MYC overexpression: adding another piece to the puzzle of high-risk mantle cell lymphoma

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Although mantle cell lymphoma (MCL) has a common genetic hallmark t(11;14), juxtaposing *IGH* and *CCND1* gene loci, which leads to cyclin D1 overexpression, MCL is markedly clinically and biologically heterogeneous, ranging from an indolent to highly aggressive disease. Characterizing high-risk MCL is an area of ongoing interest not only in order to refine prognostication in this disease, but also to identify subgroups of patients who may benefit from novel therapeutic approaches beyond standard chemoimmunotherapy. The MCL International Prognostic Index (MIPI), high proliferation (estimated by Ki-67 in routine clinical practice), blastoid/pleomorphic morphology, complex cytogenetics, and *TP53* aberrations are clinical and pathobiological risk factors associated with poor prognosis in MCL.[1] There are ongoing efforts to identify additional factors that underlie the diversity of MCL and measures of increased genomic and epigenomic complexity as well as *TP53* and *C-MYC* alterations have been associated with more aggressive clinical behavior and poor survival outcomes.[2]

In a paper published in this issue of *Haematologica*, Rodrigues and colleagues add to the evolving story of high-risk MCL by demonstrating that MYC protein overexpression is an independent prognostic factor associated with inferior progression-free and overall survival outcomes.[3] In their retrospective analysis of 252 MCL patients (154 from the Swedish Lymphoma Register and 98 from the Nordic Lymphoma Group clinical trials MCL2 and MCL3), MYC overexpression assessed by immunohistochemistry (defined as >20% positive cells with nuclear staining using an anti-MYC antibody) was identified in 14% of samples (35/252). The MYC overexpression correlated with increased *MYC* mRNA expression levels by RNAscope®. Interestingly, *C-MYC* translocation (identified by fluorescence *in situ* hybridization [FISH]), *C-MYC* copy number gains, or *C-MYC* genetic mutation were rarely observed in this cohort and did not correlate with MYC protein overexpression. *MYC* rearrangements and mutations have been rarely reported in previously published retrospective series and case reports, and thus have not become a routine part of the cytogenetic/molecular evaluation of MCL cases.[4-11] MYC overexpression, assessed by immunohistochemistry, in contrast, appears more prevalent based on this study and, thus, a potentially more robust prognostic marker.

In the study by Rodrigues *et al.*, MYC overexpression correlated with inferior progression-free survival and overall survival and remained an independent prognostic factor in multivariable Cox proportional hazards models when adjusting for other high-risk features. Of interest, a subgroup of patients (n=13) with evidence of MYC overexpression and *TP53* alteration (TP53 overexpression and/or mutation) had a particularly poor prognosis with an increased risk of progression (hazard ratio=16.9, 95% confidence interval: 7.4-38.3) and death (hazard ratio=7.8, 95% confidence interval: 4.4-14.1). *TP53* aberrancy is widely recognized as one of the strongest prognostic factors in MCL and, despite optimal intensive chemoimmunotherapy, this subset of patients has markedly inferior survival outcomes compared to patients with wild-type *TP53* status.[12] However, molecular clustering data (incorporating whole exome sequencing and RNA-sequencing analyses) suggest that *TP53* mutations can be seen in both non-nodal leukemic patients with an overall favorable prognosis (cluster 1) and also in patients with dismal survival outcomes enriched for highly proliferative and non-classical histology MCL (cluster 4), suggesting that the prognostic relevance of TP53 is context-dependent and that not all mutations are created equal.[13] Interestingly, cluster 4 also had gene signatures of an active MYC pathway. Thus, as suggested in the work by Rodrigues *et al.*, the combination of alterations in both TP53 and C-MYC may have an additive negative prognostic effect.[3]

C-MYC is an essential transcription factor that regulates various cellular functions, including proliferation, growth,

and apoptosis, and has been implicated in the pathogenesis of a number of B-cell lymphomas. Although *C-MYC* gene rearrangements (assessed by FISH) are commonly seen in Burkitt lymphoma and high-grade B-cell lymphoma ("double-hit diffuse large B-cell lymphoma [DLBCL]"), MYC overexpression assessed by immunohistochemistry in the absence of the *C-MYC* gene rearrangement has been shown to be prognostically relevant in the so-called "double expressor" DLBCL.[14] In MCL, the acquisition of a *C-MYC* translocation 8q24 has been referred by some as "double-hit" MCL and has been associated with blastic transformation and an aggressive disease course in various case reports.[4-11] From the study by Rodrigues *et al.*, we learn that MYC overexpression in MCL, without evidence of *C-MYC* translocation or mutation, is more common than previously recognized, prognostically relevant, and is likely driven by transcriptional dysregulation.

High-risk MCL patients, defined by *TP53* mutation and other factors, remain a challenging population to treat and ongoing clinical trials are investigating integration of targeted therapies and novel immunotherapeutics. Although it is recognized that standard chemoimmunotherapy is likely inadequate for *TP53* aberrant MCL, the optimal alternative therapeutic approach remains unclear. Given the heterogeneous chemotherapies applied in the retrospective series described in the study by Rodrigues *et al.*, this study does not provide any insights into optimal treatment pathways for the high-risk subsets with MYC^{high} or MYC^{high} with *TP53* alterations, but emphasizes the need for a broader assessment of MYC expression in MCL to validate these findings and perhaps to facilitate future development of individualized therapies for high-risk MCL.

Disclosures

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References

1. Jain P, Dreyling M, Seymour JF, Wang M. High-risk mantle cell lymphoma: definition, current challenges, and management. J Clin Oncol. 2020;38(36):4302-4316.
2. Nadeu F, Martin-Garcia D, Clot G, et al. Genomic and epigenomic insights into the origin, pathogenesis, and clinical behavior of mantle cell lymphoma subtypes. Blood. 2020;136(12):1419-1432.
3. Rodrigues J, Hollander P, Schmidt L. MYC protein is a high-risk factor in mantle cell lymphoma and identifies cases beyond morphology, proliferation and TP53/p53 – a Nordic Lymphoma Group study. Haematologica. 2024;109(4):1171-1183.
4. Au WY, Horsman DE, Viswanatha DS, Connors JM, Klasa RJ, Gascoyne RD. 8q24 translocations in blastic transformation of mantle cell lymphoma. Haematologica. 2000;85(11):1225-1227.
5. Felten CL, Stephenson CF, Ortiz RO, Hertzberg L. Burkitt transformation of mantle cell lymphoma. Leuk Lymphoma. 2004;45(10):2143-2147.
6. Hao S, Sanger W, Onciu M, Lai R, Schlette EJ, Medeiros LJ. Mantle cell lymphoma with 8q24 chromosomal abnormalities: a report of 5 cases with blastoid features. Mod Pathol. 2002;15(12):1266-1272.
7. Hu Z, Medeiros LJ, Chen Z, et al. Mantle cell lymphoma with MYC rearrangement: a report of 17 patients. Am J Surg Pathol. 2017;41(2):216-224.
8. Michaux L, Wlodarska I, Theate I, et al. Coexistence of BCL1/CCND1 and CMYC aberrations in blastoid mantle cell lymphoma: a rare finding associated with very poor outcome. Ann Hematol. 2004;83(9):578-583.
9. Reddy K, Ansari-Lari M, Dipasquale B. Blastic mantle cell lymphoma with a Burkitt translocation. Leuk Lymphoma. 2008;49(4):740-750.
10. Tirier C, Zhang Y, Plendl H, et al. Simultaneous presence of t(11;14) and a variant Burkitt's translocation in the terminal phase of a mantle cell lymphoma. Leukemia. 1996;10(2):346-350.
11. Vaishampayan UN, Mohamed AN, Dugan MC, Bloom RE, Palutke M. Blastic mantle cell lymphoma associated with Burkitt-type translocation and hypodiploidy: short report. Br J Haematol. 2001;115(1):66-68.
12. Eskelund CW, Dahl C, Hansen JW, et al. TP53 mutations identify younger mantle cell lymphoma patients who do not benefit from intensive chemoimmunotherapy. Blood. 2017;130(17):1903-1910.
13. Yi S, Yan Y, Jin M, et al. Genomic and transcriptomic profiling reveals distinct molecular subsets associated with outcomes in mantle cell lymphoma. J Clin Invest. 2022;132(3):e153283.
14. Green TM, Young KH, Visco C, et al. Immunohistochemical double-hit score is a strong predictor of outcome in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol. 2012;30(28):3460-3467.