Mantle Cell Lymphoma

Is It Time for a New Treatment Paradigm?

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KEYWORDS

• Mantle cell • Stem cell transplantation • Maintenance • MRD • Novel therapies • Bortezomib • Ibrutinib • Lenalidomide

KEY POINTS

- Mantle cell lymphoma (MCL) outcome has improved thanks to the achievement of deeper remission (complete remission [CR] and molecular CR), which translates into much longer progression-free survival (>5 years) and greater overall survival (OS).
- Maintenance rituximab in responders (post-R-CHOP [rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone] and post-high-dose therapies–autologous stem cell transplantation) improves duration of response and might improve OS in some cases.
- Novel therapies (bortezomib, lenalidomide, ibrutinib) which have shown durable responses in the relapsed/refractory setting, including in chemorefractory patients, offer an opportunity to build up on current regimens as either combination and/or maintenance strategies, while also offering hope for non-chemotherapy-based options, particularly in elderly MCL patients.
- Integrating biologicals into current regimens will likely improve quality and durability of response in both combination and maintenance settings.
- Biologicals-only combinations might help develop non-chemotherapy-based options, particularly in elderly MCL patients.
- A shift in the MCL paradigm is definitely seen. Finally, a greater awareness of biological heterogeneity might serve to stratify patients better in the clinic.

BACKGROUND

The field of mantle cell lymphoma (MCL) has changed dramatically since its recognition as a separate entity more than 30 years ago. The concept of mantle-zone lymphoma first introduced in 1982 by Weisenburger and colleagues[1] was confirmed by the International Lymphoma Study Group in 1992 and refined in the Revised European-American Lymphoma and World Health Organization classification in 1994.[2] MCL recognition was based on its distinct morphologic and molecular features (hallmark t(11;14) translocation),[3,4] but also its immunophenotype and distinct clinical course, with much poorer outcome among "indolent lymphomas."

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MCL represents 6% to 10% of non-Hodgkin lymphomas with a median age at diagnosis in the mid to late 60s and a clear predominance in men (ratio 3:1). Some data suggest a possible increase in MCL incidence over the last two decades, albeit likely reflecting improved diagnostics. Although most MCL cases are thought to derive from an antigen-naive pre-germinal center B cell, there is definite evidence of cases with restricted immunoglobulin gene repertoire (particularly IGHV3-21 and IGHV4-34 genes), which together with precise somatic hypermutation patterns suggest a role for chronic antigenic stimulation. Moderate associations with MCL risk have been reported for *Borrelia burgdorferi* infection,[5] lifestyle-related factors, family history of hematopoietic malignancies, or genetic susceptibility (interleukin-10 and tumor necrosis factor genes),[6] while others suggest molecularly defined antigenic specificity for B-cell receptor (BCR) in some series.[7]

The t(11;14)(q13;q32) translocation that juxtaposes the proto-oncogene *CCND1* at 11q13 to the immunoglobulin heavy chain complex (*IGH*) at chromosome 14q32 is considered the primary oncogenic mechanism (although not sufficient) for the development of MCL. This translocation forces the constitutive overexpression of cyclin D1, which can also be expressed (at a much lower level) by other B-cell lymphomas and is typically not detected in normal B lymphocytes. The overexpression of cyclin D1 leads to deregulation of the cell cycle at the G_1/S phase transition: cyclin D1 binding to CDK4/6 activates the transcription factor E2F by phosphorylating its inhibitor, retinoblastoma 1 (RB1) and further promotes cyclin E/CDK2 activation, which triggers entry into the S phase of the cell cycle. Several secondary genomic alterations targeting genes involved in key molecular pathways have been reported as involved in MCL pathogenesis and/or its aggressive clinical course. Together these genetic alterations affect important pathways such as INK4A/CDK4/RB1 and ARF/MDM2/p53 (cell cycle/survival), PI3K/AKT/mTOR (cell growth/survival), ataxia telangiectasia mutated (*ATM*) gene at 11q22-23 (genetic stability), mutations or deletions of *TP53*/*RB* or deregulation of checkpoint kinases *CHK1* and *CHK2* (DNA damage response), amplifications/overexpression of *BCL2* (cell death/fate), or constitutive activation of nuclear factor κB (cell survival).[8] Many of these genomic alterations as well as complex karyotypes have also definite prognostic value in MCL.[9] SOX11 (neuronal transcription factor of the high-mobility group) expression is typically associated with minimal somatic hypermutation and genetic instability and with worse outcome. On the opposite, SOX11-negative variants are typically associated with indolent behavior; such cases (10%–15% of MCL) present with high white blood cell count, splenomegaly, no or minimal nodal disease (ie, mimicking chronic lymphocytic leukemia [CLL] but negative for both CD23 and CD200). These cases derive from postgerminal center B cells, show hypermutated *IGHV*, low/no karyotype complexity, and longer survival with prolonged stable clinical course. Rarely, some of these indolent (SOX11-negative) MCL may "transform" into aggressive disease usually associated with 17p/*TP53* alterations.

The classical immunophenotype of MCL reflects a mature B-cell lymphoma (positive for CD19, CD20, CD22, CD79a, PAX5, and FMC7) with coexpression of CD5. MCL cells also show typically immunoglobulin M/D positivity with more frequent lambda expression over kappa (ratio 1:13) and are negative for CD23, CD10, CD200, and BCL6.[10] The diagnosis is confirmed through cyclin D1 overexpression and/or by the presence of t(11;14) translocation, more frequently seen by fluorescence *in situ* hybridization than cytogenetics.[11] A small subset of truly *cyclin D1*-negative MCL (5%–10%) will show overexpression of *cyclin D2* or *D3*[12] predominantly through alternative translocations with immunoglobulin light chain genes.[13] SOX11 expression has been reported as a tool to help diagnose such cyclin D1-negative MCL,[14] which