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Open questions in the management of mantle cell lymphoma

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SUMMARY

Mantle cell lymphoma (MCL) is one of the lymphomas with the worse prognosis (median survival 3–5 years) as it has an aggressive evolution and at the same time is incurable. Biologically it is characterized by the t(11;14)(q13;q32) translocation leading to overexpression of cyclin D1. This review focuses on a number of controversial issues in the management of this disease, as how to stage patients with a disease which often has extranodal localizations, how to recognize the small subgroup of cases with an indolent course, which treatment is suggested for the young and fit or for the elderly, the role of CNS prophylaxis, rituximab maintenance and radiotherapy, the indications to allogeneic transplantation and the place of new active anti-lymphoma drugs.

Introduction

Mantle cell lymphoma (MCL) derives from pre-germinal centre B-cells of the follicle mantle zone, marginal zone or peripheral blood memory B-cells and accounts for approximately 3–10% of non-Hodgkin's lymphomas (NHLs).[1,2] It predominantly occurs in advanced aged white men, and commonly presents with extensive lymphadenopathy and extra-nodal involvement, especially bone marrow, gastrointestinal tract, liver, spleen or Waldeyer's ring. MCL is one of the lymphomas with the worse prognosis, carrying the unfavorable characteristics of both indolent (incurable) and aggressive lymphomas (rapidly growing). Despite the existence of an indolent subgroup (10–15% of MCL patients) who survive more than 10 years, most cases follow a relatively rapid disease progression, short response to treatment, inevitable relapses, and continuously declining survival curve with a median survival of only 3–5 years.[3–5] MCL are morphologically divided into classical variants (including nodular, diffuse, mantle zone and rarely follicular growth pattern), aggressive variants (blastoid and pleomorphic) and the very indolent variant "in situ" MCL. The t(11;14)(q13;q32) translocation leading to overexpression of cyclin D1 (an important cell cycle regulator of G1/S phase) is the most important but not exclusive genetic characteristic of most MCL. Cyclin D2 or D3 is overexpressed in cyclin D1-negative MCL with similar morphologic, pathologic, clinical and molecular features of typical MCL.[6,7]

The clinical management of patients presenting with MCL has been the subject of a number of recent reviews.[8–11] In this paper, we address some issues which are still controversial and subject of frequent debate.

Which are the necessary staging examinations?

Essential staging procedures include physical examination, history enquiring for B symptoms, complete blood count (CBC), bone marrow biopsy ± aspirate, and computed tomography (CT) scan of the chest, abdomen and pelvis. Optional further examinations are ^{18}F-fluoro-deoxyglucose positron emission tomography (FDG-PET)-CT, GI-endoscopy and cerebrospinal fluid (CSF) examination.

The role of PET/CT is established in the staging and response assessment of diffuse large B-cell and Hodgkin lymphoma, while its role in other lymphomas is still debated. PET/CT is not included for MCL in the consensus recommendations for staging or surveillance based on scarce data and especially limited therapeutic consequences.[12] In MCL, extranodal sites are involved in up to 90% of patients, these being mainly bone marrow, gastrointestinal tract and liver. The involvement of these organs may be difficult to be differentiated on PET/CT from physiologic or reactive uptake (Fig. 1).

MCL patients have bone marrow and peripheral blood involvement at diagnosis in approximately 80% and 35% of cases, respectively,[13] while CSF is not routinely examined. The available data suggest that CNS involvement is rare in asymptomatic MCL patients at diagnosis and more than 50% of symptomatic patients have no morphologic or immunophenotypic evidence of CSF involvement despite multiple lumbar punctures.[14] For these

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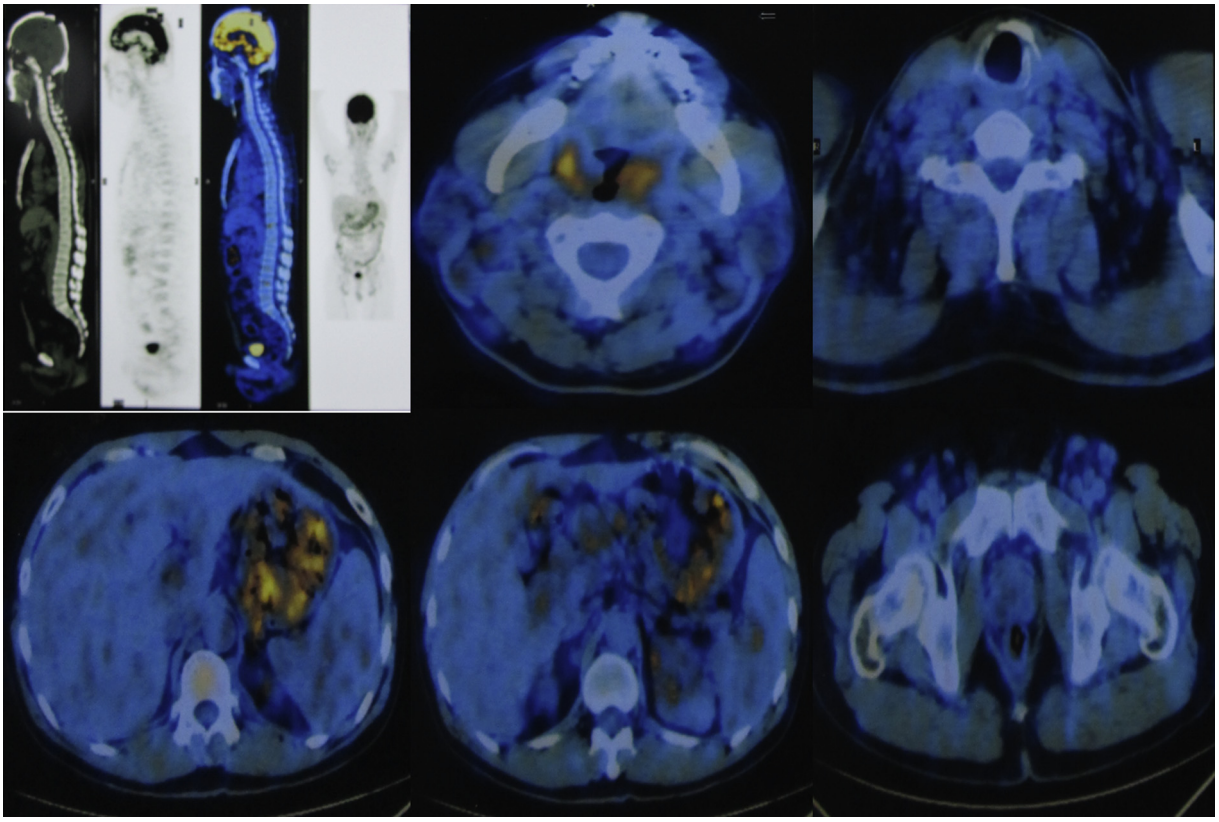

Fig.1. A total body positron emission tomography/computed tomography (PET/CT) fusion image of a 44-years old patient with indolent mantle cell lymphoma. He complained of minimal symptoms but the staging showed total body extensive lymph nodes involvement, bilateral parotids, bilateral tonsils, stomach, spleen, bilateral kidneys and bone marrow involvement with a maximal standardized uptake values (SUVmax) 2.6–5.3 in September, 2009. He preferred to choose an option of watch and wait, and has not received any anti-lymphoma treatment until presently.

reasons, CSF examination and CNS prophylaxis is not considered mandatory in MCL patients.

The estimation of GI tract involvement at presentation is variable[15] depending if one considers only symptomatic cases (25%) or histological examination of endoscopically obtained tissue (88% in the lower GI tract and 43% in the upper GI tract).[8] GI tract endoscopy examination is suggested for clinical stage I–II patients, in order to confirm the early stage and better define the indication to localized treatment, or in cases of "in situ" MCL to exclude the possible coexistence of overt MCL. GI tract endoscopy examination is also necessary to document complete response in patients included into clinical trials.[4]

How to recognize good-risk patients?

The survival of MCL patients varies from the median 18 months of the blastoid and plemorphic variants to the 5–12 years without therapy of the indolent non-nodal leukemic subset.[8] To discriminate these heterogeneous patients, prognostic factors specific for MCL have been investigated, looking at clinical characteristics and biological properties.

The international prognostic index (IPI) originally developed for DLBCL and the follicular lymphoma IPI (FLIPI) originally developed for FL fail to recognize a low-risk group in MCL.[16] A prognostic index specific for MCL (MIPI) and its simplified version (sMIPI) were developed based on four clinical variables (age, performance status, white blood cell count and lactate dehydrogenase [LDH] level).[16] The MIPI can discriminate MCL in three groups with a median survival of approximately 3, 5 or 7 years.

Gene expression profiling could be a molecular predictor of survival. MCL patients can be stratified into four prognostic groups according to a survival predictor score generated by 20 proliferation-related genes.[17] A PCR-based five-gene model was also proposed to predict survival on fresh-frozen or formalin-fixed, paraffin-embedded MCL samples.[18] Based on a genome-wide microRNA profiling platform of high-throughput quantitative real-time PCR (qRT-PCR), MCL cases could also be separated into three clusters with different biologic and clinical characteristics.[19] Although GEP warrants further validation and is currently not available for routine clinical application, it allows a better understanding of genomic alterations and may in the future lead the way to better patient-tailored and risk-adapted treatment options.

Recently, an indolent subset of MCL was identified by non-nodal presentation, hypermutated immunoglobulin variable-region heavy chain (IgVH), absence of genomic complexity, and no need of treatment for years. The SOX11, an antigen highly expressed in 90–95% of MCL, but rarely in other B-cell lymphomas, is used for the diagnosis of cyclin D1-negative MCL.[20] Recently it was proposed as a useful marker to recognize the indolent subset but its prognostic role is still controversial: in one study SOX11-negative MCL patients presenting as nodal disease had inferior OS (median OS 494 vs. 1488 days, $P = 0.0498$) while in another study, SOX-11 negative non-nodal MCL had superior OS (5-year OS 78% vs. 36%, $P = 0.001$) compared with SOX11-positive MCL patients.[21,22] Hence, the role of SOX11 in predicting MCL prognosis remains apparently controversial, and it should not be used in the routine clinical settings before prospective validation has taken place.

Which is the optimal first line therapy for young and fit patients?

There is no generally accepted standard treatment for MCL, but the majority of studies suggest that the best treatment is one