al*, 2016) and disease status at transplantation (Till *et al*, 2008; Fenske *et al*, 2014). Of note, blastic or pleomorphic morphology was not an adverse predictor of outcome in the Nordic MCL2 trial (Geisler *et al*, 2010).

A number of strategies have been tested in an attempt to improve outcome after first-line HDT: Addition of radioimmunotherapy to BEAM conditioning demonstrated acceptable toxicity but no clear improvement in disease control (Kolstad *et al*, 2014). The role of TBI in conditioning therapy has been explored only in the context of retrospective analyses, with the hypothesis that patients in PR prior to ASCT may benefit from TBI-based conditioning (Rubio *et al*, 2010; Hoster, 2016). There is however no clearly established optimal conditioning regimen for ASCT in MCL.

The timing of high-dose therapy and ASCT in the disease course has been studied in retrospective analyses from both The European Society for Blood and Marrow Transplantation (EBMT) and the Center for International Blood and Marrow Transplant Research (CIBMTR). Both studies showed that results of ASCT are superior when used in the first line setting (Vandenberghe *et al*, 2003; Fenske *et al*, 2014), concurring with single centre experience (Tam *et al*, 2009).

A major challenge in the application of HDT and ASCT in MCL is the relative age of the patient population. Registry data describes transplant-related mortality of 10% in patients aged more than 60 years treated with ASCT compared to 3% in patients under 60 of age (Jantunen *et al*, 2012). Thus, whilst many clinicians routinely consider HDT and ASCT for patients over the age of 60 years, careful evaluation in this patient group is advised. The transplant-specific co-morbidity index has been demonstrated to be predictive of non-relapse mortality (NRM) in patients undergoing allogeneic SCT (Sorror *et al*, 2005, 2014) but has not been specifically studied in the setting of ASCT for MCL.

Maintenance therapy post-ASCT

Given the pattern of continued relapse, maintenance strategies post-ASCT have been investigated. Use of bortezomib maintenance has produced conflicting results and has no current place in therapy (Doorduijn, 2015; Kaplan, 2015). Rituximab maintenance therapy for a period of 3 years post-ASCT has recently been shown to improve both PFS and OS following first line ASCT (Le Gouill *et al*, 2017). In this large, prospective, randomized trial from the LYSA group, 4-year PFS and OS were 83% and 89%, respectively, for those receiving rituximab vs. 64% and 80% in the control arm (observation only). We therefore recommend maintenance rituximab in the post-ASCT setting.

Allogeneic SCT (alloSCT)

AlloSCT offers the theoretical benefits of a stem cell graft neither contaminated by lymphoma cells nor damaged by exposure to mutagenic agents and makes the development of a graft-versus-lymphoma effect possible. Data describing alloSCT for MCL are, however, relatively limited, mostly restricted to retrospective single centre or registry studies, with few prospective single-arm studies. Interpretation of data is further hampered by inclusion of heterogeneous populations of patients, including those transplanted in first-line and relapse settings and patients who have variably received prior ASCT. These studies report significant toxicity, with NRM rates of 9–25% at 1 year (Maris *et al*, 2004; Tam *et al*, 2009; Cook *et al*, 2010; Le Gouill *et al*, 2012; Fenske *et al*, 2014). Chronic graft-versus-host disease develops in 40–50% of patients and morbidity associated with this should be considered. Relapse following alloSCT has been reported at between 15 and 38%, with a suggestion of a plateau in relapse after 4 years, even when reduced-intensity conditioning is used (Tam *et al*, 2009; Le Gouill *et al*, 2012; Fenske *et al*, 2014), suggesting that alloSCT may be able to eradicate MCL in a significant minority of patients (Tam *et al*, 2009; Fenske *et al*, 2014; Robinson *et al*, 2017). Longer term follow-up is required to determine the curative potential of alloSCT in MCL and establish the efficacy of donor lymphocyte infusions (Cook *et al*, 2010).

There is a paucity of data describing the role of alloSCT in first-line consolidation. The British Society of Blood and Marrow Transplantation (BSBMT) prospective trial of first line consolidation with a BEAM-CAMPATH conditioned alloSCT reported a treatment-related mortality rate of 8% and a 68% 2-year PFS (Rule *et al*, 2016). The CIBMTR have reported that for patients undergoing an alloSCT after only 1 or 2 lines of prior therapy (and no prior ASCT), relapse risk following a reduced intensity alloSCT was only 15% compared with 32% for those undergoing an ASCT. The benefit of a lower relapse rate after alloSCT was, however, offset by higher NRM, resulting in no difference in survival (Fenske *et al*, 2014). Whether alloSCT can produce better outcomes than ASCT in patients with high risk disease remains to be determined. Therefore, first line consolidation alloSCT should only be considered within the context of a clinical study.

Data on alloSCT used in either the relapse setting or in patients who have undergone a prior ASCT is more comprehensive (Tam *et al*, 2009; Cook *et al*, 2010; Le Gouill *et al*, 2012; Hamadani *et al*, 2013; Dietrich *et al*, 2014; Fenske *et al*, 2014). As to be expected, the results of alloSCT when used later in the disease course are not as good as when used earlier (Fenske *et al*, 2014). However, patients relapsing after prior ASCT (Dietrich *et al*, 2014) and even those with refractory disease at the time of alloSCT (Hamadani *et al*, 2013) may achieve a prolonged PFS, suggesting that a minority of such high-risk patients may be cured.

Both myeloablative and reduced-intensity conditioning regimens may be considered but there is no clear evidence of the superiority of either approach (Hamadani *et al*, 2013). Rather, the conditioning regimen should be selected according to age, comorbidities, Haematopoietic Cell

Transplantation-Comorbidity Index (HCT-CI) and prior therapy, on an individual patient basis. Data from retrospective studies suggests the use of T-cell depletion is associated with a higher relapse rate (Cook *et al*, 2010; Robinson *et al*, 2017). However, the overall impact of T-cell depletion on survival post-alloSCT remains controversial (Cook *et al*, 2010; Hamadani *et al*, 2013; Robinson *et al*, 2017). Haploidentical alloSCT enables provision of multiple donors for the majority of patients, but this form of transplantation requires further evaluation in MCL (Dietrich *et al*, 2016). The sequencing of alloSCT relative to the emerging novel therapies also requires further assessment.

Recommendations

- **ASCT should be considered as consolidation of first line therapy for all patients deemed fit for intensive therapy. Patients over 60 years of age should be thoroughly assessed for the suitability of this approach (1A)**
- **ASCT to consolidate first response is most likely to benefit those who achieve a complete remission. (1A)**
- **ASCT can significantly prolong duration of disease response though at present there is insufficient data to demonstrate whether there is a significant overall survival benefit. (1A)**
- **Maintenance rituximab is recommended post-ASCT in fit patients treated with intensive induction. (1A)**
- **AlloSCT may be considered in second remission for fit patients with an appropriate donor. The intensity of the conditioning regimen should be selected on an individual patient basis. (1C)**
- **AlloSCT can be effective at rescuing patients who relapse post-ASCT. (1B)**
- **AlloSCT as part of first-line therapy should be considered only for patients with high-risk disease and preferably within the context of a clinical trial. (1C)**

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

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 www.b-s-h.org.uk.

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