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A British Society for Haematology Good Practice Paper on the Diagnosis and Investigation of Patients with Mantle Cell Lymphoma

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Methodology

This Good Practice Paper was compiled according to the British Society for Haematology (BSH) process at **www.b-s-h.org.uk**. The BSH produces Good Practice Papers to recommend good practice in areas where there is a limited evidence base but for which a degree of consensus or uniformity is likely to be beneficial to patient care.

Literature review details

MEDLINE, EMBASE, DYNAMED, TRIP and NHS EVIDENCE were searched systematically for publications in English from 1980 to 2017 using the key words '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

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. It has also been reviewed by patient representatives identified by the Lymphoma Association; these organisations do not necessarily approve or endorse the contents.

Introduction

The guidance for the investigation and management of mantle cell lymphoma (MCL), published in 2012 (McKay*, et al* 2012), has been updated and divided into two papers – this Good Practice Paper incorporating new information on pathology, in particular molecular pathology, and use of positron emission tomography/computed tomography (PET/CT)

scanning in staging and response assessment and a Guideline on the Management of MCL including new therapeutic options and transplant data (McKay *et al* 2018).

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), which results in overexpression of the cell cycle protein cyclin D1 (Akiyama*, et al* 1994, Campo*, et al* 1999).

MCL arises mainly in older adults (median age of presentation is 60-65 years) and has 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, the 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).

A number of studies have described the clinical presentation of MCL (Argatoff*, et al* 1997, Bosch*, et al* 1998, Tiemann*, et al* 2005, Zucca*, et al* 1995). 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 peripheral blood involvement are common. Bulk disease at diagnosis and B symptoms are less common. Extra nodal involvement is frequent, particularly affecting the gastro-intestinal 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 2 extra nodal sites is seen in 30-50% of patients (Jares and Campo 2008). Spread to the central nervous system (CNS) can occur (see below) but is rare at diagnosis.

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The clinical course of MCL is heterogeneous. Clinical presentation can correlate with pathological sub-type; notably patients with blastoid histology tend to have an aggressive clinical course, show refractoriness to treatment and have short survival. In contrast, a proportion of cases may present with more indolent disease (Eve*, et al* 2009, Martin*, et al* 2009), characterized by splenomegaly, peripheral blood lymphocytosis, and little or no nodal disease (Nodit*, et al* 2003, Orchard*, et al* 2003). Survival in this group is of the order of 5-12 years. Furthermore, 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). Outside these extremes, the heterogeneity of the disease and the age of patients in which it presents, frequently necessitate an individualized approach.

CNS disease

Three recent publications (Cheah*, et al* 2013, Chihara*, et al* 2015, Conconi*, et al* 2013) have reported a CNS relapse rate between 4.1 and 7.8% with high Ki67 and blastoid histology identified as risk factors in multivariate analysis. CNS relapse tends to occur early (median of 15 to 20 months) and survival is poor (3 to 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

Morphology: the diagnosis of MCL may be made by an excision or adequate core biopsy of an involved site, endoscopic biopsy, bone marrow trephine biopsy or peripheral blood specimen in cases with a leukaemic presentation.

In the classical variant (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 (Argatoff*, et al* 1997, Swerdlow*, et al* 1983, 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 scattered epithelioid histiocytes, especially in cases with a higher proliferation fraction. A small cell variant (3.6% of cases) resembling small lymphocytic lymphoma, though lacking proliferation centres, is recognized. Other subtypes include the blastoid variant (2.6%), morphologically resembling lymphoblastic lymphoma and the pleomorphic variant (5.9%), which may be confused on morphological grounds with diffuse large B cell lymphoma (DLBCL) (Argatoff*, et al* 1997, Norton*, et al* 1995, Ott*, et al* 1997, Swerdlow*, et al* 1983, Tiemann*, et al* 2005). Cases with more than one variant pattern may also occur (Tiemann*, et al* 2005). Identical cytomorphological features are identified in biopsies of extranodal sites. In trephine biopsy specimens, the infiltrate is most commonly nodular and interstitial and less often paratrabecular or diffuse (Argatoff*, et al* 1997, Cohen*, et al* 1998).

Immunophenotype [formalin-fixed paraffin-embedded (FFPE) tissue]: the majority of MCL cases co-express CD20, CD5, BCL2, cyclin D1 and SOX11 and are usually negative for CD10, BCL6 and CD23 (Alkan*, et al* 1995, Argatoff*, et al* 1997, Sander*, et al* 2007, Soldini*, et al* 2014, Swerdlow*, et al* 1995). CD21 highlights a diffuse disorganized network of follicular dendritic cells though this may be variable in extent. With modern antibodies to cyclin D1 (SP4 clone) nuclear expression of cyclin D1 is seen in the great majority of cases (Alkan*, et al* 1995, Swerdlow*, et al* 1995) and false negativity is usually related to poor fixation or inadequate antigen retrieval (Fu*, et al* 2005). In cases with equivocal staining, immunohistochemistry (IHC) for the neuronal transcription factor SOX11 and fluorescence *in situ* hybridization (FISH) for *IGH/CCND1* should be added (Dictor*, et al* 2009, Ek*, et al* 2008, Remstein*, et al* 2000, Sander*, et al* 2007, Soldini*, et al* 2014). An aberrant

immunophenotype, such as CD5 negativity or expression of CD10, BCL6 or CD23, occurs in 5–18% of cases and may lead to an erroneous diagnosis (Camacho*, et al* 2004, Espinet*, et al* 2010, Gualco*, et al* 2010, Schlette*, et al* 2003, Wlodarska*, et al* 1999, Zanetto*, et al* 2008),

Flow Cytometry (peripheral blood or bone marrow): typically, MCL expresses CD19, CD20, CD79b, CD22, CD5 and FMC7 with moderately intense expression of surface light chains, more commonly lambda (Bertoni*, et al* 1999). CD10 expression is seen in a small proportion of cases, particularly in those with blastoid morphology (Zanetto*, et al* 2008). Although cyclin D1 expression cannot be assessed by flow cytometry, SOX11 expression is detectable and may assist in distinguishing CLL from MCL on peripheral blood samples (Wasik*, et al* 2015). Lack of expression of CD200 in MCL in contrast to CLL (Spacek 2014) may also discriminate between these entities.

Cyclin D1-negative MCL

Genuine cyclin D1-negative cases of MCL lacking the *IGH*/*CCND1* rearrangement have been recognized through gene expression profiling and are rare (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 a rearrangement of *CCND2* in 55% of cases (Salaverria*, et al* 2013). Some cases involve *CCND3*. SOX11 is expressed within the nucleus of almost all cyclin D1-negative cases enabling this entity to be reliably identified (Carvajal-Cuenca*, et al* 2012, Ek*, et al* 2008, Mozos*, et al* 2009). Immunocytochemistry for SOX11 should be added in all cases of CD5-positive/cyclin D1-negative B-cell lymphoma.

***In situ* MCL**

This rare entity is characterised by the presence of CD5+ cyclinD1+ small lymphocytes in the mantle zone of the follicle in a morphologically reactive lymph node (Richard*, et al* 2006). In a recent study**,** only one of 12 patients with *in situ* MCL developed clinically overt disease over a follow-up period of four years (Carvajal-Cuenca*, et al* 2012). In view of the non-

progressive nature of this entity in the majority of cases, it has been renamed as mantle cell neoplasia (ISMCN) in the recent update of the WHO lymphoma classification (Swerdlow*, et al* 2016)

Indolent MCL

There are two types of indolent MCL. The first presents with limited stage disease, displays the typical morphology and immunophenotype of classical MCL, often with a nodular or mantle zone pattern and has a very low proliferation fraction. It tends to be SOX11- and cyclin D1-positive (Jares*, et al* 2012, Saeow 2016). The second type presents as a leukaemia with splenomegaly and lack of (or low volume) lymphadenopathy. It has highly mutated *IGHV* genes, a simple karyotype, kappa (rather than lambda) restriction and absent or low *SOX11* expression (Fernandez*, et al* 2010, Nodit*, et al* 2003, Ondrejka*, et al* 2011). It is associated with an indolent course although transformation may occur, which may be the first indication of a diagnosis of MCL (Kiel and Smith 2012)**.**

Genetics and molecular diagnostics

The characteristic cytogenetic abnormality of MCL is the t(11;14)(q13.3;q32.33) translocation, resulting in overexpression of cyclin D1 contributing to deregulated cell cycle progression at the G1-S phase boundary (Vandenberghe*, et al* 1991, Williams*, et al* 1993). In practice, the translocation, which is usually detected by FISH on fresh or FFPE tissue (Belaud-Rotureau*, et al* 2002, Dubus*, et al* 2002, Reichard*, et al* 2006), should be demonstrated in cases with atypical morphology, an aberrant immunophenotype, equivocal cyclin D1 positivity or unusual clinical presentation. Secondary cytogenetic abnormalities are common in MCL and the degree of karyotypic complexity is negatively associated with patient survival (Cuneo*, et al* 1999) (Katzenberger*, et al* 2008, Parry-Jones*, et al* 2007, Wlodarska*, et al* 1999). The majority of MCL cases are characterised by an unmutated *IGHV* gene. A small proportion possess a highly mutated *IGHV* gene that is most commonly seen

in the indolent leukaemic group with low or absent expression of *SOX11* (Nodit*, et al* 2003). A detailed account of the molecular pathogenesis of MCL can be found in several recent review articles (Campo and Rule 2015, Dreyling*, et al* 2015, Jares*, et al* 2012, Vose 2013).

Biological prognostic factors

Many biological features have been examined such as growth pattern, blastoid morphology, TP53 expression, *IGHV* gene mutation status and secondary cytogenetic abnormalities with varying reports as to their significance (Argatoff*, et al* 1997, Jares*, et al* 2012, Katzenberger*, et al* 2006, Nordstrom*, et al* 2014, Norton*, et al* 1995, Ott*, et al* 1997). Identification of blastoid morphology may be difficult in view of variation in fixation and the subjective nature of assessing cell size. Proliferative activity by Ki67 index is the most important prognostic factor in routine diagnostic practice (Determann*, et al* 2008, Katzenberger*, et al* 2006, Tiemann*, et al* 2005) with an index of >30% associated with a poorer outcome.

Inter-observer variability in assessment of the proliferation index is well recognized. The European MCL Network suggest that counting the Ki67 positive cells among 100 lymphoma cells in each of two representative high-power fields generates improved consistency (Klapper*, et al* 2009).

TP53 mutations predict a very poor outcome that appears not to be overcome by intensive up front therapy in younger patients (Eskelund, *et al* 2017). In patients with true leukaemic (non-nodal) disease, SOX11 negativity can help predict an indolent phenotype but this does not apply in nodal disease. Kappa rather than lambda restriction may indicate indolent disease (see above)**.** 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.

Differential diagnosis

Cyclin D1 may be expressed in a number of other lymphoproliferative disorders, such as hairy cell leukaemia, multiple myeloma and 3% of DLBCL (Ehinger*, et al* 2008). Adequate assessment of morphology and an appropriate panel of immunocytochemistry should prevent erroneous diagnosis. In the case of DLBCL, lack of a demonstrable *IGH*/*CCND1* translocation and lack of immunoreactivity for SOX11 differentiates this group from pleomorphic variants of MCL (Hsiao*, et al* 2012).

Recommendations

- **Lymph node excision or adequate core biopsy is required for the diagnosis of nodal mantle cell lymphoma (MCL). In a non-nodal presentation, tissue biopsy or peripheral blood may provide the diagnosis.**
- **All cases should be subject to routine central review by an experienced haematopathologist.**
- **Immunohistochemical panels for the investigation of all B cell lymphomas should include cyclin D1.**
- **SOX11 immunostaining is required for the diagnosis of cyclin D1-negative MCL and should be included in panels where there is a suspicion of MCL.**
- **The presence of the t(11;14) translocation should be demonstrated by fluorescence *in situ* hybridization in cases with atypical morphology, aberrant immunophenotype, equivocal cyclin D1 positivity or unusual clinical presentation.**
- **It is recommended that the Ki67 Proliferation Index be recorded at baseline, with an index of > 30% suggestive of poorer outcome.**

Initial Investigations, Staging and Prognostic Scores

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Laboratory investigations:

Full blood count and blood film

Immunophenotyping by flow cytometry if peripheral blood lymphocytosis is seen (20-40% of patients)

Biochemical investigations including lactate dehydrogenase (LDH)

Virology - it is recommended that patients undergo testing for hepatitis B (surface antigen and core antibody), hepatitis C and human immunodeficiency virus (HIV) prior to therapy

Bone marrow aspirate and trephine biopsy – recommended for staging. May be omitted in the presence of peripheral blood involvement or, if flow cytometry is available, to assess marrow involvement in aspirate sample, trephine biopsy may be avoided

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**.**

Imaging in MCL

Computed tomography (CT) of the neck, chest, abdomen and pelvis should be performed (contrast-enhanced unless contraindicated). Magnetic resonance imaging (MRI) may be useful for assessment of CNS disease where clinical suspicion is high (Ferrer*, et al* 2008, Gill*, et al* 2009, Gill and Seymour 2008). (^{18}F) Fluorodeoxyglucose positron emission tomography (FDG-PET) is now used in the assessment of many types of lymphoma. 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 lymphomas, FDG-PET has been shown to have lower sensitivity in staging MCL, particularly extranodal disease and has not been shown to upstage compared with CT scan (Hosein, *et al* 2011). Routine use of FDG-PET for

this purpose cannot currently be recommended outside the context of a clinical trial. Although the role of FDG-PET in early stage MCL remains unproven, it may be considered if radical radiotherapy is being proposed.

Endoscopy – some authorities recommend routine colonoscopy and upper gastro-intestinal (GI) endoscopy as part of staging investigations in MCL (Zelenetz& Hoppe, 2001), on the basis that prospective studies have identified microscopic involvement by MCL of the GI tract in 92% of cases (Salar *et al*, 2006). This finding rarely (less than 4% of cases) changes clinical management (Romaguera*, et al* 2003). Endoscopy should be performed on the basis of clinical symptoms, particularly in those patients with features of GI bleeding or if clinical stage 1A disease is present and radiotherapy with curative intent is planned. Where endoscopy is performed, biopsies of any suspicious lesions, and also macroscopically normal areas, should be taken for histological examination.

Pregnancy testing in women of childbearing age prior to chemotherapy

Staging

The modified Ann Arbor staging system (Lister *et al* 1989) is used. As most patients with MCL have blood and bone marrow involvement at presentation, clinical stage in isolation is not of great prognostic significance.

Clinical prognostic scoring systems

The international prognostic index (IPI) is not reliable in MCL (Hoster*, et al* 2008, Moller*, et al* 2006). A prognostic scoring system specifically for MCL, the MCL international prognostic index (MIPI) has been devised (Hoster*, et al* 2008). A simplification of this score (sMIPI) assigns patients to three groups (low, intermediate and high risk) according to values of four clinical variables: age, Eastern Cooperative Oncology Group performance status, serum

LDH and white blood cell count. The combined MIPI (MIPI-c) (Hoster*, et al* 2016), which also includes Ki-67 index, refines the prognostic score further by dividing patients into four groups: low, low-intermediate, high-intermediate or high risk. The sMIPI and MIPI-c can be calculated on line at **http://www.european-mcl.net/en/clinical_mipi.php**. Whilst these scores provide clear prognostic information, they do not usually influence treatment decisions at the present time.

Recommendations

- **Performance status should be recorded at baseline**
- **Routine blood tests including full blood count and film, and biochemical tests including lactate dehydrogenase should be performed**
- **Virological testing for hepatitis B, hepatitis C and human immunodeficiency virus is recommended prior to immunochemotherapy**
- **Patients should undergo staging bone marrow aspirate and trephine biopsy unless there is peripheral blood involvement; trephine may be avoided if flow cytometry is carried out on aspirate sample**
- **Patients should undergo clinical staging with computed tomography of neck, chest, abdomen and pelvis**
- **Routine use of (^{18}F) Fluorodeoxyglucose positron emission tomography in the staging or response assessment of MCL is not recommended**
- **Colonoscopy and other endoscopy should only be performed for clinical indications, or if radiotherapy for stage IA disease is considered**
- **Lumbar puncture with cytospin and immunophenotyping if clinical suspicion of central nervous system involvement**
- **All patients should have their simplified or combined MCL international prognostic index (sMIPI or MIPI-c, respectively) score recorded at baseline**

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Declaration of Interests

The BSH paid the expenses incurred during the writing of this good practice paper.
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**.

Disclaimer

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