79.2. Hodgkin and Non-Hodgkin Lymphomas: Mantle Cell Lymphoma

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Emerging Prognostic Factors for Clinical Care

Given the variable natural history of MCL, identification of robust factors that predict outcome and guide therapy are essential to make progress in the disease.

SOX11. MCL often expresses the transcription factor SOX11.[1] This may be very helpful in distinguishing MCL lacking expression of cyclin D1 from variant CLL lacking CD23 expression. However, another role for evaluation of SOX11 expression in MCL is emerging. Some cases of MCL lack the expression of SOX11, which appears to correlate with an indolent clinical course.[2-4] However, there are cases of MCL with an indolent behavior that express SOX11. Nonetheless, lack of SOX11 expression in MCL may become a routine biomarker to help identify patients with an indolent course.

Immunoglobulin Heavy Chain Variable Gene (*IGHV*) Mutation Status. The role of *IGHV* mutation status is well established in CLL/SLL.[5,6] Data are emerging suggesting that the situation in MCL may mirror the experience in CLL/SLL.[4,7-10] Patients with MCL who have a germline (unmutated) *IGHV* have the more aggressive clinical course and shorter OS compared with patients with *IGHV* mutation, who have a more indolent course. The lack of SOX11 expression and the presence of *IGHV* mutation are highly correlated. Therefore, testing for SOX11 and *IGHV* mutation would be unnecessary. The advantage of testing for *IGHV* mutation status is that there is a clear result, in contrast to a negative IHC result with SOX11 that is potentially complicated by a false negative result.

***TP53* Mutation/del(17p).** There is extensive evidence that mutation or deletion of *TP53* is associated with an adverse outcome in MCL.[7,11-14] Although these lesions may be present at diagnosis, they appear to be enriched in relapsed/refractory disease. Nonetheless, it has not become routine to evaluate for these lesions. However, with the emergence of treatments that may be effective in the presence of TP53 mutation or del(17p), such as ibrutinib and venetoclax, it may become more important to know whether these lesions are present to help guide treatment decisions.

MDM2 Overexpression. MDM2 is a negative regulator of TP53. Overexpression of MDM2 is seen in a subset of MCL cases and is associated with a poor prognosis.[14-16] This is consistent with the data discussed earlier that loss of TP53 is associated with a more aggressive course. The net result of MDM2

overexpression is loss of TP53. However, the clinical data are relatively sparse, and additional information is needed to confirm the importance of MDM2 expression in the prognosis of MCL.

Factor	***Definition***	***Clinical significance***	***Level of evidence***
SOX11[2,4]	Expression or lack of expression of SOX11 by IHC	In typical MCL with t(11;14), lack of SOX11 is associated with an indolent course; some indolent MCLs are SOX11 positive.	III
IGHV mutation status[4,7,8,10]	Determination of the sequence of the rearranged *IGHV* to determine whether the tumor is pre– or post–germinal center	*IGHV*-mutated cases appear to have a much more indolent course of MCL and may be more reliable than IHC for SOX11; however, results are variable.	III
del(17p); *TP53* mutation[7,11-14]	FISH for 17p or sequencing of *TP53*	del(17p) or *TP53* mutation predicts a poor outcome.	II
MDM2 overexpression[14-16]	IHC for *MDM2*	Overexpression of *MDM2* is associated with poor prognosis.	III

Risk Assessment Models

Risk assessment models and prognostic tools play an important role in cancer medicine because they provide a mechanism to integrate disparate data elements into a process that leads to decreased prognostic heterogeneity. Such processes are useful for (1) identifying and characterizing important prognostic factors, (2) improving prognostic predictions for individual patients, and (3) designing, conducting, and analyzing clinical trials.[17] The most common type of prognostic tool is a prognostic calculator that provides time-specific outcome (e.g., 5-year OS) probability predictions for individual patients based on their demographic, clinical, and tumor characteristics. The prognostic nomogram developed by Yang et al[18] is an example of a risk calculator. Another type of prognostic tool is a prognostic classifier that places patients into ordered prognostic risk classes (either directly or based on cutoffs for individual probability estimates). The remaining tools referenced in this chapter (e.g., IPI, MIPI, FLIPI, and CLL-IPI) are prognostic classifiers. The AJCC Precision Medicine Core (PMC) developed and published criteria for critical evaluation of prognostic calculators,[19] which are presented and discussed in Chapter 4. The prognostic nomogram developed by Yang et al[18] meets all but one of the AJCC PMC criteria because it lacks discussion of how missing data were treated.

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Recommendations for Clinical Trial Stratification

The authors have not provided any recommendations for clinical trial stratification at this time.

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