Molecular profiling and management of mantle cell lymphoma

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Mantle cell lymphoma (MCL) is a distinct subtype of B-cell non-Hodgkin lymphoma characterized by the t(11;14)(q13; q32) translocation leading to cyclin D1 overexpression and cell cycle dysregulation. Molecular profiling with gene expression and deep sequencing analyses has identified genomic and epigenomic alterations in pathways regulating the cell cycle, DNA damage response, proliferation, and survival, which contribute to disease progression with important prognostic and therapeutic implications. Clinically, the nonnodal MCL subset is notable for leukemic presentation, indolent behavior, and association with hypermutated IGHV and lack of SOX11 expression, which differentiates it from the conventional nodal MCL. In addition to the Mantle Cell Lymphoma International Prognostic Index score and proliferative gene signatures, 17p/TP53 and 9p/CDKN2A alterations, and genomic complexity have emerged as clinically useful biomarkers of high-risk disease associated with aggressive disease behavior, resistance to chemotherapy, and poor overall survival. Although intensive chemoimmunotherapy regimens that incorporate high-dose cytarabine and stem cell transplantation have improved survival in young and fit MCL patients, the introduction of Bruton tyrosine kinase inhibitors and other novel agents has made effective outpatient-based treatment accessible to nearly all MCL patients. Optimizing combinations of novel agents in the relapsed setting and moving novel agents to the first-line setting have the potential to fundamentally change the MCL therapeutic landscape for the better, especially for patients ineligible for chemotherapy or those with high-risk mutations that are resistant to chemotherapy.

Learning Objectives

- Review evidence from molecular profiling that differentiates high-risk from low-risk diseases
- Understand the roles of chemotherapy and novel agents in the treatment algorithm
- Develop a treatment approach that adapts to individual patient's disease risk

Case presentation

A previously healthy 58-year-old man presented for evaluation of painless left groin mass which grew over 2 months causing his left leg to swell. He felt well otherwise. A magnetic resonance imaging scan of his pelvis showed massive retroperitoneal and pelvic lymphadenopathy up to 7 × 12 cm. Lymph node (LN) biopsy was performed.

A physical examination showed a palpable large mass raised over the left inguinal region, scattered small cervical and axillary nodes bilaterally, and no palpable hepatosplenomegaly. Laboratory studies included a complete blood cell count: white blood cell count, 9.6 × 10^3 cells per μL; hemoglobin, 11 g/dL; and platelets, 124 × 10^3/μL. Blood chemistry was within normal limits, and lactate dehydrogenase and uric acid were elevated. An inguinal LN biopsy revealed mantle cell lymphoma (MCL) with a blastoid variant that was SOX11 positive and Ki-67 ~50%. Fluorescent in situ hybridization (FISH) showed near-tetraploid abnormal karyotype, including loss of chromosomes Y, 1, 2, 4, 5, 6, 9, 12, and 21 (including loss of 2 copies in 5, 9, and 21), gain of chromosomes 3 and 7, and t(11;14) translocation. The sample was negative for TP53 by immunohistochemistry. A bone marrow biopsy showed nodular bone marrow (BM) involvement of MCL occupying 10% of the intertrabecular space. A FISH assay showed a near-tetraploid abnormal karyotype, similar to the results from the LN biopsy. A positron emission tomography/computed tomography scan showed extensive and bulky abdominal, pelvic, and left inguinal lymphadenopathy with standardized uptake value up to 22; fluorodeoxyglucose-avid marked splenomegaly.

Clinical course

The patient received induction chemoimmunotherapy with rituximab plus cyclophosphamide- doxorubicin-vincristine-prednisone (R-CHOP) alternating with rituximab plus dexamethasone- high-dose cytarabine-oxaliplatin (R-DHAX) for a total of 6 cycles, and he achieved a complete response (CR) by Lugano criteria. He underwent autologous stem cell transplantation (ASCT) with rituximab plus carmustine-etoposide-cytarabine-melphalan (R-BEAM) conditioning in June 2018 and subsequently initiated rituximab maintenance.

In April 2019 (10 months after ASCT), he presented to the emergency department with acute onset of lower back pain and lower extremity weakness. He was found to have a new extramedullary mass at T11 with cord compression and diffuse leptomeningeal enhancement. Analysis of the cerebrospinal fluid confirmed MCL relapse. He subsequently started salvage therapy with a central nervous

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system–directed methotrexate-cytarabine-thiotepa-rituximab (MATRIX) regimen that included a plan for allogeneic stem cell transplantation.

Introduction

MCL, which accounts for 5% to 8% of all lymphomas, is a distinct subtype of B-cell non-Hodgkin lymphoma that primarily affects individuals at a median age of 65 years.[1] Initial treatment is not standardized, but it usually includes chemotherapy regimens that are not curative; more intensive regimens are often prescribed for young and fit patients. Relapsed and refractory (R/R) diseases are common that become progressively resistant to subsequent treatment. Making effective treatment broadly applicable to all patients on the basis of individual risk profile and overcoming treatment resistance in high-risk patients remain unmet needs in MCL management.

MCL is a heterogeneous disease unified at the molecular level by the initiation driver event of t(11;14)(q13;q32) translocation leading to cyclin D1 overexpression and cell cycle dysregulation. Cyclin D1–negative MCL patients who overexpress either cyclin D2 or cyclin D3 are rare, and they share similar clinical and gene expression profiles with cyclin D1–positive MCL.[2] Histologically, nearly 90% of the patients have the classic morphology, whereas up to 10% have blastoid features that are inseparable from Ki-67 and are significantly associated with shorter overall survival (OS) in multivariable analysis.[3] Clinically, MCL can be subdivided into 2 main clinical entities: conventional MCL (cMCL) with nodal disease and more aggressive clinical course, and nonnodal MCL (nnMCL) characterized by indolent leukemic presentation with no or minimal lymphadenopathy, which may eventually transform to aggressive disease by acquiring additional mutations.[1] The broad spectrum of clinical behaviors reflects multistep pathogenic alterations targeting pathways that regulate DNA damage response, cell cycles, and survival. Molecular profiling has identified proliferative gene signatures and individual genetic mutations with important prognostic and therapeutic implications that provide a biomarker-driven framework for stratifying a management approach tailored to the individual patient's disease risk.

Molecular profiling of MCL

Pathogenic dysregulation of cell cycle and DNA damage response

Dysregulation of cyclin D1 plays an important role in the pathogenic initiation of MCL by overcoming cell cycle inhibitory effects of retinoblastoma and p27kip1 to accelerate the G_1/S phase transition, allowing for secondary chromosome alterations necessary for disease progression and transformation. In MCL patients, selective CDK4/6 inhibition with palbociclib has demonstrated antiproliferative effects with reduced retinoblastoma phosphorylation and clinical responses.[4] The INK4a/CDK4/RB1 and ARF/MDM2/p53 cell cycle pathways are connected through the *CDKN2A* locus (9p21), which encodes for both the CDK inhibitor INK4a and the positive p53 regulator ARF. Genomic deletions of the INK4a/ARF locus, which can be detected in ~20% of MCL patients, can lead to simultaneous inhibition of the cell cycle regulatory and the p53 pathway, contributing to aggressive clinical behavior and treatment resistance.[5,6] The next most frequently observed cytogenetic alterations are deletions of the ATM gene, which controls phosphorylation and activation of p53 in response to DNA damage and during normal immunoglobulin V-D-J recombination. Approximately 40% to 75% of MCL patients carry ATM mutations, which are associated with chromosomal instability and a high number of chromosomal alterations.[5] Although p53 inactivation is rarely observed in classic MCL with low proliferative activity, it is found in ~30% of patients with blastoid MCL with a high proliferation rate and is associated with a poor prognosis.

Molecular profiling of cMCL and nnMCL

The 2016 World Health Organization classification subdivides MCL into 2 main clinical entities, cMCL and nnMCL, which have distinct molecular, genomic, and epigenomic features.[1,7] nnMCL generally has a low proliferation index, simple karyotypes, frequent hypermutated *IGHV*, and lack of SOX11 expression, a transcription factor that promotes oncogenic growth of cMCL.

Gene expression analysis showed that *IGHV*-mutated patients were enriched for gene signatures similar to memory B cells. A 13-gene signature showed that negative SOX11 expression was associated with indolent disease and a favorable 5-year OS of 78% compared with SOX11-positive MCL, which had a 5-year OS of 36% ($P = .001$).[5] In multivariable analysis, *IGHV* mutational status and *SOX11* expression were identified as independent risk factors for OS. For example, patients with mutated *IGHV* and negative *SOX11* expression had the more favorable 5-year OS of 73% compared with 38% for patients with unmutated *IGHV* and positive *SOX11*.[8] However, genomic complexity, such as acquiring mutations in 17p/TP53 in the same mutated *IGHV* and negative *SOX11* group, could lead to significantly worse outcome (5-year OS, 92% vs 36%; $P = .003$).

Genome-wide DNA methylation analysis in 82 MCL patients revealed 2 major MCL subgroups, C1 and C2.[9] The C1 and C2 subgroups displayed methylation patterns similar to normal germinal center inexperienced and germinal center–experienced B cells, respectively, indicative of different cellular origins resembling naive (C1) and memory B cells (C2). The 2 subgroups displayed distinct clinical-biological features, with C1 resembling cMCL and C2 resembling nnMCL. Analysis of the differential methylation showed association between DNA hypomethylation of a distant enhancer for SOX11 and the expression of SOX11 in the C1 subtype, suggesting a novel epigenetic mechanism for de novo SOX11 upregulation and development of aggressive clinical course. In addition, epigenetic burden was found to be closely linked to clinical outcome. These findings of epigenetic dysregulation in MCL pathogenesis and clinical correlations have raised the prospect of developing epigenetic agents for treating MCL.

Proliferative signature of gene expression

Gene expression profiling demonstrated that a proliferative signature of gene expression was the strongest molecular predictor of survival in MCL, which integrated the prognostic power of other individual molecular markers such as levels of cyclin D1 expression and INK4a/ARF locus deletions.[2] The Ki-67 proliferation index, measured by using immunohistochemistry, has been used clinically as a surrogate measure of the proliferation signature and has been shown to be prognostic both alone and in combination with the Mantle Cell Lymphoma International Prognostic Index (MIPI) score.[3]

The original MCL gene profiling by the Leukemia Lymphoma Molecular Profiling Project identified a 48-gene tumor cell proliferation signature as a continuous variable that integrated oncogenic events and correlated with survival.[2] The INK4a/ARF locus deletions were detected in 21% of the patients, deletions at p53 were found in 11% of the patients, and deletions of ATM were found in about one-third of the patients. Clinical application of the gene expression signature was

limited by technical reliance on fresh-frozen materials and microarray-based technology. Several recent studies explored expression signatures based on the Nanostring platform using routinely available formalin-fixed paraffin-embedded biopsy samples. The MCL35 gene expression proliferation assay provided a 17-gene proliferation signature which was developed in a training set of 47 MCL patients and validated in an independent cohort of 110 patients uniformly treated with R-CHOP.[10] The MCL35 assay assigned patients to high-risk (26%), standard-risk (29%), and low-risk (45%) groups that correlated with OS and Ki-67 independent of the MIPI score in multivariable analysis and could potentially be useful as biomarkers to support risk-adapted clinical trials. To reproducibly differentiate nnMCL from cMCL, a 16-gene expression profile based on the NanoString platform for leukemic samples was established in a training set of 19 samples and validated in an independent cohort of 70 samples.[11] The assay assigned 37% of patients to nnMCL and 56% to cMCL, with nnMCL having a better OS than cMCL (3-year OS, 92% vs 69%; $P = .006$) from the time of diagnosis and longer time to first treatment. Genomic complexity and TP53/CDKN2A aberrations predicted for shorter OS in the entire series and cMCL, whereas genomic complexity alone was associated with shorter time to first treatment and OS in nnMCL.

Recurrent genetic alterations relevant to therapy

Next-generation sequencing has led to comprehensive mutational characterization of MCL. Whole-genome and/or whole-exome sequencing of 29 MCL patients, followed by targeted sequencing in an independent cohort of 172 MCL patients, identified 25 significantly mutated genes.[12] Included were known drivers such as ATM, cyclin D1, and TP53; genes encoding the antiapoptotic protein BIRC3 and Toll-like receptor 2 (TLR2), which are implicated in the alternative NF-κB signaling pathway; and the chromatin modifiers WHSC1, MLL2, and MEF2B. NOTCH1/NOTCH2 mutations were found to be associated with blastoid/pleomorphic morphology and dismal prognosis. In 183 patients treated uniformly with chemoimmunotherapy on the Nordic MCL2 and MCL3 studies, TP53 deletions, CDKN2A deletions, TP53 mutations, and NOTCH1 mutations were significantly associated with poorer outcome in univariable analyses, whereas TP53 mutations showed independent prognosis in multivariable analysis. The presence of TP53 mutations was significantly associated with NOTCH1 mutations, deletions of CDKN2A, and TP53 deletions. TP53 mutations and/or deletions occurred in 23% patients, and both aberrations occurred in 5% of patients.[13]

Genomic mutational profiles have been extensively explored to determine the molecular basis for treatment response or resistance to BTK inhibition in MCL. In cell lines, sensitivity to BTK inhibitors correlated with activation of the classical NF-κB pathway, whereas resistance was associated with an alternative NF-κB pathway. Deep sequencing in 165 MCL samples identified recurrent mutations in TRAF2 or BIRC3 in 15% of individuals associated with an alternative NF-κB pathway, dependence on NIK signaling, and ibrutinib insensitivity.[14] Another study compared gene expression profiles of 55 tumor samples from either LNs or peripheral blood (PB), which demonstrated that activation of BCR and canonical NF-κB signaling is dependent on interaction with the nodal microenvironment, and it correlated with response.[15] Cell autonomous signaling from mutations and polymorphisms in BCR and NF-κB pathways may contribute to intrinsic ibrutinib resistance, whereas C481S mutation at the ibrutinib binding site of BTK was associated with acquired ibrutinib resistance, with both mediated in part by sustained PI3K-AKT activation.[16] These alterations may be useful biomarkers for selecting targeted therapies in MCL.

Management of MCL

MCL has a broad spectrum of clinical, biological, and genetic features. Treatment selection is influenced by lymphoma characteristics, such as disease burden, proliferation, and mutational profile, as well as patient factors, such as age, comorbidities, and individual preferences. Optimal management must balance efficacy and accessibility with quality of life in this still incurable disease for most MCL patients, many of whom are elderly with comorbidities. Molecular profiling has identified proliferative gene signatures and individual genetic mutations with important prognostic and therapeutic implications that provide a potential biomarker-driven framework to stratify a management approach tailored to an individual patient's disease risk.

Initial treatment of MCL

Chemoimmunotherapy-based initial therapy. **Intensive chemoimmunotherapy for young and fit patients.** Initial treatment of MCL is variable, but historically, it includes chemoimmunotherapy and often involves intensive hospital-based approaches with high-dose chemotherapy and hematopoietic cell transplantation for young and fit patients (age younger than 65 years) (Table 1), despite lack of evidence of a cure. High-dose cytarabine has made a positive impact on progression-free survival (PFS) in younger patients (age younger than 65 years), delivering a median PFS of up to 7 to 8 years and a median OS of more than 10 years. It has been included in induction regimens such as the MD Anderson Cancer Center rituximab plus hyperfractionated cyclophosphamide-vincristine-doxorubicin-dexamethasone (R-hyperCVAD) regimen alternating with methotrexate and cytarabine.[17] Another example is the European Mantle Cell Lymphoma Network rituximab plus dexamethasone-cytarabine-cisplatin (R-DHAP) regimen alternating with R-CHOP followed by consolidative ASCT.[18,19] A third example is the Nordic MCL2 protocols with dose-intensified CHOP (maxi-CHOP) plus rituximab alternating with high-dose cytarabine followed by consolidative ASCT.[20] The role of high-dose cytarabine in induction chemotherapy was conclusively demonstrated in the randomized phase 3 European Mantle Cell Lymphoma Network MCL Younger study. R-CHOP alternating with R-DHAP was associated with a significantly longer time-to-treatment-failure rate, higher CR rate, and longer PFS, although OS was similar in the 2 treatment arms, suggesting that inclusion of high-dose cytarabine is unlikely to cure MCL.[19] Furthermore, rituximab maintenance, given every 2 months for 3 years after R-DHAP induction and consolidative ASCT, was shown to prolong event-free survival (EFS), PFS, and OS.[21] Given the significant toxicities of the intensive approach, it is important to try to identify those younger patients who might do just as well with more conservative strategies and those who would do poorly despite intensive regimens because of chemotherapy resistance.

The ECOG-ACRIN/NCI EA4151 study (NCT03267433) is an ongoing randomized phase 3 US intergroup trial evaluating minimal residual disease (MRD)–adapted consolidation after chemoimmunotherapy induction regimens. Patients with MRD-negative CR following chemoimmunotherapy induction will be randomly assigned to either standard-of-care ASCT plus rituximab maintenance or the experimental arm of rituximab maintenance alone without ASCT.

Outpatient chemoimmunotherapy for elderly fit patients. Most MCL patients are older than age 65 years; therefore, conventional outpatient-based chemoimmunotherapy is the primary treatment modality for elderly fit patients (Table 1). R-CHOP–based or

Table 1. Contemporary MCL first-line treatment

Regimen	Trial name or sponsor	Phase	N	Median age, y (range)	ORR (%)	CR (%)	EFS/PFS/TTF	OS	Predictive biomarkers	MRD negativity	References
Intensive chemotherapy											
R-hyperCVAD/R-MA	MD Anderson Cancer Center	2	97	61 (41-80)	97	87	Median EFS, 4.8 y	Median OS, 10.7 y	MIPI	N/R	17
Maxi-CHOP/HDAC/ rituximab → ASCT	Nordic MCL2	2	160	56 (32-65)	96	54	Median PFS, 8.5 y	Median OS, 12.7 y	MIPI, MIPI-B, MIPI-B-miR, MRD TP53 mutation	ASCT: 49%	20
R-CHOP/R-DHAP → ASCT	Groupe d'Etude des Lymphomes de l'Adulte (GELA)	2	60	57.5 (40-66)	95	57	Median EFS, 83 mo	5-y OS rate, 75%	N/R	N/R	18
R-CHOP/R-DHAP → ASCT	MCL Younger	3	232	56 (50-60)	EOI, 94; ASCT, 98	EOI, 55; ASCT, 83	Median TTF, 9.1 y	Median OS, 9.8 y	MIPI, Ki-67, MRD CDKN2A/TP53 deletions	EOI: PB, 79%; BM, 61%; ASCT: PB, 85%; BM, 79%	6, 19
R-DHAP/R-CHOP → ASCT → rituximab maintenance	LYSA	3	120	57 (27-65)	EOI, 99; ASCT, 100	EOI, 85; ASCT, 94	4-y PFS rate, 83%	4-y OS rate, 89%	MIPI	N/R	21
Outpatient chemotherapy											
Rituximab-bendamustine	StiL	3	46	64 (34-83)	93	40	Median PFS, 35 mo	N/R	N/R	N/R	24
Rituximab-bendamustine	BRIGHT	3	36	60 (28-84)	94	50	5-y PFS rate, 40%	5-y OS rate, 59%	N/R	N/R	25
R-CHOP/rituximab maintenance	MCL Elderly	3	267	70 (60-87)	86	34	4-y PFS rate, 57%	4-y OS rate, 87%	MIPI, MRD	PB, 48%	23
VR-CAP		3	243	65 (26-88)	92	53	Median PFS, 25 mo	4-y OS rate, 64%	MIPI-B, Ki-67	N/R	22
R-BAC	Fondazione Italiana Linfomi	2	57	71 (67-75)	91	91	3-y PFS rate, 76%	N/R	MIPI, Ki-67, blastoid	PB, 78%; BM, 54%	26
RiBVD	LYSA	2	74	73 (64-83)	84	75.5	4-y PFS rate, 58%	4-y OS rate, 71%	MRD	PB, 87%	27
Lenalidomide-bendamustine-rituximab	NLG/MCL4	1/2	51	71 (62-84)	80	64	Median PFS, 42 mo	3-y OS rate, 73%	N/R	PB, 68%; BM, 56%	28
Novel agents											
Rituximab-lenalidomide		2	38	65 (42-86)	92	64	5-y PFS rate, 64%	5-y OS rate, 77%	MIPI correlates with OS	PB, 80%	46,47

EOI, end of induction; HDAC, high-dose cytarabine; miR, microRNA; N/R, not reported; RiBVD, rituximab plus bendamustine, bortezomib, and dexamethasone; R-MA, rituximab, methotrexate, and cytarabine; TTF, time-to-treatment failure.

rituximab-bendamustine–based regimens provide a median PFS of 2 to 4 years, with median OS exceeding 5 years. Phase 3 studies have established that building upon R-CHOP, with either the biologic agent bortezomib during induction (eg, rituximab-cyclophosphamide-doxorubicin-bortezomib plus oral prednisone [VR-CAP]) or with rituximab maintenance after R-CHOP induction (European MCL Older study) would significantly extend PFS and OS compared with R-CHOP.[22,23] The rituximab-bendamustine combination, which has been increasingly adapted in outpatient practice, has demonstrated noninferiority in efficacy compared with R-CHOP in the StiL and BRIGHT studies, albeit with a different toxicity profile.[24,25] Additional strategies for enhancing the rituximab-bendamustine regimen have been explored in phase 2 trial settings: adding low-dose cytarabine at 500 mg/m^2 (the FIL study: rituximab plus bendamustine-cytarabine [R-BAC],[26] introducing bortezomib (the LYSA study: rituximab plus bendamustine, bortezomib, and dexamethasone [RiBVD]),[27] and incorporating lenalidomide (the NLG/MCL4 study: lenalidomide-bendamustine-rituximab).[28] These regimens seemed to improve CR rates compared with rituximab-bendamustine (40% to 50% CR rate with rituximab-bendamustine *v* 91% CR with R-BAC, 76% with R-BVD, and 64% with lenalidomide-bendamustine-rituximab). However, toxicities were generally greater in the rituximab-bendamustine-plus combinations. In particular, the combination of lenalidomide-bendamustine-rituximab was associated with a high degree of severe infections and second primary malignancies, which limited further clinical application.[28] Maintenance rituximab after bendamustine-rituximab in MCL was evaluated in the randomized MAINTAIN study, which did not show survival difference after a median follow-up time of 4.5 years.[29]

Predictive biomarkers in the context of chemoimmunotherapy. **MIPI score and Ki-67.** The continuous variables of patient age and white blood cell count can have an impact on the MIPI score; therefore, is not always a reliable predictive marker for risk assignment. MIPI-B combines Ki-67 as a continuous variable with the MIPI score, which was shown to improve risk assessment, especially identifying high-risk disease in young patients.[30] Combined MIPI (MIPI-c) incorporates the dichotomized Ki-67 with a 30% cutoff level, which provides a more refined risk stratification than MIPI-B by differentiating survival outcome into 4 risk groups with 5-year OS ranging between 17% and 85%.[3]

Recurrent genetic alterations involving TP53 aberrations. In the randomized European MCL Younger study, evaluation of somatic gene copy number alterations showed frequent genetic changes, including MYC amplification (18%), and deletions in RB1 (26%), ATM (25%), CDKN2A (p16) (25%), and TP53 (22%). Deletions of RB1, CDKN2A, TP53, and CDKN1B were associated with shorter OS independent of the MIPI score. Importantly, simultaneous deletions for CDKN2A and TP53 were associated with dismal outcome (median OS, 1.8 years) compared with single deletions (median OS, 4.3 and 5.1 years) or without these deletions (median OS, 7 years),[6] suggesting that high-risk younger patients with deletions of CDKN2A (p16) and TP53 are candidates for alternative initial therapeutic strategies. In the Nordic MCL2 and MCL3 studies, univariable analysis showed inferior survival with mutations of TP53 (11%) and NOTCH1 (4%) and deletions of TP53 (16%) and CDKN2A (20%). In multivariable analyses, TP53-mutated patients had an OS of 1.8 years, and 50% of them relapsed at 1.0 years compared with TP53-unmutated patients who had a median OS of 12.7 years ($P < .0001$).[20] These data suggest that TP53 mutations identify a highly aggressive form of MCL with extremely poor response to contemporary optimized intensive chemoimmunotherapy regimens that incorporate cytarabine, rituximab, and ASCT. These high-risk patients with TP53 mutations should be considered for experimental first-line trials exploring novel agents.

MRD. MRD status has been shown to be predictive of MCL clinical outcome, including remission duration and survival in chemotherapy-based clinical trials.[31] In intensive-treatment protocols that incorporate high-dose cytarabine and consolidative ASCT, including the Nordic MCL2 and MCL3 studies, the European Mantle Cell Lymphoma Network MCL Younger study, and the US CALGB 59909 study, as well as outpatient-based chemotherapy regimens such as the MCL Elderly trial, molecular remission after induction treatment was highly predictive of response duration and disease progression. In addition, sustained molecular remission was associated with improved survival outcome in the MCL Younger study after ASCT, the MCL Elderly study during maintenance [32], and after rituximab preemptive treatment after molecular relapses in the Nordic MCL2 and MCL3 studies.[33] MRD assays are increasingly incorporated into prospective clinical trials as correlative biomarkers for measuring response quality and sometimes as a treatment end point anchoring MRD-adjusted treatment strategies.

Application of novel therapy in R/R MCL

Over the past decade, 4 non-chemotherapy options—bortezomib, lenalidomide, ibrutinib, and acalabrutinib—have been approved by the US Food and Drug Administration for treating MCL. Other agents, such as the BCL2 inhibitor venetoclax and PI3K inhibitors, have also demonstrated significant clinical activity (Table 2). The introduction of novel agents is transforming MCL management by making effective and potentially less toxic chemotherapy-free treatment accessible to all patients in the R/R setting, as well as challenging the traditional chemotherapy-based treatment paradigm in the first-line setting by moving rationally designed novel combinations to an earlier time in the treatment course.

Clinical evidence with lenalidomide-based regimens. In MCL-001 and MCL-002 studies for R/R disease, single-agent lenalidomide 25 mg on days 1 to 21 every 28 days showed an overall response rate (ORR) of 28% to 40%, CR rate of 5% to 8%, and duration of response (DOR) of more than 16 months.[34,35] The addition of rituximab 375 mg/m^2 once per week during cycle 1 to lenalidomide 20 mg was safely tolerated, and it demonstrated activity in relapsed patients with an ORR of 53%, CR rate of 31%, median PFS of 14 months, and DOR of 18 months.[36] Exploratory analyses showed that the proliferation index for Ki-67 (30% cutoff) was significantly associated with a lower CR rate, DOR, and survival in the MCL-001 study.[37] The combination of lenalidomide with other novel agents and with chemotherapy has been evaluated in numerous studies.

Clinical evidence with BTK inhibitors. Single-agent ibrutinib, the first-in-class BTK inhibitor, demonstrated an ORR of 68% with a 21% CR rate, a median DOR of 17.5 months, a 24-month PFS of 31%, and an OS of 47% in R/R MCL when given at 560 mg once per day.[38] In the pooled data of 3 ibrutinib MCL studies (PCYC1004, SPARK, and RAY [n = 370]), multivariable analyses identified that 1 previous line of therapy was favorably associated with PFS, whereas high-risk simplified MIPI (sMIPI) score, bulky disease, and blastoid histology were adversely associated with OS and PFS.[39] When the rituximab-ibrutinib combination was given to 50 relapsed MCL patients, the ORR was 88% with a CR rate of 44%. A Ki-67 of 50% or more was significantly associated with worse treatment outcome.[40] The second-generation BTK inhibitor acalabrutinib is a highly selective inhibitor of BTK with minimal off-target activity. In the ACE-LY-004 study, acalabrutinib 100 mg twice per day until

Table 2. Chemotherapy-free novel agents and combinations in R/R MCL

Regimen	Phase	N	Median age, y (range)	ORR (%)	CR (%)	PFS	OS	Predictive biomarkers	MRD negativity	References
Single agent										
Bortezomib	2	33	65 (42-89)	32	8	Median, 6.5 mo	Median, 23.5 mo	Ki-67	N/R	48
Lenalidomide	2	134	67 (43-83)	28	8	Median, 4 mo	Median, 21 mo	Ki-67	N/R	37
	3	170	68.5 (44-88)	40	5	Median, 8.7 mo	Median, 27.9 mo	N/R	N/R	35
Ibrutinib	2	111	68 (40-84)	68	21	Median, 13.9 mo	Median, 22.5 mo	N/R	N/R	38
	2/3	370	68 (N/R)	66	20	Median, 12.8 mo	Median, 25 mo	sMIPI, blastoid histology	N/R	39,49
Acalabrutinib	2	124	68 (61-75)	81	40	1-y rate, 72%	1-y rate, 87%	N/R	N/R	41
Zanbrutinib	2	86	N/R (18-75)	84	59	24-wk rate, 82%	N/R	N/R	N/R	42
Venetoclax	1	28	72 (35-85)	75	21	Median, 14 mo	1-y rate, 82%	N/R	N/R	44
Lenalidomide combinations										
Lenalidomide-rituximab	2	52	66 (46-85)	57	36	Median, 11 mo	Median, 24 mo	N/R	N/R	36
Ibrutinib combinations										
Ibrutinib-rituximab	2	50	67 (45-86)	88	44	Median, 43 mo; 3-y rate, 68% Ki-67 <50%: N/R; Ki-67 ≥50%: 8 mo	Median, 14 mo; 3-y rate, 69% Ki-67 <50%, 81%; Ki-67 ≥50%, 27%	MIPI, Ki-67, and blastoid histology	N/R	40
Ibrutinib-venetoclax	2	23	68 (47-81)	71	71	18-mo rate, 57%	18-mo rate, 74%	Ki-67	PB 56%, BM 84%	50
Ibrutinib-palbociclib	1	27	65 (42-81)	67	37	2-y rate, 59%	2-y rate, 61%	N/R	N/R	45
Ibrutinib-lenalidomide-rituximab	2	50	69 (45-85)	76	56	Median, 16 mo	Median, 22 mo	MIPI and MRD correlate with PFS	6-mo: PB, 56% and BM, 43%; 12-mo: PB, 58% and BM, 68%	43

progression of disease provided an ORR of 81% with a CR rate of 40%, a 12-month PFS rate of 72%, and an OS rate of 87%.[41] Compared with ibrutinib, acalabrutinib is associated with less atrial fibrillation and fewer cutaneous toxicities. Zanubrutinib (BGB-3111) 160 mg twice per day has demonstrated high efficacy (ORR, 84%; CR, 59%) in 86 R/R MCL patients studied in China, with long-term efficacy and safety data continuing to mature.[42]

Novel strategies to optimize efficacy and overcome resistance to BTK inhibition. Despite the unprecedented clinical activity of the BTK inhibitors, a majority of the patients receiving ibrutinib continue to experience disease progression within 2 years, with a much shorter PFS in subgroups of patients with high-risk MIPI scores or blastoid histology as a result of treatment resistance. Major research efforts are underway to help define the optimal therapy sequence and combination needed to overcome primary disease resistance and minimize development of acquired treatment-emergent resistance.

Ibrutinib-lenalidomide combination. BTK inhibitors block chronic BCR signaling, which leads to a decrease in NF-κB activity. Lenalidomide down-modulates IRF4, leading to an increase in interferon β (IFN-β) secretion and a decrease in NF-κB activity. The combination of a BTK inhibitor and lenalidomide seems to target key pathways to augment synergy and reduce overall resistance. The Nordic Lymphoma Group reported the triple combination therapy of ibrutinib-lenalidomide-rituximab (PHILEMON study) in 50 R/R MCL patients.[43] Lenalidomide was given in combination with rituximab and ibrutinib during induction and maintenance. In evaluable patients, ORR was 76% with a CR rate of 56%. Median PFS was 16 months and OS was 22 months. Of the 28 patients evaluable for MRD at 6 months, molecular remissions were achieved at a rate of 56% in blood and 43% in BM, which were predictive of longer PFS and OS. Notably, response rates and PFS for mutant TP53 were comparable to those of patients with wild-type TP53, suggesting that the ibrutinib-lenalidomide-rituximab triple combination may overcome the

poor prognosis associated with TP53 mutations, potentially addressing an unmet therapeutic need.

Ibrutinib-venetoclax combination. Venetoclax is a BH3 mimetic that inhibits BCL2 and has marked single-agent efficacy in MCL with an ORR of 75%, CR rate of 21%, and PFS of 14 months.[44] Preclinical models of dual BTK and BCL2 inhibition predict synergy in malignant B cells by interfering in critical pathways. The AIM study evaluated the combination of ibrutinib with venetoclax in 23 R/R MCL patients; treatment consisted of monotherapy with ibrutinib 560 mg for the first 4 weeks followed by the addition of venetoclax in week 5 with a weekly ramp up to a dose level of 400 to 800 mg. The primary end point was CR at week 16. MRD was assessed by flow cytometry in BM and by allele-specific oligonucleotide polymerase chain reaction in blood. In this high-risk cohort, which included 50% aberrations of TP53 and 75% of patients with a high-risk MIPI score, the CR at 16 weeks was 42%, and MRD clearance was 67% in BM by flow cytometry and 38% in PB by allele-specific oligonucleotide polymerase chain reaction, suggesting significant improvement in outcomes with the dual targeting of BTK and BCL2 compared with historical data for ibrutinib monotherapy. Similar assessment of the dual inhibition is ongoing in a phase 1/2 study that also incorporates obinutuzumab (OASIS; NCT02558816). A randomized phase 3 study is accruing globally to ascertain efficacy of the ibrutinib-venetoclax combination (SYMPATICO; NCT03112174).

Ibrutinib-palbociclib combination. Palbociclib is an orally available specific CDK4/6 inhibitor that can overcome primary ibrutinib resistance in MCL expressing wild-type BTK by inducing prolonged early G_1 cell cycle arrest, which sensitizes MCL killing by ibrutinib.[16] In a phase 1 trial with 27 R/R MCL patients, the combination of ibrutinib 560 mg once per day with palbociclib 100 mg on days 1 to 21 of each 28-day cycle was demonstrated to be safe and effective with an ORR of 67%, CR rate of 37%, and 2-year PFS rate of 59%.[45] A phase 2 intergroup multicenter clinical trial (AFT-32; NCT03478514) is ongoing to further characterize efficacy as well as longitudinal genetic profiles that are predictive of response or resistance.

Newer agents. Chimeric antigen receptor (CAR) T-cell therapies are a promising approach for the management of refractory large

Table 3. Ongoing first-line studies under evaluation in MCL

Patient status/trial name	Phase	N	Treatment	First outcome	ClinicalTrials.gov
Transplant eligible					
TRIANGLE	3	870	R-CHOP/R-DHAP → ASCT R-CHOP + ibrutinib/R-DHAP → ASCT + ibrutinib maintenance R-CHOP + ibrutinib/R-DHAP → ibrutinib maintenance	EFS	NCT02858258
EA4151	3	689	Rituximab chemotherapy → MRD MRD positive: ASCT + rituximab maintenance MRD negative: ASCT + rituximab maintenance vs rituximab maintenance	OS	NCT03267433
Transplant ineligible					
E1411	2	332	Bendamustine-rituximab → rituximab maintenance Bendamustine-rituximab → rituximab-lenalidomide maintenance Bendamustine, rituximab, and bortezomib (Velcade) → rituximab maintenance Bendamustine, rituximab, and bortezomib (Velcade) → rituximab-lenalidomide maintenance	PFS	NCT01415752
SHINE	3	523*	Bendamustine-rituximab → rituximab maintenance Bendamustine-rituximab-ibrutinib → rituximab-ibrutinib maintenance	PFS	NCT01776840
ACE-LY-308	3	546†	Bendamustine-rituximab → rituximab maintenance Bendamustine-rituximab-acalabrutinib → rituximab-acalabrutinib maintenance	PFA	NCT02972840
MCL-R2 Elderly	3	633	First: R-CHOP vs R-CHOP/R-HAD; second: rituximab maintenance vs rituximab-lenalidomide maintenance	PFS	NCT01865110
ENRICH	2/3	400	Rituximab chemotherapy with maintenance rituximab vs ibrutinib-rituximab with maintenance rituximab	PFS	N/A
Chemotherapy free					
WINDOW I	2	131	Part 1: chemotherapy-free ibrutinib-rituximab treatment	ORR	NCT02427620
WINDOW II	2	50	Group 3: chemotherapy-free venetoclax-ibrutinib-rituximab treatment	CR	NCT03710772
ENRICH	2/3	400	Chemotherapy-free arm with ibrutinib-rituximab and a rituximab maintenance arm	PFS	N/A
ALR	2	24	Induction: acalabrutinib-lenalidomide-rituximab cycles 1-12; maintenance: cycles 13-POD	MRD-negative CR	NCT03863184
VLR	1	28	Venetoclax-lenalidomide-rituximab cycles 1-12	MTD	NCT03523975

ACE-LY-308 study, bendamustine-rituximab (BR) with rituximab maintenance vs BR plus acalabrutinib (A) with AR maintenance; N/A, not applicable; SHINE, bendamustine-rituximab (BR) with rituximab maintenance vs BR plus ibrutinib (I) with IR maintenance.

*Bendamustine-rituximab with or without ibrutinib maintenance.

†Bendamustine-rituximab with or without acalabrutinib maintenance.

B-cell lymphoma. Preliminary clinical experience with CAR T cells in MCL patients and preclinical models indicated clinical activities in MCL. The ongoing ZUMA-2 (NCT02601313) trial is assessing the safety and efficacy of the autologous KTE-X19 CAR T cells in patients with R/R MCL. The role that CAR T cells play in MCL remains to be defined and may include curative potential for refractory patients for whom treatment with BTK inhibitors fails.

Moving novel agents to first-line therapy for MCL

Several randomized phase 2/3 studies are underway to evaluate the addition of novel agents to conventional chemotherapy-based regimens or to compare novel agents with chemotherapy-based regimens (Table 3). The outcomes of these studies may have potential practice-changing impact and are therefore eagerly awaited.

Transplant-eligible patients. The TRIANGLE (NCT02858258) study is an ongoing randomized phase 3 trial being conducted by the European Mantle Cell Lymphoma Network to explore the use of ibrutinib in first-line induction and maintenance therapy and the role of consolidative ASCT. Patients younger than age 65 years are randomly assigned to 1 of 3 treatment arms: a standard arm of (1) 6 cycles of R-CHOP/R-DHAP followed by ASCT, and 2 experimental arms that include (2) 6 cycles of R-CHOP plus ibrutinib/R-DHAP followed by ASCT and 2 years of ibrutinib maintenance, or (3) 6 cycles of R-CHOP plus ibrutinib/R-DHAP and 2 years of ibrutinib maintenance.

Older patients. ECOG E1411 (NCT01415752) is a randomized phase 2 trial designed to assess the effect on PFS of the addition of bortezomib to rituximab-bendamustine induction and the addition of lenalidomide to rituximab maintenance. Patients age 60 years or older are randomly assigned to 1 of 4 arms: (1) rituximab-bendamustine followed by rituximab maintenance, (2) rituximab-bendamustine followed by rituximab and lenalidomide maintenance, (3) rituximab-bendamustine plus bortezomib followed by rituximab maintenance, and (4) rituximab-bendamustine plus bortezomib followed by rituximab and lenalidomide maintenance. The SHINE study (NCT01776840) is a randomized global phase 3 trial evaluating the addition of ibrutinib to rituximab-bendamustine induction and rituximab maintenance. The ECOG E1411 and SHINE trials have both completed accrual and are awaiting maturation of efficacy and safety data. A randomized phase 3 trial (NCT02972840) evaluating rituximab-bendamustine vs rituximab-bendamustine plus acalabrutinib is underway.

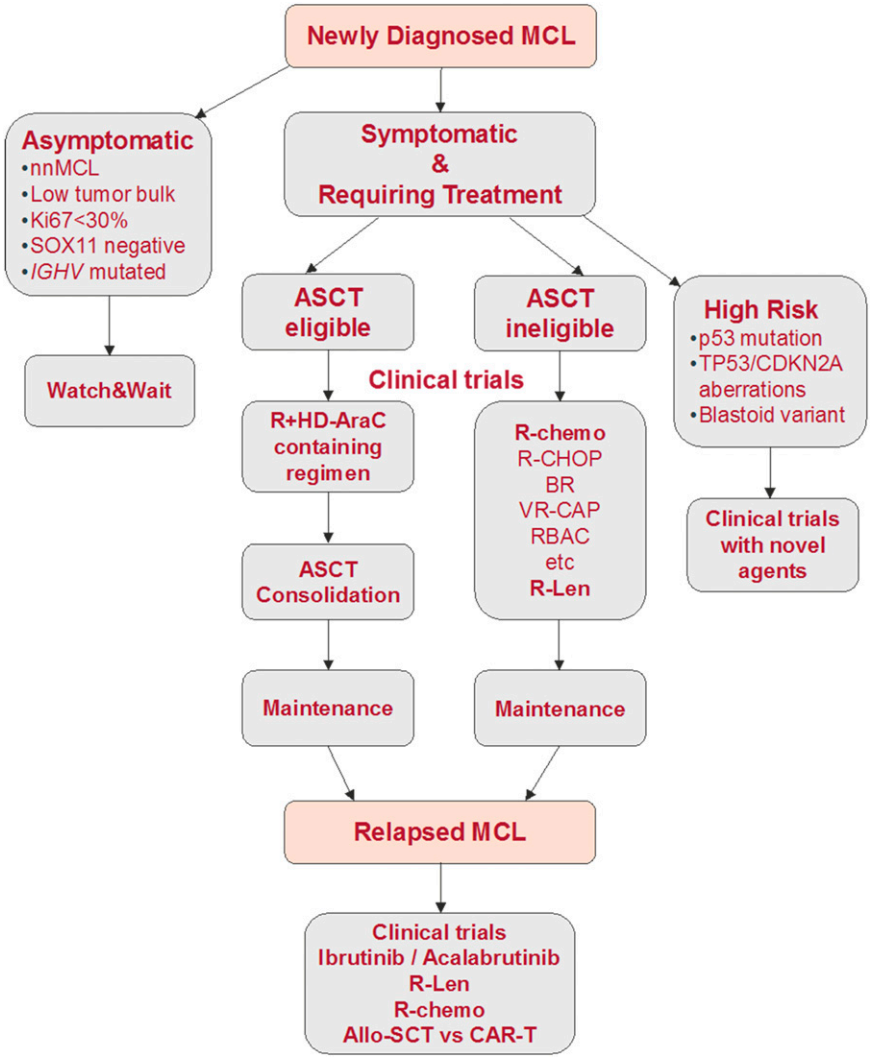

Figure 1. MCL management algorithm. Allo-SCT, allogeneic stem cell transplantation; BR, bendamustine-rituximab; R + HD-AraC, rituximab plus high-dose cytarabine; R-chemo, rituximab plus chemotherapy; R-Len, rituximab-lenalidomide.

Built upon the European MCL Older study, the phase 3 MCL-R2 Elderly trial (NCT01865110) addresses the role of cytarabine-containing induction and lenalidomide-containing maintenance in PFS in older MCL patients. This trial randomly assigns patients to induction treatment with R-CHOP vs R-CHOP alternating with rituximab plus high-dose cytarabine-dexamethasone (R-HAD) with a second random assignment to rituximab maintenance vs rituximab-lenalidomide maintenance. The United Kingdom randomized ENRICH (2015-000832-13) trial compares a chemotherapy-free ibrutinib-rituximab combination with standard rituximab and chemotherapy (either R-CHOP or rituximab-bendamustine) in MCL patients age 60 years or older to assess PFS benefit. Both trials permit rituximab maintenance.

Emerging chemotherapy-free approach. For some MCL patients, chemotherapy may be out of reach because of age and comorbidities. For others, high-risk genetic mutations that confer chemotherapy resistance call for alternative strategies with target agents. Novel combinations free of conventional chemotherapy are being explored in initial treatment settings, many with prospectively designed assays to probe the clinical feasibility and utility of biomarkers such as the MRD assay and genomic mutational profile in guiding treatment decisions.

A multicenter phase 2 study in 38 treatment-naive MCL patients has shown that the lenalidomide-rituximab combination given as induction and maintenance therapy was highly effective and produced an ORR of 92%, a CR rate of 64%, and a 5-year PFS of 64% in evaluable patients, which demonstrated the feasibility of administering novel agents as continuing maintenance therapy in the outpatient setting (Table 1).[46,47] In addition, MRD-negative remissions in PB were achieved in 8 of 10 patients with available samples, providing the first proof-of-concept evidence that a lenalidomide-based novel agent or combination has the potential to achieve MRD-negative durable remission. The ALR (NCT03863184) trial of acalabrutinib-lenalidomide-rituximab and the VLR (NCT03523975) trial of venetoclax-lenalidomide-rituximab) are exploring the safety and efficacy of building upon lenalidomide-rituximab by adding either a BTK or a BCL2 inhibitor.

The ibrutinib-rituximab combination is being evaluated in the first-line setting in the MD Anderson Cancer Center WINDOW I (NCT02427620) trial and the United Kingdom ENRICH trial (chemo-free arm). The WINDOW I study provides ibrutinib-rituximab treatment (part 1) until best response, followed by a shortened intense chemoimmunotherapy course (part 2). A preliminary report on 50 evaluable patients showed an ORR of 100% for chemotherapy-free ibrutinib-rituximab alone, a CR rate of 80%, and a partial response rate of 20%. Patient accrual and data maturation are underway for the WINDOW I and ENRICH studies. The WINDOW II (NCT03710772) study is designed to assess the efficacy of the venetoclax-ibrutinib-rituximab combination and has a study arm dedicated to the chemotherapy-free venetoclax-ibrutinib-rituximab combination without chemotherapy.

Conclusion

MCL remains a clinical challenge because of its heterogeneous clinical course and general incurability despite the advancement of intensive regimens that often include high-dose therapy administered in a hospital. Most MCL patients are elderly and less able to tolerate or wish to avoid aggressive treatment. The main therapeutic goal is to deliver the most effective therapy tailored to patient and disease factors to extend survival while preserving quality of life whenever possible.

Molecular studies that include gene expression profiling and next-generation sequencing have provided comprehensive mutational characterization of MCL and have demonstrated recurrent genetic aberrations involved in the regulation of the cell cycle, DNA repair, proliferation, and epigenetics. TP53 aberrations, including p53 mutations, as well as del(17p13) and del(9p21) (deletions of TP53 and CDKN2A), have been recurrently and strongly associated with poor clinical outcome after immunochemotherapy, and the impact of these and other mutations in the context of novel agents are being delineated in ongoing clinical trials.

State-of-the-art assessment of MCL patients should therefore include predictive biomarker analysis, such as FISH and sequencing analyses of TP53 status whenever they are available in addition to standard diagnostic tests. Clinical decisions should be guided by personalized risk assessment to determine which patients might do well with deferral of initial therapy, which patients might do well with a non-chemotherapy first-line treatment, and which patients might do well with a non-transplantation approach.

Patients with indolent MCL (eg, nnMCL, low-risk MIPI score, Ki-67 <30%, and low-burden disease) should be offered a discussion on conservative management with deferred initial therapy. Patients with high-risk symptomatic MCL, especially those with chemotherapy-resistant features of TP53 mutations, blastoid variants, complex karyotypes, and high proliferative indexes, should be prioritized for consideration of novel agent–based treatment alternatives on clinical trials. For the majority of patients with classic non-blastoid MCL who need treatment, patient factors such as age, comorbidities, and patient's preference help shape decisions regarding disease management (Figure 1). There are numerous ongoing studies that are evaluating the incorporation of novel agents into first-line induction, maintenance, and consolidation, in addition to sequencing in the R/R setting. Outcomes from randomized phase 3 studies will have practice-changing potential to help reshape and clarify the treatment landscape in the era of novel agents, which is looking ever more promising for MCL patients.

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