bjh guideline

Guidelines for the investigation and management of mantle cell lymphoma

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Background

The guideline group was selected to be representative of UK-based medical experts and patients representatives. Ovid MEDLINE, EMBASE and NCBI Pubmed were searched systematically for publications in English from 1980 to 2011 using the MeSH subheading 'lymphoma, mantle cell' and 'lymphoma, mantle cell' as a keyword, as well as all subheadings. In addition, all references to mantle cell lymphoma in the World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissue (Swerdlow *et al*, 2008) and the British Committee for Standards in Haematology (BCSH) Guideline: Best Practice in Lymphoma Diagnosis and Reporting (Parker *et al*, 2010) have been included. The writing group produced the draft guideline, which was subsequently revised by consensus by members of the Haemato-oncology Task Force of the BCSH. The guideline was then reviewed by a sounding board of approximately 50 UK haematologists, the BCSH and the British Society for Haematology Committee and comments incorporated where appropriate. The 'GRADE' system was used to quote levels and grades of evidence, details of which can be found in Appendix I. The objective of this guideline is to provide healthcare professionals with clear guidance on the investigation and management of patients with mantle cell lymphoma. The guidance may not be appropriate to patients with other lymphoma sub-types and in all cases individual patient circumstances may dictate an alternative approach.

Guideline update

This guideline is the first BCSH guideline on the topic of mantle cell lymphoma, and therefore, does not supersede any previous guidance. The section on diagnosis of mantle cell lymphoma, should be considered supplementary to the BCSH Guideline: Best Practice in Lymphoma Diagnosis and Reporting (Parker *et al*, 2010). The guideline is in date at time of publication. Any updates will be posted on the BCSH website (http://www.bcshguidelines.com/).

Introduction

Mantle cell lymphoma (MCL) is a B-cell malignancy with unique biological, pathological and clinical features, which comprises approximately 3–10% of all non-Hodgkin lymphomas (NHLs) (Swerdlow *et al*, 2008). It is characterized by the chromosomal translocation *t*(11;14)(q13;q32), which results in overexpression of the cell cycle protein cyclin D1 (Akiyama *et al*, 1994; Campo *et al*, 1999). MCL arises in older adults (median age of presentation 60–65 years) and has a male predominance (Argatoff *et al*, 1997; Bosch *et al*, 1998). The challenge of MCL is that it 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 to standard therapy. Median survival is 4–5 years (Herrmann *et al*, 2009). There is evidence to suggest that this has increased over recent years from the previous median survival of 2–3 years, as a result of improved combination chemotherapies (discussed below) and supportive care. However, no standard of care is recognized, and this disease remains very difficult to manage.

A number of studies have described the clinical presentation of MCL (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 (Ann Arbor III-IV) disease. Lymphadenopathy is generally widespread at diagnosis, and splenomegaly, bone marrow infiltration and leukaemic involvement are common. Bulk disease at diagnosis and B-symptoms are less common. Extranodal involvement is frequent, particularly affecting the gastro-intestinal (GI) tract (Romaguera *et al*, 2003) and liver, but involvement of breast, lung, skin, soft tissue, salivary gland and orbit are also seen. Involvement of more than two extranodal sites is seen in 30–50% of patients (Jares & Campo, 2008). Spread to the central nervous system (CNS) can occur, but is rare at diagnosis, tending to occur as a late event in the course of the

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disease, where it is associated with widespread relapse and short survival (Ferrer *et al*, 2008).

The clinical course is heterogeneous. Clinical presentation can correlate with pathological sub-type (discussed below); patients with the blastoid variant tend to have a very aggressive clinical course, may be refractory to treatment and have short survival. In contrast, it is recognized that a proportion of cases (10–30%) may present with more indolent disease (Eve *et al*, 2009a; Martin *et al*, 2009). These patients usually present with splenomegaly and a peripheral blood lymphocytosis, and lack significant nodal disease (Nodit *et al*, 2003; Orchard *et al*, 2003). Survival is in the order of 5–12 years. Even outside these extremes, the heterogeneity of the disease, and the elderly population in which it presents, frequently necessitate an individualized approach, although clinical trial data are beginning to provide a stronger evidence-base for treatment of patients with MCL.

Diagnosis

Morphology

The diagnosis of MCL should be made by an excision biopsy or adequate core biopsy of an involved lymph node or extranodal site or by bone marrow trephine biopsy in the majority of cases. Computerized tomography (CT)- or ultrasound-guided biopsy may be needed to obtain diagnostic material if open biopsy is difficult. A primary diagnosis may also be made on a peripheral blood specimen in cases with a leukaemic presentation.

In the classical variant, which accounts for 87% of cases, the architecture of the involved lymph node is usually completely effaced and is replaced by a diffuse or, less commonly, a nodular infiltrate composed of a monomorphic population of small to intermediate sized cells with irregular, often cleaved nuclei resembling centrocytes (Swerdlow *et al*, 1983; Argatoff *et al*, 1997; Tiemann *et al*, 2005). A mantle zone pattern is seen in a minority of cases (Tiemann *et al*, 2005). Vascular hyalinization is often conspicuous and there may also be prominent single epithelioid histiocytes, especially in cases with a higher proliferation fraction. A small cell variant resembling small lymphocytic lymphoma, though lacking proliferation centres, is recognized. Other subtypes include the blastoid variant, resembling lymphoblastic lymphoma and the pleomorphic variant, which may be confused on morphological grounds with diffuse large B-cell lymphoma (DLBCL) (Swerdlow *et al*, 1983; Norton *et al*, 1995; Argatoff *et al*, 1997; Ott *et al*, 1997; Tiemann *et al*, 2005). The same cytomorphological features are identified in biopsies of extranodal sites, such as colon, stomach and salivary gland. In trephine biopsy specimens, the infiltrate is most commonly nodular and interstitial and less often is paratrabecular or diffuse (Argatoff *et al*, 1997; Cohen *et al*, 1998). Trephine biopsy examination should include haematoxylin & eosin (H&E) and reticulin staining, in addition to immunophenotyping.

Immunophenotype

Immunophenotyping may be carried out on paraffin-embedded material by immunohistochemistry or on liquid-based specimens by flow cytometry. In order to accurately diagnose MCL, a full immunohistochemical panel including anti-cyclin D1 should be employed in all biopsies suspicious of B-cell lymphoma (see Table I).

The majority of MCL cases co-express CD20, CD5, BCL2 and cyclin D1. The infiltrate is usually negative for CD10, BCL6 and CD23 (Alkan *et al*, 1995; Swerdlow *et al*, 1995; Argatoff *et al*, 1997; Sander, 2011). CD23 highlights a diffuse disorganized network of follicular dendritic cells though this may be variable in extent. Interpretation of CD5 expression in paraffin-embedded material may be difficult in view of the presence of large numbers of reactive CD5-expressing T-cells. A close comparison with the immunostaining pattern for CD3 is essential in such cases. MCL with an aberrant immunophenotype is well described. CD5 negativity is seen in approximately 5–10% of cases (Wlodarska *et al*, 1999; Zanetto *et al*, 2008; Espinet *et al*, 2010; Gualco *et al*, 2010). Expression of CD10, BCL6 and CD23 is recognized in a minority of cases and may lead to an erroneous diagnosis (Schlette *et al*, 2003; Camacho *et al*, 2004; Zanetto *et al*, 2008; Gualco *et al*, 2010). Nuclear expression of cyclin D1 is seen in the vast majority of cases and lack of expression should call into question the diagnosis of MCL (Alkan *et al*, 1995; Swerdlow *et al*, 1995). Modern antibodies to cyclin D1 (SP4 clone) are highly sensitive and lack of staining is usually related to poor fixation or lack of adequate antigen retrieval (Fu *et al*, 2005; Krenacs, 2005). In cases with equivocal staining, fluorescence *in situ* hybridization (FISH) may be performed for the *t*(11;14) translocation on both paraffin-embedded material and peripheral blood samples to confirm the diagnosis (Remstein *et al*, 2000; Sander *et al*, 2007).

SOX11 is highly expressed in classical MCL (Ek *et al*, 2008; Dictor *et al*, 2009). It is possible that SOX11 immunostaining may have a role in the characterization of MCL in the future when sensitive and specific antibodies become generally available.

Flow cytometry on peripheral blood or bone marrow can be equally informative in terms of making a diagnosis of MCL. Typically, MCL expresses CD19, CD20, CD79b, CD22, CD5 with FMC7 and moderately intense expression of sur-

Table I. The immunophenotype of MCL by (a) immunohistochemistry and (b) flow cytometry.

(a)						
CD20	CD5	CD10	CD23	Cyclin D1	BCL6	BCL2
+	+	–	–	+	–	+
(b)						
CD19	CD20	CD5	CD10	FMC7	CD23	Surface Ig
+	+	+	–	+	–	+(bright)

face light chains (see Table I). CD10 expression is seen in a small proportion of cases, particularly in those with blastoid morphology (Zanetto *et al*, 2008). Flow cytometry is not suitable for assessment of cyclin D1, although in patients with a leukaemic presentation, cyclin D1 immunostaining may be carried out on paraffin-embedded preparations of density-gradient isolated peripheral blood lymphocytes. Although MCL, like chronic lymphocytic leukaemia (CLL), often shows CD5 positivity, these two entities should not be confused: CLL is normally FMC7 negative, CD79b negative/weak, CD23 positive, CD20 weak positive with weak surface light chain expression.

Genetics and molecular diagnostics

The characteristic cytogenetic abnormality of MCL is the *t*(11;14)(q13;q32) translocation, resulting in overexpression of cyclin D1 (encoded by the *CCND1* gene at 11q13) contributing to deregulated cell cycle progression at the G1-S phase boundary (Vandenberghe *et al*, 1991; Williams *et al*, 1993). The translocation may be detected by classical cytogenetics or FISH (Belaud-Rotureau *et al*, 2002; Dubus *et al*, 2002; Reichard *et al*, 2006). The latter has the advantage that it can be performed on paraffin-embedded material and therefore can be applied to core and endoscopic biopsies. In practice, the presence of the *t*(11;14) translocation should be demonstrated in cases with atypical morphology, an aberrant immunophenotype, equivocal cyclin D1 positivity or unusual clinical presentation.

Demonstration of clonality may be achieved by detection of light chain restriction by flow cytometry or by polymerase chain reaction (PCR) for immunoglobulin heavy variable gene (*IGHV*) rearrangement. Secondary cytogenetic abnormalities are common in MCL and the degree of karyotypic complexity is negatively associated with patient survival (Cuneo *et al*, 1999; Wlodarska *et al*, 1999; Parry-Jones *et al*, 2007; Katzenberger *et al*, 2008).

Histopathological prognostic factors

MCL is associated with a relatively poor prognosis, though there is some variation in outcomes within the group. Many biological features have been examined such as growth pattern, blastoid morphology, *TP53* (p53) expression and secondary cytogenetic abnormalities with varying reports of their significance (Norton *et al*, 1995; Argatoff *et al*, 1997; Ott *et al*, 1997; Katzenberger *et al*, 2006). Identification of blastoid morphology may be difficult in view of variation in fixation and the subjective nature of assessing cell size.

Proliferative activity is the most important prognostic factor in routine diagnostic practice (Table II) (Tiemann *et al*, 2005; Katzenberger *et al*, 2006; Determann *et al*, 2008). Inter-observer variability in assessment of the proliferation index is well recognized; guidance has been produced by the European MCL Network, which suggested that counting the positive cells among 100 lymphoma cells in each of two representative high-power fields generated improved consistency in this respect (Klapper *et al*, 2009).

Table II. The association between proliferation index and survival [data from Tiemann *et al* (2005)].

Ki67 proliferation index (%)	Median survival (months)
<10	42
11–40	30
>40	15

As mentioned in the introduction, a proportion of patients present with indolent disease. Identification of this variant at presentation is difficult. Some suggest that lack of nuclear expression of SOX11 is associated with indolent disease (Fernandez *et al*, 2010). The leukaemic cells in indolent MCL have been found to be kappa light chain-restricted in contrast to the lambda restriction usually seen in classical MCL. Some CD23 expression is also detected in this group by flow cytometry (Ondrejka *et al*, 2011). None of these factors is currently robust enough to serve as a basis for modification of treatment.

Pitfalls and differential diagnosis

Failure to diagnose MCL can occur as a result of omission of immunostaining for cyclin D1 in the standard lymphoma panel, especially when CD5 is negative or weakly expressed. Poor quality immunohistochemistry and inadequate antigen retrieval may lead to false negative reactions and failure to achieve diagnosis. An aberrant immunophenotype, such as CD23 or CD10 positivity, may mislead the reporting pathologist. Cyclin D1 is weakly expressed by hairy cell leukaemia and may be detected in up to 25% of multiple myeloma cases, which may give rise to confusion in bone marrow trephine biopsy assessment. Performing a full immunohistochemical panel, reviewing the bone marrow aspirate and clinicopathological correlation should enable accurate diagnosis. A small proportion of CD5-negative DLBCL cases express cyclin D1 weakly (Ehinger *et al*, 2008). Epithelial malignancies often display nuclear positivity for cyclin D1, which may cause confusion in biopsies of undifferentiated nasopharyngeal carcinoma where the epithelial nature of the malignancy is often obscured by an intense lymphocytic reaction.

Cyclin D1-negative MCL

Genuine cyclin D1-negative cases of MCL lacking the *t*(11;14) translocation have recently been recognized through gene expression profiling (Fu *et al*, 2005; Herens *et al*, 2008; Quintanilla-Martinez *et al*, 2009). The cytomorphology,

immunophenotype (other than cyclin D1 negativity) and clinical course are identical to cases of classical MCL. The lymphoma is characterized by overexpression of cyclin D2 or cyclin D3, and has a variant translocation. These lymphomas have an identical gene expression profile to typical MCL and are therefore regarded as a variant of this condition and should be treated as such. The detection of nuclear SOX11 expression has been suggested as a simple means of recognizing this entity (Mozos *et al*, 2009). Variable results have been obtained with this antibody, and as yet, a reliable simple diagnostic test is not widely available. It is important for the haematopathologist to be aware of this entity and to consider the diagnosis when confronted with a CD5-positive/cyclin D1-negative B-cell lymphoma with morphological features of MCL. Referral to a specialist centre for further investigation should be considered.

Recommendation

- **Lymph node excision or adequate core biopsy is usually required for the diagnosis of nodal MCL. In non-nodal presentation, tissue biopsy or peripheral blood may provide the diagnosis. (Strong, Moderate)**
- **All cases should be subject to routine central review by an experienced haematopathologist. (Strong, Moderate)**
- **Immunohistochemical panels for the investigation of all B-cell lymphomas should include cyclin D1. (Strong, High)**
- **The presence of the *t*(11;14) translocation should be demonstrated by FISH in cases with atypical morphology, aberrant immunophenotype, equivocal cyclin D1 positivity or unusual clinical presentation. (Strong, High)**
- **It is recommended that the Ki67 Proliferation Index be recorded at baseline, with an index of > 30% suggestive of poorer outcome. (Weak, Moderate).**

Initial investigations

Initial investigations performed in a patient with confirmed MCL serve to provide information to guide management. Such investigations are useful to describe the stage or extent of disease, prognosticate and evaluate fitness for therapy. Assessment of performance status at baseline using a standard tool such as the World Health Organization/Eastern Cooperative Oncology Group (ECOG) performance status (Oken *et al*, 1982) is recommended.

Imaging in MCL

CT of the neck, thorax, abdomen and pelvis should be included with oral contrast and intravenous contrast where appropriate.

Magnetic resonance imaging (MRI) may be useful for assessment of CNS disease, with gadolinium enhancement where clinical suspicion is high (Ferrer *et al*, 2008; Gill & Seymour, 2008; Gill *et al*, 2009).

(^{18}F)Fluorodeoxyglucose positron emission tomography (FDG-PET) is now used in the assessment of many types of lymphoma, although its exact role remains to be established in many cases. It has been shown that MCL is FDG-avid, particularly the blastoid variant and nodal disease (Brepoels *et al*, 2008). However, in contrast to other high grade NHLs, FDG-PET has been shown to have lower sensitivity in staging MCL, particularly extranodal disease (Rusconi *et al*, 2010) and routine use of FDG-PET in the staging of MCL, outside the context of a clinical trial, cannot be recommended.

Laboratory investigations

Baseline peripheral blood tests should include a full blood count and peripheral blood film morphology. A frank peripheral blood lymphocytosis is seen in 20–40% of patients with MCL, and when present, immunophenotyping by flow cytometry is recommended. Baseline biochemistry should include urea, creatinine and electrolytes, liver function tests, adjusted calcium, albumin, urate and lactate dehydrogenase. Bone marrow examination should include an aspirate for immunophenotyping by flow cytometry, and a trephine biopsy for histological examination (as discussed above). Lumbar puncture and cytological examination of cerebrospinal fluid by cytospin, together with flow cytometry should be performed if there is any clinical suspicion of CNS disease, and can be considered in blastoid variant disease.

Other investigations

Enteroscopy – some authorities recommend routine colonoscopy and upper GI endoscopy as part of staging investigations in MCL (Zelenetz *et al*, 2011), on the basis that prospective studies have identified microscopic involvement by MCL of the GI tract in 92% of cases (Salar *et al*, 2006). However, it has been demonstrated that this finding only rarely (in <4% of cases) changes clinical management. (Romaguera *et al*, 2003) Therefore, routine endoscopy and colonoscopy cannot be recommended for all patients at baseline. Instead, enteroscopy should be performed on the basis of clinical indication, where there are any significant enteric symptoms, or if clinical stage 1A disease is present and radiotherapy with curative intent is planned. Where enteroscopy is performed, biopsies of any suspicious lesions, and also macroscopically normal areas, should be taken for cyclin D1 immunohistochemistry.

Virology – where rituximab therapy is considered, it is recommended that patients undergo testing for hepatitis B and C; hepatitis B surface antigen and core antibody in patients with no other risk factors hepatitis e antigen should be added where risk factors exist. Where testing confirms hepatitis B or C infection, viral load should be assessed using local protocols, and the patient discussed with the local infectious disease or

gastroenterology service. Similarly, serological testing for human immunodeficiency virus (HIV) is recommended prior to commencement of therapy, but is not essential.

Pregnancy testing – although MCL is uncommon in women of childbearing age, it is recommended that a pregnancy test be performed before chemotherapy is administered in this group.

Staging and clinical prognostication

Although previously regarded as a disease with generally poor outcome, it has become clear that MCL behaves more heterogeneously than previously thought, and for this reason, attempts have been made to identify features that may influence prognosis. As has been discussed above, histological features may be important indicators of outcome.

Staging. The staging system used to assess MCL is the same as the modified Ann Arbor staging used in Hodgkin lymphoma and most other types of NHL (see Table III). As most patients with MCL have blood and bone marrow involvement at presentation, clinical stage used in isolation is not prognostically useful.

Clinical prognostic scoring systems. The international prognostic index (IPI) does not perform well when used in populations of patients with MCL, and is therefore not applicable in this setting (Moller *et al*, 2006; Hoster *et al*, 2008a). A prognostic scoring system specific for MCL, the MCL international prognostic index (MIPI) has been devised, based on modeling using features of the IPI in 455 patients with advanced stage MCL (Hoster *et al*, 2008a).

This model separates patients into three groups; low risk (LR), intermediate risk (IR), and high risk (HR) with good separation of the survival curves. For ease of access to this score, the European MCL Network provides an online calculator at http://www.european-mcl.net/en/clinical_mipi.php. However, acknowledging that simplifying the scoring system would make its use more practical and accessible, the authors also modelled a simplified scoring system, allocating weighted point scores at cut-offs of age, ECOG performance score, lactate dehydrogenase and white blood cell count (see Table IV). This simplified MIPI (sMIPI) also clearly separated patients into the three groups of LR, IR and HR, and was just as powerful as the MIPI whilst being simpler to use. Both the MIPI and the sMIPI have been validated in large independent cohorts (Budde *et al*, 2011; van de Schans *et al*, 2010). It is acknowledged by the authors of the score that prospective, external validation of its prognostic value will be required before it can be used for the selection of therapies in individual patients (van de Schans *et al*, 2010; Hoster *et al*, 2008b; Ghielmini & Zucca, 2009). In spite of this, as a practical tool, it can still provide valuable information to the clinician at baseline.

As Ki67, as described above, is prognostic independent of the MIPI, an alternative is to combine these, to provide a more powerful prognostic system, [the MIPI biological (MIPIb); Hoster *et al*, 2008a]. The MIPIb and sMIPIb retained prognostic significance in independent validation cohorts (Geisler *et al*, 2010). Provided that more reproducible methods of Ki67 quantification are used, the MIPIb may be a useful prognostic marker at baseline.

Table III. Staging of MCL – modified ann arbor staging.

Stage I	Involvement of single lymph node region or localized extranodal site*
Stage II	Involvement of two or more lymph node regions or localized extranodal sites*, or both, on the same side of the diaphragm
Stage III	Involvement of lymph node regions or localized extranodal sites*, or both, on both sides of the diaphragm
Stage IV	Diffuse or disseminated involvement of one or more extra-lymphatic organ(s), with or without associated lymph node involvement. Involvement of liver or bone marrow is considered stage IV

*Designated by the suffix E, e.g. stage IE, IIE etc.
Subsets A and B are designated by the absence (A) or presence (B) of systemic symptoms, namely night sweats, weight loss of at least 10% of body weight or unexplained fever.

Recommendation

- **Performance status should be recorded at baseline. (Strong, Moderate)**
- **Full blood count and peripheral blood film morphology should be performed. (Strong, Moderate)**
- **Peripheral blood urea, creatinine & electrolytes, liver function tests, adjusted calcium, albumin, urate, lactate dehydrogenase should be measured. (Strong, Moderate)**
- **Patients should undergo staging bone marrow aspirate and trephine biopsy examination. (Strong, Moderate)**
- **Patients should undergo clinical staging with CT of neck, chest, abdomen and pelvis. (Strong, Moderate)**
- **Colonoscopy and endoscopy do not form part of the standard work-up of patients with MCL, and should be performed for clinical indications, or if radiotherapy for stage IA disease is considered. (Weak, Moderate)**
- **A low threshold for investigation of the CNS by lumbar puncture with cytospin and immunophenotyping should exist where there is any clinical suspicion of CNS involvement. (Strong, Moderate)**
- **Routine use of FDG-PET in the staging of MCL is not recommended. (Strong, Moderate)**
- **If immunotherapy is considered, virological testing for hepatitis B, hepatitis C and HIV is recommended. (Strong, Moderate)**
- **It is good practice that all patients should have their MIPI or sMIPI recorded at baseline. (Weak, Moderate).**

Table IV. The simplified MCL international prognostic score (sMIPI).

Points	Age (years)	ECOG	LDH/ULN (iu/l)	WBC (10^9/l)
0	<50	0–1	<0·67	<6·7
1	50–59	–	0·67–0·99	6·7–9·999
2	60–69	2–4	1·000–1·49	10·0–14·999
3	≥ 70	–	≥ 1·5000	≥ 15·0

For each prognostic factor, 0–3 points were given to each patient and points were summed up to a maximum of 11.
Patients with 0–3 points in summary were classified as low risk.
Patients with 4–5 points as intermediate risk.
Patients with 6–11 points as high risk.
Eastern Cooperative Oncology Group (ECOG) performance status was weighted with two points if patients were unable to work or bedridden (ECOG 2–4). Lactate dehydrogenase (LDH) was weighted according to the ratio to the upper limit of normal (ULN). Thus, for an example ULN of 240 iu/l, the cutpoints were 180 iu/l, 240 iu/l, and 360 iu/l.
– indicates not applicable.
Data from Hoster *et al* (2008a).

First-line management

There is a lack of definitive data to guide treatment of MCL, partly because it is a relatively uncommon condition and partly because it was only recognized as a specific entity in the revised European-American classification of lymphoid neoplasms (REAL classification) published in 1994 (Harris *et al*, 1994). In addition, MCL patients have frequently been included with other NHL types in clinical studies. Therefore, it is recommended that, where possible, patients with MCL should be managed within the context of a clinical trial. Details of how to obtain information regarding UK clinical trials for patients with MCL can be found in Appendix II. The guidance below suggests options and recommendations for patients not treated in a clinical trial. Where possible, discussion is restricted to published studies including more than 15 MCL patients. Four very large studies currently published in abstract form are considered of major significance in the field (Le Gouill *et al*, 2010; Kluin-Nelemans *et al*, 2011; Hermine *et al*, 2010; Rule *et al*, 2011) and, as other published data are not available to answer the research questions they address, are included in the discussion.

Early stage MCL

A very small proportion of patients will present with localized MCL. As such, evidence for management of this group is scarce. However, in this situation, involved field radiotherapy may be appropriate and can result in long-term remissions. MCL is radiosensitive, and radiotherapy has been used as single agent therapy for localized disease with good responses (Rosenbluth & Yahalom, 2006). Another retrospective study reported outcomes in 26 patients with low-bulk stage IA and IIA MCL (Leitch *et al*, 2003). Radiotherapy was administered to 17 of the patients, in combination with chemotherapy in six of those patients. In spite of small numbers, the study did demonstrate an advantage of radiotherapy in this group; 5-year progression-free survival (PFS) of 68%, compared with 11% for those not receiving RT. In addition, a retrospective analysis from the British National Lymphoma Investigation Group (BNLI) (Vandenberghe *et al*, 1997) examined 65 cases treated with non-intensive therapy. Fifteen patients had stage I or II disease, and were treated with local radiotherapy. Twelve (80%) of these patients attained a complete response (CR). Responses were sustained; eight of the 12 responding patients relapsed at 8–90 months and three patients remained in sustained CRs at 156, 190 and 192 months, suggesting that localized MCL may be curable with radiotherapy in a small proportion of cases. If early-stage disease is suspected, staging should be confirmed with bone marrow examination and GI investigations as described above. Outside the context of a clinical trial, radiotherapy, with or without chemotherapy, would be a reasonable approach.

Advanced stage MCL

MCL is now recognized as having the worst outlook of all subtypes of lymphoma. Although many patients respond well to initial chemotherapy, remission duration is short and overall survival (OS) is poor.

As has been discussed in the introduction, a small subgroup of patients has disease that behaves in a more indolent fashion. If they are asymptomatic, it is reasonable to adopt a watch and wait policy. A retrospective study of 97 patients demonstrated that for 30% of patients who were managed initially by observation only ('watch and wait'), treatment was deferred for a median of 12 months (range 4–128 months) with acceptable outcomes (Martin *et al*, 2009). It is of note, however, that patients in this study were monitored closely, and generally started treatment after months rather than years.

The majority of patients will, however, require chemotherapy. Once the decision is made to treat the patient, the choice of regimen will depend on the overall aim of therapy. Clinical trials of first-line treatment in MCL are summarized in Table V. An early distinction should be made between younger patients fit to undergo autologous peripheral blood stem cell transplantation (ASCT), and those less fit patients for whom this is not an option. For younger, fitter patients where the aim is to proceed to high dose (HD) therapy and autograft in first remission, chemotherapy should be given with the aim of obtaining as good a remission as possible.

However, the majority of patients are elderly, where a high-dose therapy approach is not feasible. For these patients, a range of chemotherapy options is available, in combination with rituximab, and these are discussed below. It is acknowledged however, that for this group, there is no gold-standard therapy, and it is difficult to recommend any specific regimen.

Table V. Clinical trials of combination chemotherapies in MCL in patients treated first-line.

Chemotherapy	Study	*n*	Overall response rate (Combined CR/CRu rate)	Median PFS (months)	Median OS (months)
Conventional					
FC	Cohen *et al* (2001)	30	63% (30%)	4·8	17·5
FC	Lefrere *et al* (2002)	10	80% (40%)	na	na
CHOP	Lenz *et al* (2005)	60	75% (7%)	19	NR
COP	Meusers *et al* (1989)	37	84% (41%)	10	32
CHOP	Meusers *et al* (1989)	26	89% (58%)	7	37
FC	Rule *et al* (2011)	184	79·8% (46·9%)	16·1	na
CVP	Teodorovic *et al* (1995)	35	60% (40%)	20	45
COP	Unterhalt *et al* (1996)	46	81% (16%)	na	na
Fludarabine	Zinzani *et al* (2000)	11	72% (27%)	na	na
Fludarabine/idarubicin	Zinzani *et al* (2000)	18	61% (33%)	na	na
MCP	Herold *et al* (2008)	46	63% (15%)	18	50
Combined immunochemotherapy					
R-chlorambucil	Bauwens *et al* (2005)	14	64% (36%)	26	na
R-CHOP	Howard *et al* (2002)	40	96% (48%)	17	na
R-CHOP	Lenz *et al* (2005)	62	94% (34%)	20	Not reached
R-FC	Rule *et al* (2011)	186	90·6% (64·7%)	30·6	na
R-cladribine	Spurgeon *et al* (2011)	31	87% (61%)	37·5	85·2
R-MCP	Herold *et al* (2008)	44	714% (32%)	20	56
Dose-intense regimens					
Maxi-CHOP-cytarabine, ASCT	Geisler *et al* (2008)	160	90% CR	6-year PFS 56%	4-year OS 75%
R- Hyper-CVAD/high-dose MTX & cytarabine	Romaguera *et al* (2010)	97	97% (87%)	4·6 years	Not reached at 10 years
Hyper-CVAD/high-dose MTX & cytarabine	Khouri *et al* (1998)	45	93·5% (38%)	72% at 36 months	92% at 36 months
R-hyper-CVAD	Ritchie *et al* (2007)	13	92% CR	92% at 36 months	92% at 36 months

CR(u), complete response (unconfirmed); PFS, progression-free survival; OS, overall survival; FC, fludarabine, cyclophosphamide; CHOP, cyclophosphamide, vincristine, doxorubicin, prednisone; COP, cyclophosphamide, vincristine, prednisone; CVP, cyclophosphamide, vincristine, prednisone; MCP, melphalan, chlorambucil, prednisone; R, rituximab; hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; MTX, methotrexate; ASCT, autologous stem cell transplantation; na, not applicable.

Conventional chemotherapy for patients not fit for high-dose regimens. Historically, MCL was grouped with low-grade lymphomas in clinical studies and treated with regimens including CVP (cyclophosphamide, vincristine, prednisone) (Meusers *et al*, 1989; Teodorovic *et al*, 1995; Unterhalt *et al*, 1996), fludarabine-based regimens (Cohen *et al*, 2001), and CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone) (Meusers *et al*, 1989; Lenz *et al*, 2005; Nickenig *et al*, 2006). Most of the studies had small numbers but the general pattern was of reasonable overall response rates (ORR, 60–88%), but short PFS (7–21 months) and poor OS of 40–85% at 2 years. No particular combination appears superior in terms of OS. In particular, addition of an anthracycline in the only randomized controlled trial (RCT) performed (Meusers *et al*, 1989) did not confer a survival benefit. This has been confirmed in large retrospective analyses. The Nebraska Lymphoma Study Group demonstrated that, although 79% of patients were treated with anthracycline-containing regimens, no survival benefit of anthracycline could be demonstrated (Weisenburger *et al*, 2000). Similarly, the Barcelona experience showed an ORR of 61% in patients receiving anthracycline-containing regimens, and 66% in those treated without anthracyclines (Bosch *et al*, 1998). In those not fit for the more intensive induction regimens discussed below, there is no evidence that adding anthracycline confers any advantage. However, despite the lack of robust evidence, R-CHOP (CHOP + rituximab) remains a widely used combination chemotherapy regimen in this disease and forms the control arm in many randomized studies. For this reason, we have included it as a treatment option.

The effectiveness 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, ORRs increase to approximately 60% (Zinzani *et al*, 1999, 2000; Cohen *et al*, 2001). The haematological toxicity of the purine analogues must not be forgotten however, and, in addition to the recognized infectious morbidity, they may cause difficulty with stem-cell mobilization when this is undertaken (Dreyling & Hiddemann, 2008; Eve *et al*, 2009b). A large study of the European MCL Network

randomized 560 elderly patients between R-CHOP ×8 and R-FC (rituximab, fludarabine, cyclophosphamide) ×6 (Kluin-Nelemans *et al*, 2011). Response rates were poorer in the R-FC arm and, of note, OS was lower in the R-FC arm (40 vs. 60 months, $P = 0{\cdot}0072$), with particularly high infection rates, reinforcing the notion that the haematological toxicities of purine analogues mean that caution should be exercised when administering these agents to elderly MCL patients. Age, platelet count and renal function should be taken into any decision to include a purine analogue in treatment, and purine analogues are not recommended as part of first-line treatment where ASCT is considered.

Chlorambucil has activity in MCL, however the evidence suggests that it be used in combination with rituximab for meaningful responses to be seen (Bauwens *et al*, 2005; Sachanas *et al*, 2011). 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 to play in treatment, particularly where less aggressive therapy is preferred. The combination of bendamustine and rituximab demonstrated an ORR of 75% (CR 50%) (Rummel *et al*, 2005). A CR rate of 22% was reported with the BOP regimen (bendamustine, vincristine and prednisone), however this study (Herold *et al*, 2006) included patients with different types of indolent lymphoma.

Role of rituximab in MCL. Rituximab has less activity in MCL than in other B-cell lymphomas e.g. follicular lymphoma and DLBCL. However, it has been shown that the addition of rituximab to chemotherapy regimens improves the response rate, including CR rate (Howard *et al*, 2002; Lenz *et al*, 2005; Schulz *et al*, 2007a).

A systematic review and meta-analysis of R (rituximab)-chemotherapy versus chemotherapy alone (Schulz *et al*, 2007b) showed that rituximab with chemotherapy may be superior to chemotherapy alone with respect to OS in MCL [calculated hazard ratio for death was 0·60, 95% confidence interval (CI) 0·37–0·98]. Unfortunately only a small number of RCTs showing marked heterogeneity were available within this analysis. The results of a recent phase III randomized trial, however, comparing FCR (rituximab, fludarabine, cyclophosphamide) with FC (fludarabine, cyclophosphamide) chemotherapy (Rule *et al*, 2011) has provided further evidence of the benefit of rituximab in MCL with improvement in response rate, PFS and OS.

Other rituximab-chemotherapy regimens with demonstrated benefit in MCL include rituximab and cladribine (Spurgeon *et al*, 2011), and rituximab and chlorambucil (Bauwens *et al*, 2005). Details of response are given in Table V; however, it is worth noting that the median age of patients in these studies was 67 and 63 years, respectively, suggesting that such regimens may be tolerated in an older patient group.

Rituximab monotherapy has been investigated in several trials confirming that single agent rituximab has only modest activity in MCL (Foran *et al*, 2000; Ghielmini *et al*, 2005; Weigert *et al*, 2007). Responses are similar in chemotherapy naïve and pre-treated patients. Single agent rituximab is not recommended but may be an option in patients in whom systemic chemotherapy is contraindicated.

Rituximab maintenance appears to prolong duration of response after R-chemo but not OS (Forstpointner *et al*, 2006; Kahl *et al*, 2006). The European MCL Network study, *MCL elderly*, confirmed the value of rituximab in addition to chemotherapy (Dreyling *et al*, 2010), and is currently examining whether maintenance rituximab will be of benefit. Data from this study, available only in abstract form, suggest that rituximab maintenance may increase remission rates and OS, particularly following R-CHOP (as compared with R-FC) as initial therapy (Kluin-Nelemans *et al*, 2011).

The role of cytarabine and dose-intense regimens. CHOP (or R-CHOP) is not as efficacious as more intensive regimens for induction prior to transplant (Lefrere *et al*, 2002; Andersen *et al*, 2003; Dreyling *et al*, 2005). There is an increasing awareness of the cytotoxic activity of cytarabine in MCL with excellent responses (ORR and CR rates) when this drug is incorporated into first line chemotherapy regimens. Most studies have shown an ORR of $> 90\%$ and CR rate of $> 50\%$.

High-dose cytarabine was first exploited in this context as part of the dose-intense hyper-CVAD regimen (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone) with good results in single-arm, single-centre settings (Khouri *et al*, 1998). The addition of rituximab to this regimen gives extremely high CR rates of 87–92% (Ritchie *et al*, 2007; Romaguera *et al*, 2010), which appear durable (see Table V), in spite of the fact that this regimen does not include ASCT consolidation. The main concern of this regimen remains its acute marrow and infectious toxicities, and long-term toxicities, which include a 5% rate of myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML). A recent large multi-centre study (Merli *et al*, 2012) supported the conclusion that, while R-hyperCVAD is an active regimen for first-line therapy in MCL, it comes with significant toxicity. In a young population (median age 57 years), response rates to R-hyperCVAD/cytarabine and methotrexate were high (72% CR). However responses were not sustained (46% 5-year failure-free survival), and of 63 patients treated with R-hyperCVAD, only 37% of patients were able to complete the planned four cycles of treatment due to toxicities. The initial strong results with this regimen seem not to be reproducible in the multi-centre setting.

The effective doses of high-dose cytarabine derived from these regimens were subsequently incorporated into other combination chemotherapies. The results of the Nordic MCL2 study (Geisler *et al*, 2008) were far superior to the Nordic MCL1 trial with the main differences between the two trials being the addition of rituximab and high-dose cytarabine in

MCL2. The European MCL Network study, *MCLYounger*, evaluated alternating courses of 3× R-CHOP and 3× R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin), followed by a high-dose cytarabine-containing conditioning regimen for ASCT, compared to 6× R-CHOP and conventional myeloablative conditioning. Prior to the ASCT, the group undergoing dose-intense induction with alternating DHAP had higher ORR (94% vs. 90%, $P = 0{\cdot}19$), and higher CR rate (39% vs. 26%, $P = 0{\cdot}012$). This translated into a longer time to treatment failure (NR vs. 49 months, $P = 0{\cdot}0384$), although not yet an improvement in OS (Hermine *et al*, 2010).

The ongoing phase III GOELAMS and GELA LyMa trial uses four cycles of R-DHAP as induction therapy prior to an ASCT with R-BEAM (rituximab, carmustine, etoposide, cytarbine, melphalan) conditioning, and then randomization to rituximab maintenance or not. Data on 63 evaluable patients have been presented to date (Le Gouill *et al*, 2010). This regimen was well tolerated, with 92% of patients receiving the four cycles as planned, and the response rates following the four cycles of R-DHAP were excellent, with ORR 92% and CR/CR (unconfirmed) rate of 82·5%. Whilst these results are early, and do not provide any survival data, the outcomes are certainly superior to those normally seen with standard induction regimens, and support the use of dose-intense induction regimens.

These intensive cytarabine-containing regimens are generally unsuitable for the older patient (>65 years) due to increased toxicity (Romaguera *et al*, 2005).

Despite increasing the response rate and response quality i.e. CR rather than partial response (PR), the duration of response remains disappointing with a continuing pattern of relapse. In view of this, there is an increasing tendency to consolidate the response in younger patients with HD therapy and peripheral blood stem cell transplantation. This has been shown to increase event-free survival (EFS) and possibly OS – see transplant section.

Summary: treatment of advanced stage disease. Recommendations for the treatment of advanced stage disease are summarized in Fig 1. The initial treatment in elderly (usually > 65 years) or less fit patients (patients < 65 years who are not suitable for HD therapy and transplant), should consist of rituximab plus chemotherapy. As has been discussed, it is recognized that no gold-standard exists. Options include R-FC, R-CVP, R-CHOP, R-bendamustine and R-chlorambucil. The choice and combination of chemotherapy will be guided by patient performance status and co-morbidities, and particular caution should be exercised when including purine analogues or anthracyclines in the treatment of elderly patients.

For young and fit patients (<60–65 years with no significant comorbidities), current evidence suggests that optimal treatment is intensive chemotherapy with a view to achieving a CR prior to autograft. Suitable regimens would include rituximab and high-dose cytarabine.

Assessment of treatment response

Treatment response in MCL is assessed using conventional CT scanning. As mentioned previously, the role of FDG-PET imaging in MCL is not yet established, and this modality of imaging should not be used to assess response outside the context of a clinical trial (Cheson *et al*, 2007).

Although minimal residual disease (MRD) monitoring [using quantitative PCR for the $t(11;14)$ translocation] has been shown to have predictive value, particularly following ASCT (Pott *et al*, 2010), it cannot be routinely recommended at present outside of a trial protocol.

Recommendation

- **When considering how to treat MCL, the clinical presentation (with recognition of the 'indolent' form), proliferation index, clinical risk scores (MIPI) and performance status, should be taken into account. (Strong, Moderate)**
- **For patients with confirmed early-stage MCL, outside the context of a clinical trial, involved field radiotherapy is recommended. (Strong, Moderate)**
- **For patients presenting with indolent disease, a period of observation ('watchful waiting') may be appropriate,**

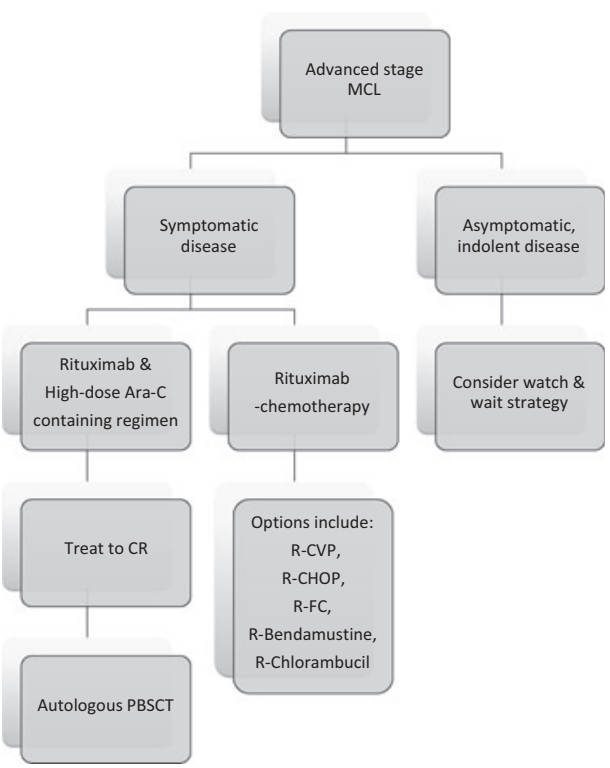

Fig 1. Flow-chart of recommendations for first-line treatment of MCL (outside the context of a clinical trial). MCL, mantle cell lymphoma; Ara-C, cytarabine; R, rituximab; CVP, cyclophosphamide, vincristine, prednisone; CHOP, cyclophosphamide, vincristine, doxorubicin, prednisone; FC, fludarabine, cyclophosphamide; CR, complete response; PBSCT, peripheral blood stem cell transplantation.

prior to initiation of definitive therapy. (Weak, Moderate)

- **Addition of rituximab to combination chemotherapy regimens improves outcomes. Rituximab should therefore be included in the first line chemotherapy regime in the treatment of MCL. (Strong, Moderate)**
- **Older, less fit patients should receive R-chemo e.g. R-FC, R-CVP, R-CHOP, R-bendamustine, R-chlorambucil. (Strong, Moderate)**
- **Younger, fit patients should receive rituximab with a regimen containing HD cytarabine with a view to proceeding to autograft in first remission. (Strong, Moderate)**
- **Single agent rituximab is not generally recommended but may be an option in patients in whom systemic chemotherapy is contraindicated. (Strong, High)**
- **Maintenance therapy is not currently recommended outside a clinical trial. (Strong, Moderate)**
- **Treatment response should be assessed using conventional CT scanning. FDG-PET and assessment of MRD are not currently recommended outside the context of a clinical trial. (Strong, Moderate)**

Management, second-line and beyond

If one excludes patients where transplantation is a therapeutic option, after first relapse in MCL the median survival is approximately 1–2 years. Where the patient has not received autologous peripheral blood stem cell transplantation (PBSCT) as part of first-line therapy, but is considered fit for such therapy at relapse, consideration of consolidation of a second response with an ASCT is a clinical option (discussed below).

There is no standard second-line chemotherapeutic regimen. Treatments generally produce fewer CRs and the duration of the responses are shorter than following initial therapy. The duration of responses in second line and beyond is generally of the order of 9 months. There are many publications looking at therapeutic regimens in lymphoma that include patients with MCL. These are almost always single arm studies and usually contain fewer than 15 patients, as such these have not been considered. In addition for all of the relapsed studies the inclusion/exclusion criteria are different and therefore it is impossible to comment on comparative efficacy. It is acknowledged that there is no-gold standard therapy for relapsed MCL, and clinicians will choose the treatment most appropriate for the individual patient. The choice of therapy will be determined by patient age, performance status, initial therapy, bone marrow reserve and history of infections.

In young patients who have previously undergone autologous PBSCT, an assessment should be made as to whether the patient is fit for allogeneic transplantation. If so, the aim should be to obtain a CR, and then allograft. A HD cytarabine-containing regimen should be considered, even if previously used in first line therapy. Hyper-CVAD and HD methotrexate/cytarabine are less applicable in the relapsed setting than as front line therapy. In the early studies of this combination, 20 patients with relapsed disease were included with a 25% OS and 17% EFS at 3 years. However five patients (25%) died as a consequence of therapy (Khouri *et al*, 1998).

If the patient is not fit for allogeneic transplantation, or has no suitable donor, then a number of treatment options exist, discussed in this section. It is logical that where the patient has received one previous line of treatment, a different agent be chosen at relapse, such that where purine analogues, bendamustine or anthracycline are not used in first-line treatment, then they should be considered at first relapse. Combination chemotherapy can be used, and combinations with demonstrated efficacy include PEP-C (prednisone, etoposide, procarbazine and cyclophosphamide) (Coleman *et al*, 2008), FCR and bendamustine-R. If the patient has had more than one previous line of treatment, there are a number of additional agents with activity. These are summarized in Table VI. Some of these are currently in trials in combination with chemotherapy, where some beneficial synergy is suggested.

Ritixumab

Rituximab as a single agent in the relapsed/refractory setting produces responses in approximately 35% of patients (Coiffier *et al*, 1998; Foran *et al*, 2000) with a median duration of response projected to be 1·2 years. There is only one randomized study exploring the use of rituximab in combination with chemotherapy in the relapsed setting (Forstpointner *et al*, 2004). This trial evaluated the use of fludarabine, cyclophosphamide and mitozantrone (FCM) with or without antibody. There were only 48 evaluable patients with MCL in this trial. Whilst there was no statistically significant difference in response between arms, there was a significant survival benefit following the addition of rituximab (OS not reached vs. 11 months $P = 0{\cdot}0042$). In a subsequent extension to the study, a further, 56 MCL patients were treated with RFCM (FCM + rituximab). Following therapy they were randomized between rituximab maintenance and no further therapy (Forstpointner *et al*, 2006). The median response duration was identical between the arms; however a higher proportion of patients in the maintenance arm experienced remissions beyond 2 years (45% vs. 9%).

Bortezomib

Bortezomib has been approved by the Federal Drug Administration (FDA) in the United States of America for use in relapsed/refractory disease. Four single centre phase II trials investigating the activity of bortezomib in lymphoprolifera-

Table VI. Clinical studies in relapsed and refractory MCL.

Agent	Study	*n*	Overall Response Rate (Combined CR/CRu rate)	Median PFS (months)	Median OS (months)	Median lines of previous therapy (range)	Comment
Proteasome inhibitor							
Bortezomib (Pinnacle trial)	Fisher *et al* (2006)	155	33% (8%)	6·2	Not reached	2 (1 to 3)	
Bortezomib (Pinnacle trial) (Update)	Goy *et al* (2009)	155	32% (8%)	6·7	23·5	3 (1 to 3)	
Bortezomib- gemcitabine	Kouroukis *et al* (2011)	26	58% (12%)	11·4	na	1 (1 to 3)	15% previous ASCT
Bortezomib-rituximab	Agathocleous *et al* (2010)	19	58% (16%)	na	na	na	Part of larger NHL study
mTOR inhibitor							
Temsirolimus	Witzig *et al* (2005)	35	38% (3%)	6·5	12	3 (1 to 11)	
Temsirolimus	Ansell *et al* (2008)	29	41% (3·7%)	6	na	4 (1 to 9)	
Temsirolimus (175/75 mg)	Hess *et al* (2009a)	54	22% (1%)	4·8	2·8	3 (2 to 7)	
Temsirolimus (175/25 mg)	Hess *et al* (2009b)	54	6% (0%)	3·4	10	3 (2 to 7)	
Immunotherapy							
Rituximab	Coiffier *et al* (1998)	13	33% (not stated)	na	na	1 (1 to 3)	
Rituximab	Foran *et al* (2000)	40	37% (14%)	14·4	na	3 (1 to 7)	
R-FCM	Forstpointner *et al* (2004)	24	58% (29%)	8	Not reached	1 (not specified)	Part of larger study with follicular NHL
Purine analogues							
Fludarabine	Decaudin *et al* (1998)	15	33% (0%)	14	na	2 (0 to 3)	Study included 2 treatment-naïve patients
Fludarabine-cyclophosphamide	Cohen *et al* (2001)	20	45% (10%)	3·19	na	1 (1 to 2)	
Fludarabine-cyclophosphamide +/− Rituximab	Thomas *et al* (2005)	16	75%	11	na	2 (1 to 6)	
Cladribine	Inwards *et al* (2008)	25	46% (21%)	5·4	22·8	Not specified	
Other cytotoxic chemotherapy							
FCM	Forstpointner *et al* (2004)	24	46% (0%)	4	11	1 (not specified)	Part of larger study with follicular NHL
Gemcitabine-Dexamethasone	Morschhauser *et al* (2007)	12	36·4% (6%)	3	15	1 (1 to > 3)	
Gemcitabine-Dexamethasone-Cisplatin	Morschhauser *et al* (2007)	18	44·4% (9%)	8·5	Not reached	1 (1 to > 3)	
Bendamustine-Rituximab	Rummel *et al* (2005)	16	75% (50%)	18	na	1 (1 to 3)	
Immunomodulatory agents							
Lenalidomide	Habermann *et al* (2009)	15	53% (20%)	5·6	na	4 (2 to 7)	33% previous ASCT
Lenalidomide	Witzig *et al* (2011)	57	24% (12%)	5·7	na	3 (not specified)	
Thalidomide-rituximab	Kaufmann *et al* (2004)	16	81% (31%)	20·4	Not reached	1 (not specified)	2 patients previous ASCT, 1 RIC-allo SCT
PEP-C/Thalidomide/Rituximab	Coleman *et al* (2008)	22	82% (46%)	Not stated	Not stated	2 (1 to > 3)	Median time on therapy 17 months

Table VI. (*Continued*)

Agent	Study	*n*	Overall Response Rate (Combined CR/CRu rate)	Median PFS (months)	Median OS (months)	Median lines of previous therapy (range)	Comment
Other small molecules							
Flavopiridol	Kouroukis *et al* (2003)	30	11% (0%)	3	na	na	Included 11 treatment-naïve patients
Enzastaurin	Morschhauser *et al* (2008)	60	0%	na	na	2 (1 to 4)	37% FFP for 2·8 months

CR(u), complete response (unconfirmed); PFS, progression-free survival; OS, overall survival; R, rituximab; FCM, fludarabine, cyclophosphamide, mitoxantrone; PEP-C, prednisone, etoposide, procarbazine and cyclophosphamide; ASCT, autologous stemm cell transplantation; NHL, non-Hodgkin lymphoma; RIC-allo SCT, reduced intensity conditioning allogeneic stem cell transplantation; FFP, freedrom from progression, na, not applicable.

tive disorders demonstrated response rates of up to 46% in MCL with CR rates up to 20% in relapsed/refractory disease (Goy *et al*, 2005; O'Connor *et al*, 2005; Strauss *et al*, 2006; Belch *et al*, 2007). This lead on to a registration study (the Pinnacle trial) (Fisher *et al*, 2006) using bortezomib at a dose 1·3 mg/m^2 bi-weekly ×2. One hundred and forty-one patients were assessable and a confirmed response rate of 33% (CR/CRu rate of 8%) observed. The median time to response with bortezomib was 1·3 months and these can be very durable in those patients achieving a CR. In the recently reported update of the Pinnacle trial (Goy *et al*, 2009) the median duration of response observed was 9·2 months but for those patients achieving a CR this has yet to be reached. Bortezomib demonstrates synergistic activity with a number of agents. Studies of bortezomib in combination with chemotherapy are a focus of intense clinical trial activity, and trials with fludarabine, hyper-CVAD, CHOP, HD cytarabine and radioimmunotherapy are on-going. The combination of bortezomib with gemcitabine in 26 patients produced an encouraging ORR of 60% (11·5% CR) but a PFS of only 11·4 months (Kouroukis *et al*, 2011). The scheduling of bortezomib is also being explored with evidence that a weekly schedule (at a higher dose of 1·6 mg/m^2) in combination with rituximab may be as efficacious but less toxic (Agathocleous *et al*, 2010).

Temsirolimus

Temsirolimus, a mTOR (mammalian Target Of Rapamycin) inhibitor, has been approved by the European Medicines Agency (EMA) for use in relapsed/refractory MCL. Temsirolimus, administered intravenously at a dose of 250 mg weekly for 6–12 cycles in 35 heavily pre-treated MCL patients, produced an ORR of 38% (3% CR) and median duration of response of 6·9 months (Witzig *et al*, 2005). A subsequent study (29 patients) used a much lower dose (25 mg weekly) for up to a maximum of 12 cycles (Ansell *et al*, 2008). The ORR was 41% with one patient achieving a CR and a median duration of response of 6 months. These results are remarkably similar; however toxicity was less with the lower dose, 71% vs. 50% grade III haematological toxicity.

The registration study involved a randomization between two dosing schedules of temsirolimus (175 mg/week for 3 weeks and then 75 mg or 25 mg/week) versus investigator-choice single agent therapy (Hess *et al*, 2009a). A total of 162 with relapsed/refractory disease patients were randomized. Those treated with the higher dose of temsirolimus had a significantly longer PFS than the investigator choice arm and a higher objective response rate (22% vs. 2%). The lower dose arm showed a trend towards longer PFS. The median OS for the HD temsirolimus group and the investigator choice arms were 12·8 and 9·7 months respectively.

Temsirolimus requires continuous therapy, with quick progressions reported on cessation of the drug. In spite of this, as

the only drug licensed in Europe for the treatment of relapse, it is included in this guideline as a possible treatment option.

Other agents

There are a number of drugs that have demonstrable activity in this disease setting. Fludarabine has activity in MCL (Foran *et al*, 1999). In previously treated patients, response rates with single agent fludarabine were 31% (only 13 patients), with a short response duration of 4–8 months (Decaudin *et al*, 1998). As observed with other lymphoproliferative disorders, this activity is enhanced by the addition of other agents. The use of cyclophosphamide with fludarabine (FC) increased response rates to 45% with 10% CR (Cohen *et al*, 2001). In a study of patients at first relapse following CHOP therapy, FC was used with or without rituximab in a non-randomized retrospective analysis (Thomas *et al*, 2005). The ORR was 75% with 57% CR and response duration of 11 months.

The addition of mitozantrone to FC (FCM) as described previously (Forstpointner *et al*, 2004), lead to an ORR of 46% (0% CR) and the subsequent addition of rituximab improved the quality of the responses; 58% ORR with 29% CR.

Cladribine as a single agent in the relapsed setting lead to response rates of 46% with 21% CR and a median PFS of 5·4 months (Inwards *et al*, 2008).

Gemcitabine has activity in MCL. In a small study of 30 patients with relapsed/refractory disease it was given in combination with dexamethasone (12 patients) or dexamethasone and cisplatin (18 patients) (Morschhauser *et al*, 2007). The ORRs were similar at 36% and 44%, respectively, but the PFS was very short at 3 months.

Bendamustine is widely used in MCL. In the relapsed setting there are two small combinations studies. Bendamustine with rituximab (16 patients) demonstrated an 81% ORR with 31% CR and a PFS of 20·4 months (Rummel *et al*, 2005). When mitoxantrone was added to this combination, responses appeared a bit higher (92% ORR and 42% CR) but the number of patients was too small (12) to make meaningful comparisons (Robinson *et al*, 2008).

Lenalidomide is an oral immunomodulatory agent that exhibits activity in a range of haematological malignancies. Two trials have included patients with relapsed/refractory MCL. The first, NHL-002, treated 15 patients with single agent lenalidomide, producing an ORR of 53% with a 20% CR rate and a duration of response of 13·7 months (Habermann *et al*, 2009). A second larger study included 57 MCL patients, with an ORR of 42% (CR rate of 21%) (Witzig *et al*, 2011). The major toxicity with this drug is haematological with just over 50% patients requiring dose reductions in the study reported by Habermann *et al* (2009). As a well-tolerated oral agent, lenalidomide is being explored within multiple combinations in MCL.

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 the ORR was 81% with a 31% CR (Kaufmann *et al*, 2004). These responses were durable with a PFS of 20·4 months. Similar studies are exploring the addition of rituximab to lenalidomide. Rituximab and thalidomide have been added to the low dose continuous PEP-C regimen. In a trial of 22 patients the ORR was 82%with a 46% CR. The median duration of therapy was 17 months (Coleman *et al*, 2008). The addition of thalidomide and rituximab did not appear to improve these results. Twenty-five patients were treated on this regimen with an ORR of 73% with 32% CR and a median PFS of 10 months (Ruan *et al*, 2010).

Two other single agent drugs have been evaluated in MCL with disappointing results. Flavopiridol, given as a single agent to 30 patients, achieved a partial response in only three patients with a median duration of response of only 3·3 months (Kouroukis *et al*, 2003). Enzastaurin, a protein kinase C beta inhibitor, produced no objective responses in a study of 60 patients, although a small number of patients had freedom from progression > 6 months (Morschhauser *et al*, 2008).

Recommendation

- **There is no gold-standard therapy for relapsed MCL. The choice of therapy at relapse will be determined by patient age, performance status, bone marrow reserve and initial therapy. (Strong, Moderate)**
- **Hyper CVAD is not recommended at relapse due to high induction mortality. (Strong, Moderate)**
- **Rituximab may be considered for inclusion in therapy at relapse. (Strong, Moderate)**
- **Bortezomib may be considered for inclusion in therapy at relapse. (Strong, Moderate)**
- **Combination chemotherapy may be considered for inclusion in therapy at relapse. (Strong, Weak)**
- **Temsirolimus is licensed in Europe and is a possible option for treatment of relapsed MCL. (Weak, Moderate)**
- **Flavopiridol and enzastaurin are not recommended for treatment of relapsed MCL on the basis of inadequate response. (Strong, Moderate)**

The role of transplantation in the management of MCL

Background

Stem cell transplantation (HD chemotherapy supported by ASCT or allogeneic stem cell transplantation (alloSCT) have been shown to be effective consolidation therapy in MCL, and, as has been discussed above, forms part of the recommended first-line therapy in younger, fitter patients. Allogeneic SCT offers the curative potential of graft-versus-lymphoma effect in this otherwise incurable disease. It is

important to remember, however, that age precludes the application of this treatment option in the majority of patients with MCL.

Autologous stem cell transplantation

Despite being first reported in the mid 1990's (Stewart *et al*, 1995), to date there has only been one RCT examining the role of ASCT in consolidation of MCL induction therapy (Dreyling *et al*, 2005). In this study, patients responding to CHOP-like induction therapy were randomized to α-interferon (IFN-α) or a cycle of BEAM and dexamethasone (Dexa-BEAM) followed by ASCT (cyclophosphamide and total body irradiation (TBI) conditioning). The median PFS was significantly prolonged in the ASCT group compared with the IFN-α maintenance group (39 months vs. 17 months, $P = 0{\cdot}01$). There was no significant difference in 3-year OS (83% after ASCT compared with 77% in the IFN-α maintenance group, $P = 0{\cdot}18$). The only PFS benefit was seen in those who achieved a CR with induction therapy and underwent ASCT. At 5 years, the difference in OS remained non-significant at 70% in the ASCT and 50% in the IFN-α group ($P = 0{\cdot}18$).

Other studies have been single arm, small or retrospective but, despite this, have provided valuable insight into the role of ASCT (Decaudin *et al*, 2000; Khouri *et al*, 2003). Lefrere *et al* (2004) reported a >6 years median survival and a PFS of 51 months when ASCT (TBI, cytosine and HD melphalan) was used to consolidate first CR in 28 patients. Others have reported 5-year relapse rates, 5-year EFS and OS of 56%, 39% and 47%, respectively, following primary induction therapy, including patients with first CR (34%), induction therapy failure but chemo-sensitive disease (39%) and chemo-sensitive disease at first relapse (10%) (Ganti *et al*, 2005). In an European Group for Blood and Marrow Transplantation (EBMT) study of 195 patients, with a median follow up of 3·9 years, the 5-year OS and PFS was 50% and 33%, respectively. Disease status at transplant was the most important factor in determining outcome, with those in first CR benefiting most from ASCT (Vandenberghe *et al*, 2003). In a retrospective analysis of 118 patients undergoing ASCT, it was demonstrated that ASCT was capable of inducing long-term remission up to 16 years after treatment, but the outcome of patients with MCL who relapsed after ASCT was poor (Dietrich *et al*, 2010).

Our current recommendation as discussed above, is that younger fitter patients receive an ASCT as consolidation as part of the first-line treatment, following high-dose therapy. Where the patient has not received ASCT as part of first-line therapy, but is considered fit for such therapy at relapse, ASCT may be considered (Josting *et al*, 2000), although the evidence that ASCT in relapsed disease is of benefit is weak, with no RCTs to demonstrate benefit. A single centre analysis of ASCT in 48 patients, 38% of whom had been treated beyond first-line treatment, demonstrated no difference in OS by number of previous therapies (Reddy *et al*, 2012) suggesting that benefit may still be seen beyond first-line.

There is no evidence to suggest that ASCT is curative in this condition, with no plateau seen in survival curves from these studies. Attempts to improve the results of ASCT have included *in vivo* purging with rituximab, rituximab maintenance post-ASCT and incorporation of radioimmunotherapy (RIT) in the conditioning regimen. Mangel *et al* (2004) used rituximab at the time of stem cell mobilization to 'purge' the stem cell product followed by maintenance rituximab after ASCT. PFS was 89% and OS 88% at 3 years, which compared favourably with historical controls. Another study used rituximab as part of the conditioning regimen without an antibody-based maintenance strategy, demonstrating superior durable disease responses compared to controls (Gianni *et al*, 2003). *In vivo* purging with rituximab does not alter engraftment kinetics post-ASCT (Buckstein *et al*, 1999) and does not appear to produce a MRD-negative state. RCT data of the efficacy of rituximab-based *in vivo* purging in MCL is lacking. There is some evidence that pre-emptive use of rituximab post-ASCT, i.e., in the setting of molecular relapse, may delay or even prevent clinical relapse (Ladetto *et al*, 2006; Andersen *et al*, 2009).

The incorporation of RIT into the conditioning regimen (^{131}I-tositumomab, etoposide and cyclophosphamide) was pioneered by Gopal *et al* (2002). Sixteen patients with relapsed disease were enrolled with 91% CR and 93% OS at 3 years. The authors reported a PFS of 61% at 3 years with no treatment-related deaths. Others (Behr *et al*, 2002) reported the effect of this strategy in patients with relapsed or chemo-refractory disease. Significant logistical and regulatory difficulties associated with the administration of RIT limit its availability and clinical use in the UK.

The role of MRD post-ASCT has been studied. Attainment of molecular remission post-ASCT is associated with a prolongation of the median PFS (92 vs. 21 months, $P < 0{\cdot}001$) and median OS (not reached vs. 44 months, $P < 0{\cdot}003$) (Pott *et al*, 2006). As such, MRD detection post-ASCT may identify patients at risk of early relapse who may be potential candidates for additional therapy.

Allogeneic stem cell transplantation

Patients who relapse after ASCT have few options for long-term disease control. In this setting, non-randomized clinical studies have demonstrated long-term disease control with conventional, myeloablative-conditioned alloSCT though the high treatment-related mortality (TRM: 30–40%) has limited the use of this strategy (Milpied *et al*, 1998; Kroger *et al*, 2000; Peniket *et al*, 2003; Izutsu *et al*, 2004; Ganti *et al*, 2005). As with many other disease groups, transplant physicians have turned to non-myeloablative alloSCT (reduced intensity conditioning [RIC] alloSCT), aiming to harness the graft-versus-tumour effect whilst limiting the TRM. Initial

experience of RIC alloSCT in MCL demonstrated a potential effect, more so in patients relapsing post-ASCT with chemosensitive disease (Faulkner *et al*, 2004). Results of a retrospective study (22 patients) reported by the Lymphoma Working Party of the EBMT (Robinson *et al*, 2002) were very disappointing with 2-year OS and PFS of 12·8% and 0%, respectively. Subsequent studies have shown more encouraging results. A study of RIC alloSCT, using a T cell-replete strategy (Maris *et al*, 2004), recruited 33 patients with relapsed/refractory MCL (17 patients with prior ASCT). With a median follow-up of 24·6 months, no patient transplanted in CR and only one patient with chemo-sensitive disease at transplant has relapsed. Relapse risk at 2 years was 9% and TRM was reported as 24%. The probabilities of OS and PFS at 2 years were 65% and 60%, respectively.

Early experience of RIC alloSCT in patients with MCL was reported with other lymphomas under-going similar protocols. In a retrospective analysis of RIC alloSCT in the UK, the British Society of Blood and Marrow Transplantation (BSBMT) reported a cumulative relapse risk of 65% at 5 years, with a 5-year OS and PFS of 37% and 14%, respectively (Cook *et al*, 2010). The evidence of a graft-versus-lymphoma effect was supported by the increased relapse risk associated with alemtuzumab use and the salvage of relapsing patients with donor lymphocyte infusions.

The variable results published to date using RIC alloSCT in relapsed/refractory MCL relate to the small numbers in each of these studies, variation in patient selection between transplant centres and the different conditioning regimens used. Nonetheless, evidence exists for the presence of an effective graft-versus-MCL effect and as such, alloSCT has a role in the management of chemosensitive disease. Little evidence exists for a role for alloSCT in refractory disease (Cook *et al*, 2010). The role in first line consolidation remains speculative. Currently alloSCT is considered a *Clinical Option* under the BSBMT Indications listings (www.bsbmt.org.uk/indications-table/).

Recommendations

- **ASCT as consolidation therapy in patients deemed fit for intensive therapy is most likely to benefit those who achieve a complete remission. (Strong, High)**
- **ASCT can significantly prolong disease response though at present there is insufficient data to demonstrate a significant OS benefit. (Strong, High)**
- **Molecular monitoring post-ASCT can determine those who are likely to relapse early as determined by MRD positivity, although it is not routinely recommended. (Strong, Moderate)**
- **AlloSCT should be considered in second remission for fit patients with an appropriate donor. Conventional alloSCT is associated with high TRM. RIC alloSCT can be effective at rescuing patients who relapse post-ASCT. (Strong, Moderate)**
- **RIC alloSCT as first-line therapy is a clinical option. Patients should be entered into clinical trials where possible. (Strong, Low)**

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

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Appendix I

The GRADE system

From January 2010 BCSH guidelines have used the GRADE nomenclature for assessing levels of evidence and providing recommendations in guidelines. For laboratory tests guidance is related specifically to clinical utility (that is the ability of a test to alter clinical outcome). GRADE stands for: Grading of Recommendations Assessment, Development and Evaluation. (Guyatt *et al*, 2008).

Strength of Recommendations:

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade two recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what we know or our certainty.

(A) High Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from RCTs without important limitations.

(B) Moderate Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from RCTs with important limitations (e.g. inconsistent results, imprecision - wide confidence intervals or methodological flaws - e.g. lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g. large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Appendix II

Clinical Trials

Information regarding UK clinical trials for patients with MCL can be found at: http://public.ukcrn.org.uk/search/Portfolio.aspx?Level1=1&Level2=9.

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