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Mantle Cell Lymphoma: Contemporary Diagnostic and Treatment Perspectives in the Age of Personalized Medicine

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Abstract
Mantle cell lymphoma is a clinically heterogeneous disease occurring within a heterogeneous patient population, highlighting a need for personalized therapy to ensure optimal outcomes. It is therefore critical to understand the benefits and risks associated with both intensive and deintensified approaches. In the following review we provide a therapeutic roadmap to strategically guide treatment for newly diagnosed and relapsed/refractory patients highlighting pivotal and recently published results involving known and novel therapies.

Introduction

Mantle cell lymphoma (MCL) is an uncommon B-cell malignancy subtype that was officially classified as a distinct class of non-Hodgkin lymphoma (NHL) by the revised European-American classification (REAL) in 1994 [1] and characterized as a mature B cell neoplasm with morphological variants of diverse clinical behavior by the 2008 World Health Organization classification [2]. It usually accounts for 6% of all NHL in United States, and 7–9% in Europe [3,4]. New cases of MCL have increased with a recently reported incidence of 0.64 per 100,000 person years in the US population [5,6]. The disease is more commonly diagnosed in older men with a median age at diagnosis of 68 years, and a male/female ratio of 2.6:1 [5,6]. Epidemiological risk factors are incompletely defined, with data to suggest both inherited and exogenous triggers related to the development of this malignancy [7–11].

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Diagnosis

Histologically, MCL is composed of mature monomorphic small to medium size B cells with indented nuclei frequently lacking visible nucleoli [2,12]. The 2008 World Health Organization classification described four different morphological variants of MCL: small cell variant that morphologically mimics small lymphocytic lymphoma; marginal zone-like variant that may resemble marginal zone lymphoma and clinically presents with massive splenomegaly in >80% of patients [13]; and pleomorphic variant and blastoid variant with lymphoblast-like cells that have a high mitotic rate [2]. In the spectrum of MCL morphological variants, the blastoid and pleomorphic types have clinical prognostic significance [2,14,15]. The classic immunophenotype of MCL includes an intense surface immunoglobulin (Ig)M/IgD more commonly associated with lambda restriction, positivity for CD5, CD19, CD20 (bright), CD22, weakly positive or negative CD23, and negative expression of CD10 [2]. Even though the above immunophenotypic presentation is the most typical, up to 26% of MCL are positive for CD23 at diagnosis [16]. It is also clinically relevant to acknowledge the higher prevalence of aberrant CD10 expression and/or CD5 loss among the blastoid and pleomorphic MCL variants [13,17,18]. Finally, all MCL cases are BCL2 positive and almost all express cyclin D1 [2,19—21]. The identifying cytogenetic alteration of MCL is the translocation t(11;14)(q13;32), which is found in the majority of cases [2,22]. This genetic event juxtaposes the *bcl-1* protooncogene to the Ig heavy chain locus resulting in cyclin D1 overexpression [2,11]. Notably, fluorescence in situ hybridization (FISH) is more sensitive and specific for the detection of cyclin D1 and other variants, rather than conventional cytogenetic analysis [23—26]. Cytogenetic and FISH evaluation are of importance when evaluating for blastoid/pleormorphic subtypes with aberrant antigen expression, as *bcl1* and *bcl2* overexpression can also be seen in some cases of diffuse large B-cell lymphoma. Certain rare MCL variants lacking cyclin D1 have been described, and may be identified by overexpression of the nuclear transcription factor SOX11 [27,28]. Cyclin-D1-negative MCL may show cyclin D2 and possibly cyclin D3 overexpression and/or translation instead, with small case series suggesting inferior prognosis [29].

Disease presentation and initial work-up

The initial presentation of MCL can be variable. Patients can present in a leukemic phase with marked leukocytosis, with pancytopenia, or even with localized involvement of unusual extranodal areas such as skin, central nervous system, or lacrimal glands [12,30]. However, the disease more commonly presents in advanced stages (III/IV) with disseminated lymphadenopathy, splenomegaly, and bone marrow infiltration. Remarkably, the gastrointestinal (GI) tract is one of the preferred extranodal homing sites of MCL and many will show involvement on endoscopy/colonoscopy, particularly if random biopsies are obtained in the absence of visible abnormalities [4,31,32]. Other potentially involved sites at presentation are the liver and Waldeyer's ring [28].

Retrospective studies suggest that up to 30% of newly diagnosed MCL patients may have an indolent presentation and do not require immediate treatment [11,33,34]. Clinically, such patients usually debut with modest lymphocytosis, nonbulky lymphadenopathy, splenomegaly, bone marrow infiltration and/or GI involvement [33—36]. The cellular proliferation marker Ki-67 is usually low (<30%) in these patients, consistent with an indolent course [37,38]. Serial biopsies of both indolent and classic tumors with evidence of morphological and proliferation changes suggest that the indolent MCL variant has a different natural history, and could be part of an initial low-grade disease spectrum with steady progression towards a more aggressive tumor [33—35,39]. Retrospective evaluations suggest that those with slow progression to symptomatic disease (i.e., >12 months before treatment is indicated) may have overall better prognosis [31,33,35]. It is critical to distinguish indolent tumors from in situ MCL [35]. The natural history of in situ MCL is not well characterized and in most series, the diagnosis of in situ cases is only appreciated retrospectively from biopsies obtained prior to the clinical manifestation of MCL [35,40—43]. Nonetheless, in situ MCL usually has a very long latency period and close follow-up without active treatment is indicated [35].

To obtain accurate staging and useful prognostic information, initial workup for MCL needs to include a thorough history and physical examination with detailed documentation of baseline performance status (i.e., Eastern Cooperative Oncology Group score) [44], constitutional symptoms, lymphadenopathy, hepatosplenomegaly, and/or other possible areas of extranodal involvement [4]. A complete blood count, peripheral blood flow cytometry, metabolic profile, β2 microglobulin, and lactate dehydrogenase (LDH) level should be part of the initial evaluation, as well as HIV, hepatitis B and C serology since almost all current systemic therapies include anti-CD20 monoclonal antibodies with the potential for virus-mediated complications [4]. As with other NHLs, initial staging should include a bone marrow biopsy with immunophenotyping by flow cytometry, cytogenetics with FISH evaluation, as well as a computed tomography (CT) with contrast of the neck, chest, abdomen, and pelvis [4]. When available, fluorodeoxyglucose positron emission tomography (PET)/CT should also be considered to guide nodal biopsy (to the site with highest uptake) and to improve detection of extranodal disease manifestations. Despite the high frequency of GI tract involvement, with some reports describing incidences as high as 88—92% [31,32], routine use of upper endoscopy and colonoscopy usually does not influence initial treatment approach. In accordance with current guidelines [4,13], we recommend the use of endoscopy/colonoscopy as part of the initial workup in patients that have symptoms or signs of GI involvement or to confirm Stage I/II disease that would otherwise be treated with localized therapeutic modalities. Finally, a lumbar puncture to evaluate central nervous system involvement is warranted in patients with neurological symptoms, blastoid variant MCL and/or high Ki-67 (>50%) [4,45].

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