Review Article



# Tailored treatment in mantle cell lymphoma

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**Abstract:** Mantle cell lymphoma (MCL) is a heterogeneous disease. For the last 10 years, the recommended frontline therapy has been high dose cytarabine and consolidation with autologous stem cell transplantation (ASCT) for young, otherwise healthy patients, and less intensive chemoimmunotherapy schemes for elderly patients. These therapies are very effective, with high clinical remission rates, but some patients are still refractory or relapse very early. However, less intensive therapy, sparing short- and long-term toxicity, may be sufficient for cases presenting with low tumor burden or more indolent disease. Many clinical and biological prognostic factors have been described in MCL, and patients can be stratified into different classes according to the risk of treatment failure. Nevertheless, being prognostic rather than predictive, these factors have not been used to tailor the therapeutic approach to individual patient risk thus far. However, given the most recent advances in translational research and the availability of many novel and effective drugs for MCL, the scenario is rapidly changing. In particular, the universally recognized dismal outcome associated with *TP53* disruption and the availability of diagnostic facilities is prompting clinical researchers to design dedicated, tailored, clinical trials and to intensify the current therapeutic choices for high-risk patients. Moreover, gene expression profiling (GEP) using robust commercial platforms, such as those based on NanoString, may soon become clinical routine for treatment personalization in MCL. In this review, we cover these issues in detail, starting from the description of classical and novel biomarkers, discussing the current possibilities for tailoring treatment in real world clinical practice, and ending with some well-founded hypotheses that may concretize the concept of personalized medicine for MCL patients in the near future.

**Keywords:** Biomarkers; prognostication; personalized medicine; non-Hodgkin lymphoma

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## Introduction

Mantle cell lymphoma (MCL) is a non-eradicable lymphoproliferative disorder. Despite therapeutic successes achieved with the introduction of rituximab and high-dose regimens with cytarabine and autologous stem cell transplantation (ASCT), there is no survival plateau, and the course of the disease is characterized by a pattern of continuous relapses. However, MCL is a very heterogeneous disease; though the large majority of MCL patients achieve durable remission, some patients are refractory to treatment, with a worsening of outcome (1-5). Therefore, biological factors that influence the behavior of MCL and its response to treatment need to be identified. Clinical and biological factors have been identified and prognostic scores established, allowing the stratification of patients into risk classes. Although useful, these tools are not able to effectively identify very high or very low risk

patients and cannot be applied for tailoring treatment (3). In recent decades, research has focused on identifying biological factors that affect the different clinical outcomes, such as DNA mutations (6) and specific mRNA signatures (7,8) identified by gene expression profiling (GEP) and protein expression (immunohistochemistry) (9). Moreover, minimal residual disease (MRD) analysis is an established tool in MCL; similar to other lymphoproliferative disorders, it allows us to assess the risk of recurrence during and after treatment by monitoring the residual malignant clone (5,10,11). In this review, we briefly discuss the validated tools for risk stratification in MCL and subsequently focus on the most appealing novel candidate biomarkers more extensively. Finally, we will discuss the potential application of this knowledge for tailored treatment in MCL patients.

## Validated tools for risk stratification in mantle cell lymphoma

### *MIPI score*

Given the inadequacy of the International Prognostic Index (IPI) in MCL, a dedicated prognostic tool was introduced into clinical practice in 2008, the MCL International Prognostic Index (MIPI) score (1). The MIPI score is based on independent clinical and laboratory prognostic factors: age, performance status according to the Eastern Cooperative Oncology Group (ECOG), lactate dehydrogenase (LDH), and leukocyte count. These parameters identified three groups of patients with different overall survival (OS): low risk (44% of patients, median OS not reached), intermediate risk (35%, 51 months OS), and high risk (21%, 29 months OS). This tool was subsequently validated in the context of modern rituximab and high-dose cytarabine clinical trials, the "MCL Younger" (12) and "MCL Elderly" (13) trials of the European MCL Network, in which the MIPI score identified three risk groups with 5-year OS rates of 83%, 63%, and 34% (low, intermediate, and high risk groups, respectively). Its impact was independent of treatment received and was valid for both younger and elderly patients. Moreover, high concordance was found between MIPI scores and the simplified MIPI (s-MIPI) score, which was more easily applied in clinical routine (2).

### *Ki-67 proliferative index*

The histopathological marker Ki-67 is an indirect index of cell proliferation, identifying patients with more aggressive disease and worse prognosis (14-16). Attempting to improve the prognostic impact of the MIPI score, Ki-67 was integrated, giving rise to the "biological" MIPI (MIPI-b) (1). This validated tool was able to better identify patients with high-risk disease, but did not significantly discriminate between patients at low *vs.* intermediate risk (2). Finally, an improved model using the Ki-67 index as a dichotomous value (≥30%) was developed, the MIPI-c, which is able to identify four risk groups with 5-year OS of 85%, 72%, 43%, and 17% (3).

### *Blastoid morphology*

The undifferentiated cytological aspect of MCL was identified as an unfavorable feature for both progression-free survival (PFS) and OS, regardless of the therapeutic progress with rituximab, high dose schedules, or novel combinations (3,17). Accordingly, the blastoid variant is more often associated with unfavorable clinical, immunohistochemical, and cytogenetic features, such as high MIPI score and Ki-67 index, and aberrations in *TP53*. ASCT is a valid option for young patients, but a combined approach with novel agents may be necessary to overcome the poor prognosis in elderly patients (18-21).

### *MRD analysis*

MRD is defined as the small amount of disease that remains after an effective treatment, and is not identifiable by traditional imaging or laboratory techniques. The negative prognostic impact of MRD persistence measured by standardized allele-specific oligonucleotide (ASO) quantitative polymerase chain reaction (qPCR) has been validated in large phase II and III clinical trials (4,5,10,11,22).

## Novel candidate biomarkers

### *Somatic mutations and chromosomal imbalances*

In the last couple of years, the mutational landscape of MCL has been investigated extensively. The first whole genome and exome sequencing studies describing the characteristics and frequency of somatic mutations in MCL (6) grouped them on the basis of the physiological function impaired by the single gene aberration: genes controlling the cell cycle or responsible for DNA repair (*CCND1*, *TP53*, *ATM*), epigenetic regulation (*KMT2D*, *WHSC1*), and genes controlling cell-signaling pathways (*NOTCH1/2*, *BIRC3*,

*TRAF2*). The most frequent mutations were recorded in *ATM* (41%), *CCND1* (34%), *TP53* (27%), *KMT2D* (13%), and *WHSC1* (13%). However, the patient series described in these studies were retrospective, inhomogeneous, and not fully annotated, often leading to inconclusive results in terms of clinical impact. Some signals suggest a role of TP53, which is involved in the regulation of apoptosis and genomic stability and is altered in many hematological and solid tumors (23-25), and aberrations in *NOTCH1/2*, which encodes a single-pass transmembrane receptor and is prognostic in chronic lymphocytic leukemia (26), in the negative effects of mutations. More recently, in a highly selected unicentric series, *MYC* translocations were associated with particularly dismal outcomes (27).

Interestingly, both topographical and temporal heterogeneity were described in the mutational landscape of single MCL patients. In particular, different mutations were identified in different tissues collected at diagnosis (i.e., peripheral blood *vs.* lymph node), probably originating from a common precursor clone before spatially diverging with different tropism. Different clusters of mutations were also observed over time in the same patients, in accordance with clonal evolution of MCL cells between diagnosis and relapse (6).

More recent studies have focused on select mutations, analyzing their impact on outcome in prospective patient series (*Table 1*). The European MCL Network investigated somatic gene copy number alterations (CNAs) in 135 patients enrolled in the randomized "MCL Younger MCL" trial (#NCT00209222) (28). In this study, deletions in *TP53* (22%) and *CDKN2A* [25%, encoding both the CDK4/6 inhibitor INK4a, p16, and the positive TP53 regulator ARF, p14 (30)] significantly impacted both PFS and OS. Moreover, the association of these two deletions (7%) conferred further worsening of the outcome, suggesting a synergistic negative effect.

The negative impact of *TP53* mutations in younger MCL patients was demonstrated in a combined prospective series from the "MCL2" and "MCL3" phase II trials of the Nordic Lymphoma Group (19), with mutated cases presenting a median OS of 1.8 years compared to not reached (NR) in wild type (WT) patients. In accordance with the European MCL Network study (28), deletions of *TP53* and *CDKN2A* negatively affected prognosis, but a strong association with *TP53* mutation was found in these cases.

Finally, the negative role of *TP53* alterations (both mutations and deletions) was independently validated in the Italian series of the "MCL0208" trial by Fondazione Italiana Linfomi (FIL) (21). In this study, mutations in the gene encoding lysine methyltransferase 2D (*KMT2D*, known as *MLL2*), an epigenetic regulating enzyme that acts as a tumor suppressor, also independently predicted worse PFS and OS; these results were reproduced in the Nordic series (19) when more stringent bioinformatics criteria for *KMT2D* mutation calling were applied (21). On the other hand, *NOTCH1* mutations were not confirmed as independent prognostic markers, as they often co-occurred with TP53 aberrations.

In summary, despite the increasing bulk of genomic data, the only validated biomarkers in MCL, thus far, are *TP53* aberrations (both mutations and deletions) and, to a lesser extent, *KMT2D* mutations, both of which account for a median OS of 4 years in younger patients (*Table 1*). This impact is independent from the other known prognostic factors but partially associated with blastoid morphology, Ki67 ≥30%, and high-risk MIPI (19,21). Therefore, by adding *KMT2D* mutations and *TP53* disruption to the MIPI-c backbone, the authors proposed a new genetic prognostic index, the "MIPI-g", which improved the model discrimination ability compared to the MIPI-c alone (21). Moreover, no impact of the different treatment approaches was observed in young patients receiving high-dose therapy with ASCT.

However, despite the strong prognostic value, some limitations have to be clarified before the broad introduction of *TP53* and *KMT2D* investigation to clinical routine. In particular, the tissue and analytical technique are heterogeneous, and the clinical impact in elderly patients has not yet been investigated in large prospective series (*Table 1*). These issues are currently being addressed in the context of the ongoing phase III clinical trials of the European MCL Network (e.g., "EuMCL-R2", EudraCT 2012-002542-20 and "Triangle", EudraCT 2014-001363-12). Nonetheless, these biomarkers are able to consistently select a population (~25% of patients) with a biologically different high-risk disease. These patients do not seem to benefit from the standard, high-dose chemo-immunotherapy, the current standard of care in young patients.

### *Immunohistochemistry*

Immunohistochemical staining can be used to study the expression of some proteins in tissue for the diagnosis and characterization of MCL. In particular, increased expression of SOX11, a neural transcription factor not expressed in normal lymphoid tissue, is found in most MCL cases and

 

**Table 1** Clinical impact of genomic aberrations in front-line prospective MCL trials

| Clinical trial | Patients (analyzed/ enrolled) and age | Therapeutic schedule | Tissue | Technique | Candidate gene aberrations | Median PFS (pooled arms) | Median OS (pooled arms) |
|---|---|---|---|---|---|---|---|
| MCL Younger (NCT00209222) Ph III EuMCLNet trial (28) | 135/497, ≤65 years old | 6RCHOP *vs.* 3RCHOP/3RDHAP + ASCT | BM; PB; FFPE sections | Copy number variation analysis | del *CDKN2A* | *CDKN2A*: del 1.5 years *vs.* WT 5.8 years | *CDKN2A*: del 2.6 years *vs.* WT 6.8 years |
| | | | | | Del *TP53* | *TP53*: del 2.1 years *vs.* WT 5.8 years | *TP53*: del 4.1 years *vs.* WT 7 years |
| MCL2 (ISRCTN 87866680); MCL3 (NCT00514475) NLG ph II trial (19) | 183/320, ≤65 years old | MCL2: MaxiCHOP/ HDAraC + ASCT; MCL3: RmaxiCHOP/HDAraC ± Zevalin + ASCT | Unselected BM cells | NGS targeted resequencing | Mut *TP53* | *TP53*: mut 0.9 years *vs.* WT 10.2 years | *TP53*: mut 1.8 years *vs.* WT NR |
| MCL0208 (NCT02354313) ph III FIL trial (21) | 186/300, ≤65 years old | RCHOP + HDAraC + ASCT ± lenalidomide maintenance | CD19-selected BM cells | NGS targeted resequencing/ copy number variation analysis | Mut *KMT2D* | (4 year-PFS) *KMT2D*: mut 33% *vs.* WT 64% | (4 year-OS) *KMT2D*: mut 62% *vs.* WT 87% |
| | | | | | Mut/Del *TP53* | *TP53*: mut/del 25% *vs.* WT 63% | *TP53*: mut/del 55% *vs.* WT 88% |
| MCL4 (NCT00963534) ph II NLG trial (29) | 46/50, ≥65 years old or ≤65 frail | Lenalidomide-bendamustine-rituximab | Unselected BM and PB cells | NGS targeted sequencing | Mut *TP53* | *TP53*: mut 0.8 years *vs.* WT 3.5 years | *TP53*: mut 2.1 years *vs.* WT 5.8 years |

EuMCLNet, European Mantle Cell Lymphoma Network; NLG, Nordic Lymphoma Group; FIL, Fondazione Italiana Linfomi; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; DHAP, cisplatinum, Ara-C, dexamethasone; ASCT, autologous stem cell transplantation; HDAraC, high-dose AraC; Lena-BeRit, lenalidomide, bendamustina, rituximab; BM, bone marrow; PB, peripheral blood; FFPE, formalin-fixed, paraffin-embedded; NGS, next-generation sequencing; Mut, mutation; Del, deletion; WT, wild type; mPFS, median progression-free survival; mOS, median overall survival; CDKN2A, cyclin-dependent kinase inhibitor 2A; TP53, tumor protein 53; KMT2D, histone-lysine N-methyltransferase 2D.

in some cases of hairy cell leukemia (31), and it seems to be implicated in the regulation of cell differentiation (32). In small retrospective studies, the absence of SOX11 has been associated with a subgroup of patients with better prognosis, characterized by leukemic and splenic, but not nodal, disease (33), and frequently with hypermutated IGHV genes and low genome complexity (34), so-called "indolent MCL". Recent studies with larger cohorts of patients have had contradictory results regarding the prognostic significance of this immunohistochemical marker. In Nordic studies, SOX11 expression was negatively associated with Ki-67 and p53 expression, identifying a population with low proliferative index and non-blastoid morphology, which is suggestive of it being a somewhat protective factor (25,35). In the cohort of patients from the European MCL Network trials, the presence of SOX11 did not correlate with time to treatment failure (TTF) or OS in a multivariate analysis with MIPI and Ki-67 (9). Therefore, data about this marker are still contradictory, and a possible explanation may be underrepresentation of indolent MCL cases in clinical trials.

On the other hand, the expression of p53 is considered a surrogate for the mutational status of *TP53* (36). For a long time, increased expression of p53 has been associated with aggressive MCL. In large clinical trials from both the Nordic group and the European MCL Network, expression of p53 was significantly associated with poor outcomes (9,25). In particular, a high level of expression (>50% of cells) was strongly predictive of short TTF and OS in both univariate and multivariate analyses. In addition, most patients with high p53 expression have a high Ki-67 and high-risk MIPI. An epiphenomenon of p53 aberration may be a higher proliferative index and more aggressive clinical behavior. Moreover, Aukema *et al.* reported that a lack of p53 expression is associated with worse outcome, which may be a consequence of *TP53* mutation, deletion, or epigenetic alterations negatively affecting the protein function. In summary, as the clinical value of p53 expression has been validated in numerous large prospective trials, independently of MIPI and Ki-67, incorporation of p53 staining into routine diagnostic practice is now recommended (37). However, its use is not yet widespread, and strict assessment guidelines need to be followed to ensure inter-laboratory reproducibility (38).

### *GEP*

GEP has mostly been used in the last 20 years to improve the characterization of lymphoproliferative diseases, targeting both the malignant cell and the tumor microenvironment, mainly in diffuse large B-cell lymphoma (39-42) and follicular lymphoma (43,44). More recently, GEP has been applied to MCL studies in order to develop new stratification risk models. The main features of currently available GEP-based tools for risk stratification in MCL are summarized in *Table 2*.

Initially, the proliferative gene signature was investigated in MCL as a quantitative integrator of multiple oncogenic aberrations (49), resulting in a better outcome predictor than single factor models based on individual oncogenic events. Four subgroups with significantly different median OS (6.7 *vs.* 3.3 *vs.* 2.3 *vs.* 0.8 years) were categorized. Nonetheless, as GEP requires fresh tissue, it is not applicable to everyday diagnostic routine, and Ki-67 staining was introduced as a surrogate index of cell proliferation, as it is easier to apply in clinical practice (14,15).

More recently, activation of B-cell receptor (BCR) and canonical NF-kB signaling was specifically described in MCL. The quantification of the BCR signaling strength was reflected by the expression of BCR-regulated genes and closely correlated with tumor proliferation. In particular, the autonomous signaling correlated with mutations and polymorphisms in these pathways and, thus, is apparently independent of microenvironment support. Activation of BCR identified a subset of patients with inferior survival after cytotoxic therapy. After a median follow-up of 7.5 years, the OS in patients with $BCR^{high}$ scores was 68%, compared to 96% for patients with $BCR^{low}$ scores (HR =6.88, P=0.05) (7).

To provide an easy-to-use prognostic tool for the identification of high-risk MCL patients, Bomben *et al.* proposed a six-gene BCR signature to be assessed by qPCR (45). The analysis was performed in the context of the frontline FIL "MCL0208" phase III trial on CD19-selected peripheral blood (PB) cells and formalin-fixed paraffin-embedded (FFPE) samples from lymph node biopsies. Among this younger population, the signature targeting *AKT3*, *BCL2*, *BTK*, *CD79B*, *PIK3CD*, and *SYK* was able to identify a $BCR^{high}$ group characterized by discouraging outcomes, with a median PFS of 42 months versus "not reached" in $BCR^{low}$ patients (P<0.01). Combining the BCR signature with the Ki-67 index achieved further refinement of outcome discrimination; the median PFS and OS were 21 and 47 months for $BCR^{high}$ with Ki-67 ≥30%, respectively, versus "not reached" for all other combinations (P<0.01 for PFS and P<0.05 for OS, respectively).

Recently, with technical improvements due to the

 

**Table 2** Currently available GEP-based tools for MCL risk stratification

| Clinical trial/ reference | Tissue | Technology | Genes studied | Median PFS (pooled arms) | Median OS (pooled arms) |
|---|---|---|---|---|---|
| NCT00114738 (7) | 55 PB/FFPE samples | GEP | 27-gene BCR signature; 18-gene NF-kB signature; 28-gene NIK signature | BCR≥upper tercile 2 years; BCR<upper tercile 2.9 years | (7.5-year OS) BCR≥upper tercile 68%, BCR<upper tercile 96% |
| MCL0208 (NCT02354313) (45) | 83 PB/FFPE samples | GEP/qRT-PCR | 6-gene signature | $BCR^{high}$ 3.5 years; $BCR^{low}$ not reached | NA |
| Retrospective series (8) | 110 FFPE samples | NanoString (MCL-35 assay) | 17-gene proliferation signature | NA | High risk 1.1 years; standard risk 2.6 years; low risk 8.6 years |
| MCL "Younger" (NCT00209222); MCL "Elderly" (NCT00209209) (46) | 169 FFPE samples | NanoString (MCL-35 assay) | 17-gene proliferation signature | High risk 0.7 years; standard risk 2.6 years; low risk 5.3 years | "Younger": high risk 0.8 years, standard risk 4.7 years, low risk 10 years; "Elderly": high risk 2 years, standard risk 3 years, low risk NR |
| MCL2 (ISRCTN 87866680); MCL3 (NTC 00514475) (47) | 74 FFPE samples | NanoString (MCL-35 assay) | 17-gene proliferation signature; 18-housekeeping genes | High risk 2.8 years; standard risk NR; low risk 6.5 years | High risk 5 years; standard/ low risk NR |
| Retrospective series (48) | 70 PB samples | NanoString (L-MCL16 assay) | 16-gene proliferation signature | (3-year TTT); nnMCL 31%; cMCL 88% | (3-year OS) nnMCL 92%; cMCL 69% |

FIL, Fondazione Italiana Linfomi; EuMCLNet, European MCL Network; NLG, Nordic Lymphoma Group; GEP, gene expression profile; PB, peripheral blood; FFPE, formalin-fixed and paraffin-embedded; qRT-PCR, quantitative real-time polymerase chain reaction; mPFS, median progression-free survival; mOS, median overall survival; mFFS, median failure-free survival; TTT, time to first treatment from diagnosis; BCR, B-cell receptor; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; NA, not available; NR, not reached; nnMCL, non-nodal MCL; cMCL, classical MCL.

availability of NanoString analysis on a digital platform, a new molecular assay to test the proliferation signature in FFPE samples was introduced in MCL (8). Scott *et al.* trained the assay using 47 FFPE biopsies and microarray gene expression data from matched fresh frozen biopsies as a gold standard. Subsequently, a model was developed using the expression of 17 proliferation genes to replicate the proliferation signature score described by Rosenwald *et al.* (49). This locked assay ("MCL35") was validated in an independent cohort of 110 MCL patients. This signature defined groups of patients with significantly different OS, independent from MIPI score and treatment received (R-CHOP ± ASCT). Accordingly, patients were classified into three risk groups (high 26%, standard 29%, and low 45%) with significantly different median OS: 1.1, 2.6, and 8.6 years, respectively (P<0.001). Notably, the MCL35 assay clustered MCL cases with adverse "classical" biological characteristics, such as blastoid morphology and elevated Ki-67, as high-risk patients according to their proliferative signature (8). Finally, the strong prognostic value of this assay was validated in the prospective cohorts of the European MCL Network "MCL Younger" and "MCL Elderly" phase III clinical trials (46), as well as the Nordic "MCL2" and "MCL3" phase II trials (47). Alone or combined with MIPI or MIPI-c scores, the MCL35 assay could identify patients with dismal outcome despite intensified treatment.

In addition, a novel NanoString-based prognostic tool was recently described. The 16-gene signature "L-MCL16" is able to distinguish conventional (c) and leukemic non-nodal (nn) MCL (48); this clinical variant, characterized by splenomegaly, lymphocytosis, and no or minimal nodal involvement, has an overall excellent prognosis, even without treatment. Early and precise identification of these MCL patients would allow an alternative approach, rather than conventional, chemotherapy-based regimens. The

L-MCL16 assay was applied to a cohort of 70 MCL patients with leukemic presentation, assigning 37% of cases to nnMCL and 56% to cMCL. These patient groups differed in some clinical and biological characteristics (i.e., nodal presentation, immunoglobulin heavy chain gene mutational status, genomic complexity), with nnMCL presenting significantly better survival than cMCL (3-year OS 92% *vs.* 69%; P<0.01). In summary, even though its application may be challenging in patients with low levels of leukemic disease, the L-MCL16 assay combined with clinical and genetic data will probably help better identify this peculiar, indolent entity, allowing patients to be spared unnecessary treatment.

### *Micro-RNA based prognostic tools*

Another field of prognostication in MCL focuses on microRNA (miR) analysis. MiRs are short sequences of non-coding RNA implicated in the regulation of the expression of several genes responsible for different cellular functions and, namely, oncogenesis. Comparison of MCL samples to their normal counterparts (naive B cells) has identified differentially expressed miR with roles in cellular growth and survival pathways (50-53) in the last few years, and the clinical impact of miR in MCL has been studied in some small retrospective series; each study identified different miRs as being associated with outcome (*Table 3*) (50,55).

A distinctive miR signature was identified and validated in two small, retrospective cohorts of patients with aggressive lymphoma. Of this signature, two miRs (miR 127-3p and miR 615-3p) were significantly associated with OS in a training set of 119 MCL patients and validated in an independent cohort of 114 MCL patients. Moreover, the combined use of miR and classical prognostic factors (Ki-67 and MIPI) seemed to better identify high-risk patients (56-58).

Finally, Husby *et al.* investigated and validated the clinical effect of miR expression in two large prospective homogenously treated cohorts (59). In this study, 74 diagnostic MCL samples from the Nordic MCL2 trial were profiled for miRs, and prognostic miRs were validated in an independent series of 94 patients from the MCL3 trial. MiR-18b overexpression was able to identify patients with poor prognosis, and a new biological prognostic index was proposed combining miR-18b levels with MIPI-b (MIPI-b-miR), which identified high-risk patients in terms of both PFS and OS. These data were confirmed in the MCL2 population after 15 years of follow-up (60). Finally, the authors suggested that miR-18b may contribute to chemoresistance by decelerating cell proliferation.

### *Epigenomics and DNA methylation signatures*

The study of epigenetic patterns using unbiased genome-wide approaches is reshaping our perception of the role of DNA methylation in cancer. The epigenetic landscape is assumed to play an increasingly important role in MCL, as increasing knowledge of the genetic basis of this lymphoma has not been able to explain the variability in its clinical course (61,62).

A systematic study of methyloma in 82 MCL patients revealed two major subtypes with distinct clinicobiological features (63). Patients characterized by a DNA methylation pattern more similar to germinal center-inexperienced B cells (i.e., hypomethylation of enhancers and transcribed regions) had significantly worse OS than the antigen-experienced group. The authors also found that the number of DNA methylation changes had a significant linear association with the clinical outcome, approximately doubling the risk of death with each 10,000 methylation changes. These data suggest that patients with more epigenetic changes have a worse clinical outcome that correlates with the acquisition of genetic changes and increased cell proliferation, particularly in cases transforming from leukemic, non-nodal, indolent MCL. However, more clinically oriented studies with a better characterized and homogeneously treated series are required to validate these findings before introducing epigenetic-based tools into the current risk stratification models of MCL.

## How can we tailor therapy based on these biomarkers?

Despite many publications and validations of the prognostic impact of the different MIPI scores (*Table 4*) (1-3,64-68), none have yet been investigated as a treatment-tailoring tool in MCL, and therapeutic choices are still selected on the basis of age and comorbidities (69). Even though some new clinical entities with less aggressive behavior (i.e., MALT-like MCL) have been proposed recently (70), a de-escalation of treatment intensity for low-risk MIPI patients is still considered potentially harmful. Moreover, neither the blastoid morphology nor the Ki-67 index are used to drive different therapeutic choices, despite their strong association with poor outcomes (16). The only clinical trial specifically offering upfront single-agent high-dose

**Table 3** Micro-RNAs with a clinical impact in MCL

| Patient series | Tissue (FFPE) | Involved miR | Method | Postulated function | Median OS |
|---|---|---|---|---|---|
| (54) | 50 LNs | miR-17-5p, miR-20a | RT-qPCR | Survival and apoptosis | The association between miR and high MYC expression identifies a poor survival group |
| (50) | 29 LNs, 1 spleen sample | miR-29 family | Microarray, RT-qPCR | Cell cycle control | Based on miR 29 family expression: low mOS 1.5 years; high mOS NR |
| (51) | 54 LNs; 82 LNs | miR-17-92 cluster | RT-qPCR, microarray (mRNA) | Chemoresistance and anti-apoptotic activity via PI3K/AKT pathway | Based on level of C13orf25: high mOS 1.06 years; low mOS 2.75 years |
| (52) | 30 LNs | 6-miRNA signature (high expression of miR129-3p, miR-135a, miR-146a, miR-424, and miR-450-5p and low expression of miR-222) | RT-qPCR array | Proliferative and microenvironment signature | Good risk group mOS 4 years; poor risk group mOS 2 years (P<0.05) |
| (55) | 23 LNs; 54 LNs | miR-20b | Microarray, RT-qPCR | Survival and proliferation | Based on expression level of miR20b: low mOS 5 years; high mOS 2.5 years (P=0.032) |
| (56) | 119 FFPE | miR-127-3p; miR-615-3p | TaqMan low-density arrays | NS | Ki67 and miR expression combined in one model: good mOS 46.3 months; intermediate mOS 18.8 months; poor mOS 9.5 months |
| (57) | 53 LNs; 12 tonsils; 2 colon; 1 stomach; 1 orbit; 1 parotid | miR-17-92 | RT-qPCR | Cell cycle control and apoptosis | 2 prognostic clusters: high SOX11/SOX12/miR19b/miR92a mOS 2 years; high SOX4/miR17/miR18a mOS NR (P<0.001) |
| (58) | 21 PBMCs (cd19+) | miR-223 | RT-qPCR | Cell proliferation and apoptosis | High expression mOS 36 months; low expression mOS 12 months (P=0.021) |
| (59) | 172 FFPE | miR-18b | miRNA assay and qRT-PCR | Proliferation and apoptosis | MIPI-miR-18b combined in one model for 3 risk classes: low mOS NR; intermediate mOS 7 years; high mOS 2 years (P=0.001) |
| (60) | 61 FFPE | miR-18b | qRT-PCR | Proliferation and apoptosis | MIPI-miR-18b combined in one model for 3 risk classes: low mOS NR; intermediate mOS 8.3 years; high mOS 1.6 years (P=0.000) |

FFPE, formalin-fixed paraffin embedded; LNs, lymph nodes; miR, micro-RNA; PBMC, peripheral blood mononuclear cell; RT-qPCR, quantitative reverse-transcribed polymerase chain reaction; GEP, gene expression profiling; NR, not reached; NS, not specified; mOS, median overall survival.

cytarabine and rituximab for high-risk MIPI-b MCL rapidly stopped enrollment due to inefficacy (71).

Given the favorable outcome of MRD clearance in MCL (5,22), and considering the proposed MRD-driven pre-emptive strategies (72,73), some ongoing clinical trials (NCT02896582 and NCT03267433) are investigating modulation of the maintenance therapy based on MRD results (74). Some preliminary data suggest that maintenance therapy may benefit MRD-negative patients as well, meaning that the preservation of MRD-negativity rather than the conversion of MRD-positivity may be a valuable goal of current post-induction therapies (10). As no clear survival benefit of MRD-driven strategies has been demonstrated thus far, more data are required

 

**Table 4** Proposed and validated MIPI scores

| Authors | MIPI | Risk factors | Clinical impact (mOS) |
|---|---|---|---|
| GLSG1996, GLSG2000, European MCL Trial1 (1) | MIPI | [0.03535 × age (years)] × age (years) + 0.6978 (if ECOG >1) + 1.367 × log10(LDH/ULN) + 0.9393 × log10(WBC count) | Low NR; intermediate 51 months; high 29 months |
| MCL Younger, MCL Elderly (2) | MIPI-s (simplified MIPI) | 0–3 points for each factor; Age (years); ECOG PS; LDH/ULN; WBC ($10^9$/L) | Low NR; intermediate NR; high 2.3 years (P<0.001) |
| GLSG1996, GLSG2000, European MCL Trial1 (1) | MIPI-b (biological MIPI) | MIPI score + 0.02142 × Ki-67 (%) | Low NR; intermediate 58 months; high 37 months |
| MCL Younger, MCL Elderly (3) | MIPI-c (combined MIPI) | MIPI risk classes divided by dichotomous (cut-off 30%) Ki67 | Low NR; low-Intermediate NR; high-Intermediate 5.1 years high 1 year (P<0.001) |
| MCL0208 FIL trial (21) | MIPI-g (genetic MIPI) | MIPI-c score + KMT2D/TP53 disruption | Low 4-year OS 94%; intermediate 4-year OS 65%; high 4-year OS 45% |
| MCL2/MCL3 trials (60) | MIPI-b-miR (miRNA-18b MIPI) | MIPI-b score + 0.58317 × log-fold-change of miR-18b | Low NR; intermediate 8.3 years; high 1.6 years (P<0.001) |

MCL, mantle cell lymphoma; MIPI, MCL International Prognostic Index; mOS, median overall survival; NR, not reached; GLSG, German Low Grade Lymphoma Study Group; FIL, Fondazione Italiana Linfomi; miR, micro-RNA; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; WBC, white blood cells; KMT2D, lysine methyltransferase 2D.

before the modulation of maintenance treatments based on MRD results (69,75). Morever new techniques for MRD detection are emerging. Next-generation Sequencing (NGS) techniques (76) and cell free circulating DNA (cfDNA) monitoring (77,78) are able to overcome some limitations of standard RQ-PCR, but their application is not yet validated or standardized.

In addition, increasing evidence from mutational studies is challenging the current scenario of MCL and may soon change the clinical management of these patients. The prognostic value of *TP53* disruption (both mutations and deletions) has been uniformly confirmed by independent research groups (19,21,28). *TP53*-disrupted MCL presents dismal outcomes independent from classical prognosticators (e.g., MIPI, clinical response, or MRD negativity) and seems to not benefit from the addition of lenalidomide (29,79). Unfortunately, data on the impact of BTK inhibitors in these patients are scarce. In one study, despite an overall response in 11 out of 20 (55%) relapsing patients treated with ibrutinib monotherapy, responses to this therapy were short-lasting (median PFS 4 months) (80). However, some promising data come from combinations with venetoclax or with rituximab and lenalidomide [up to 50–64% with complete response (CR) and no difference in PFS compared to WT], but the series of *TP53*-disrupted patients described in these phase II trials (n=12 and 11, respectively) and the median follow-up (16 and 18 months, respectively) are too limited to draw firm conclusions (81,82).

Therefore, although prognostic, *TP53* disruption has not yet been established as a predictive biomarker sufficient to drive novel therapeutic approaches. Nevertheless, it is becoming increasingly clear that MCL patients with *TP53* disruption should be included in front-line clinical trials exploring novel targeted drugs rather than receiving standard immunochemotherapy. In this regard, the EuMCLNet "TRIANGLE" phase III trial is investigating the integration of ibrutinib in first-line high-dose immunochemotherapy in younger patients (EudraCT 2014-001363-12), but no mutational stratification is being applied. Other BTK inhibitors are currently being evaluated, such as acalabrutinib in association with bendamustine-rituximab in a phase II trial (NCT03863184), and zanubrutinib *vs.* bendamustine-rituximab in a phase III trial (NCT04002297). Interestingly, the recruiting FIL "V-RBAC" phase II trial (EudraCT No. 2017-004628-31) is offering consolidation with venetoclax after four cycles of R-BAC500 (17) to elderly patients characterized by *TP53* disruption, Ki-67 ≥30%, or blastoid variant.

Finally, although the real effectiveness in these high-risk patients requires investigation, front-line consolidation with reduced-intensity conditioning allogeneic transplantation may be considered in younger and fit patients (83). A similar role may be claimed by CAR-T consolidation as soon as this novel approach is available (84).

 

Therapeutic decisions on the basis of genomic aberrations other than *TP53* disruption should be discouraged. *KMT2D* mutations are the only other genomic biomarker with an independent, negative impact on OS that has been validated externally, though in a small series (21); therefore, the authors proposed the new MIPI-g (integrating both *TP53* disruption and *KMT2D* mutations) as a useful tool for selecting high-risk MCL patients for future, "tailored" experimental strategies. However, the diagnostic test for *KMT2D* mutations is currently not standardized and not available in clinical practice. Moreover, no data are available on the impact of new drugs on *KMT2D* mutations. Finally, even if both *CDKN2* deletions and *NOTCH1* mutations have been described as detrimental in terms of survival, their prognostic impact may not be independent, as they are often associated with *TP53* disruptions (19,21,28). Finally, other mutations have been proposed as predictive markers for targeted approaches, but larger series confirmation is missing (85,86). For example, a functional deficit of CDKN2 seems to attenuate the efficacy of the new CD4/6 inhibitor palbociclib, which was tested in a phase II US trial (NCT03478514) (87).

Regarding immunohistochemistry markers, although both SOX11 and p53 staining is recommended in clinical routine (37), neither should be used for tailoring treatment. Diagnosis of leukemic nnMCL is made independent of SOX11 status, and SOX11-negativity has no relevant clinical significance in classical MCL (9). However, although the clinical value of p53 expression has been validated, its use is not yet widespread, and strict assessment guidelines (38) need to be followed.

Finally, the recently developed GEP-based assays represent easily applicable and highly promising treatment-tailoring tools, particularly when available on the widespread NanoString platform (7,8,45,48). The analytical and clinical validity of the MCL35 (8) and L-MCL16 (48) assays prompts indicates they are reliable biomarkers for risk-adapted clinical trials. L-MCL16 is able to reliably distinguish indolent MCL from classical subtypes, even if the tool is mainly conceived for leukemic cases, as the analysis is done on PB, whereas MCL35 is conceived for highly infiltrated FFPE samples. However, roughly one-third of the non-nodal, indolent cases carry a high number of CNAs and a similar prognosis as classical MCL patients. Therefore, it is not untimely to foresee a tailored therapeutic approach in which patients with high CNA, regardless of subtype, are prioritized in trials (or treatments) with novel agents, whereas those with classical MCL and low CNA receive standard immunochemotherapy (88). On the other hand, patients with leukemic nnMCL and low CNA may be either observed or enrolled into innovative clinical trials in which treatment mechanisms are evaluated over time (e.g., "master protocols") (89).

Interestingly, a couple of GEP studies focusing on BCR-related signatures have shown that patients over-expressing such genes have worse prognosis, suggesting that they might be ideal candidates to receive first-line treatment with BTK inhibitors (7,8,45). Nevertheless, to test this exciting hypothesis, these signatures should first be investigated in prospective clinical trials with BTK inhibitors (e.g., the TRIANGLE trial).

In summary, some words of caution have to be added concerning these highly promising GEP-based tools before considering them for treatment-tailoring. Overall, a general limitation of gene expression signatures is that their prognostic significance is highly dependent on the specific treatment received, as demonstrated in follicular lymphoma (44,90). Therefore, the concept of current GEP tools should be limited to MCL patients receiving conventional immunochemotherapy with R-CHOP or high-dose cytarabine-containing schedules (± ASCT); thus, any putative impact on bendamustine combinations or new drugs still needs to be demonstrated (46,47). Moreover, some technical limitations need to be overcome before the effective introduction of these biomarkers into clinical practice: low infiltration (<60%) FFPE samples and bone marrow samples are currently not suitable for MCL35 or L-MCL16. Moreover, interlaboratory standardization is still needed for these tools, though feasible on NanoString technology. Until these issues are covered, GEP-based tools still remain limited to the context of translational research.

## Conclusions

In conclusion, this review discussed the current scenario of prognostic tools in MCL and their possible application in tailoring treatment in the context of both clinical trials and, more importantly, real life. Although many promising biomarkers were established during the last 10 years (*Figure 1*), the authors' main aim was to focus on the few prognostic tools, such as *TP53* disruption, that clinicians can start to use right now in the daily management of MCL patients (*Figure 2*). Moreover, a schematic picture of the most promising new biomarkers that may soon gain clinical use is presented in *Figure 3*.

In 2020, MCL is still a challenge for both clinical

 

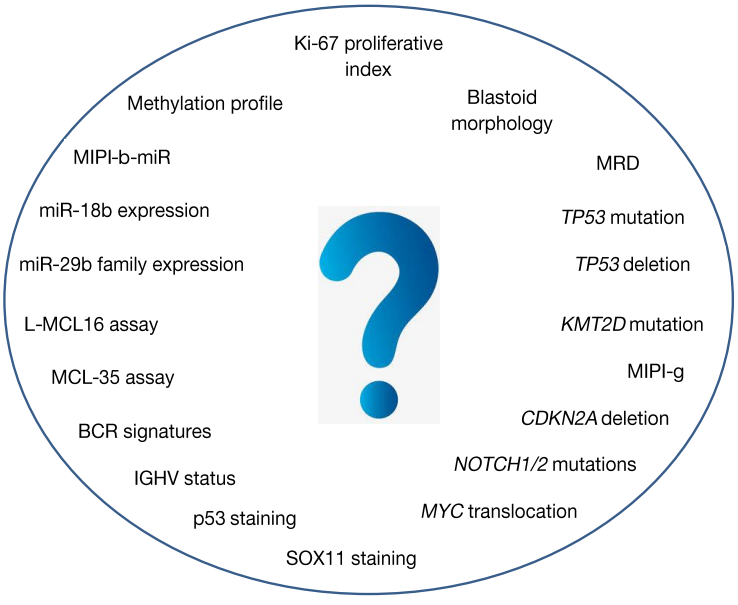


**Figure 1** Currently recognized biomarkers for MCL. MRD, minimal residual disease; TP53, tumor protein 53; KMT2D, lysine methyltransferase 2D; MIPI-g, Genetic Mantle Cell International Prognostic Index; CDKN2A, cyclin-dependent kinase inhibitor 2A; NOTCH1/2, Notch receptor 1/2; SOX11, protein 11 of SRY-related HMG-box gene; IGHV, variable region of immunoglobulin heavy chain; BCR, B-cell receptor; miR, microRNA.

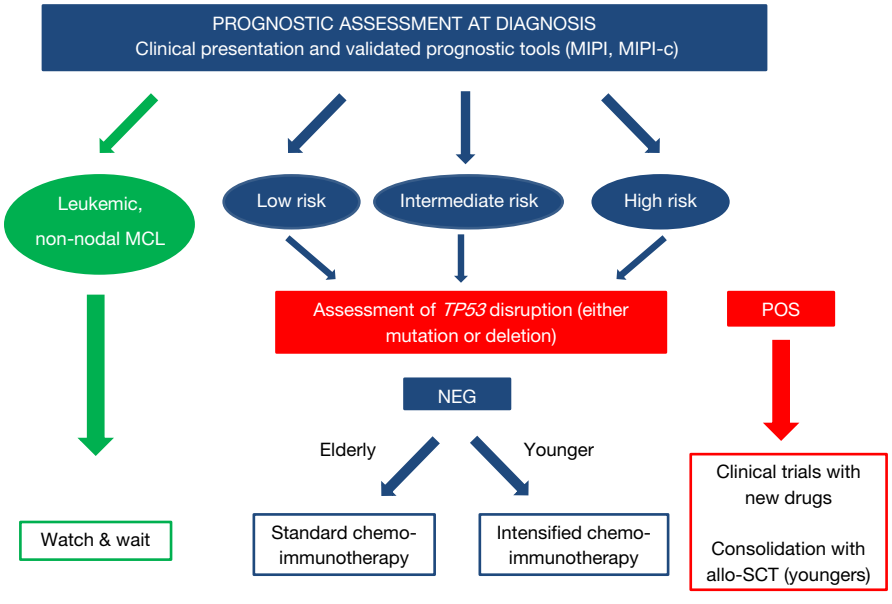


**Figure 2** Current algorithm for tailored therapy for MCL. MIPI-c, Combined Mantle Cell International Prognostic Index; Allo-SCT, allogeneic stem cell transplantation.

and translational hematologists, given its rarity and its heterogeneous natural course. However, thanks to the continuous contribution of novel biological insights, and the international collaboration in conducting innovative clinical trials, both academic and industry driven, a real opportunity to pursue personalized medicine in clinical practice is being

 

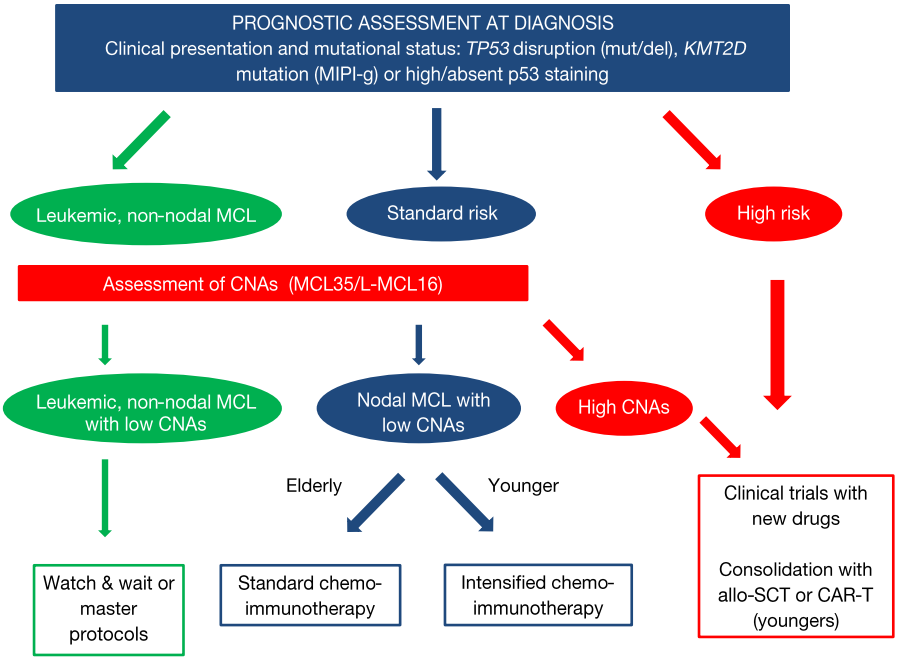


**Figure 3** Future algorithm for tailored therapy for MCL. mut/del, mutation/deletion; MIPI-g, Genetic-Mantle Cell Prognostic Index; CNA, copy number alteration; Allo-SCT, allogeneic stem cell transplantation; CAR-T cell, chimeric antigen receptor T cell.

presented, and should be the main goal of MCL research in the present decade.

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