Mantle cell lymphoma - advances in molecular biology, prognostication and treatment approaches

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Mantle cell lymphoma – advances in molecular biology, prognostication and treatment approaches

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Summary

Mantle cell lymphoma (MCL) is clinically characterised by its heterogenous behaviour with courses ranging from indolent cases that do not require therapy for years to highly aggressive MCL with a very limited prognosis. A better understanding of the complex biology of MCL has already led to the approval of several innovative agents, expanding the landscape of MCL therapies and improving therapeutic options especially for refractory/relapsed (R/R) disease.

Nevertheless, to further optimise MCL treatment, early identification of individual risk profile and risk-adapted, patient-tailored choice of therapeutic strategy needs to be prospectively incorporated into clinical patient management. The present review highlights recent advances in deciphering the molecular background of MCL, the definition of prognostically relevant factors and the identification of potential druggable targets and summarises current treatment recommendations for primary and R/R MCL including novel targeted therapies.

Keywords: Mantle cell lymphoma, pathogenesis, genetics, prognostication, therapy.

Mantle cell lymphoma (MCL) accounts for 5–7% of malignant lymphomas in Western Europe and occurs with an incidence of 1–2 per 100 000 people per year. The median age is ~65 years with a male to female ratio of about 3:1.[1]

MCL is clinically characterised by its heterogenous behaviour, with courses ranging from indolent cases that do not require therapy for years to highly aggressive MCL with very limited prognosis.[1] Patients typically present with lymphadenopathy at several sites, and most are diagnosed with advanced stage disease (Ann Arbor Stage III, IV). Extranodal manifestations occur in 90% of patients, including infiltration of the bone marrow (53–82%), blood (50%), liver (25%) and gastrointestinal tract (20–60%), presenting as polyposis coli.[1,2] The spleen is enlarged in 40% of patients.[1] In some cases, leukaemic manifestation in combination with massive splenomegaly is clinically prominent. These non-nodal, leukaemic cases are often characterised by a more indolent clinical course.[3] Accordingly, in the World Health Organization (WHO) 2016 update of lymphoid malignancies, MCL now consists of two distinct categories.[4] Nodal MCL (80–90% of cases) is characterised by unmutated immunoglobulin (Ig) heavy chain variable region (*IGHV*) genes, sex-determining region Y-box 11 (*SOX11*) overexpression and a generally more aggressive clinical behaviour. Non-nodal leukaemic MCL (10–20% of cases) typically displays mutated *IGHV*, *SOX11* negativity and presents with indolent biological behaviour.

Histologically, 'classical' MCL cases consist of small- to intermediate-size cells with irregular, cleaved nuclei, dense chromatin and indistinct nucleoli. Centroblasts and immunoblasts are typically absent, thus facilitating differentiation from other lymphoma subtypes, especially follicular lymphoma.[4,5] Besides 'classical' MCL, pleomorphic and blastoid variants can be distinguished. MCL with blastoid morphology is characterised by neoplastic cells resembling lymphoblasts, with dispersed chromatin, prominent nucleoli and high mitotic figures and often featuring high proliferation rates, displaying a more aggressive clinical course.[4–6]

Detection of the genetic hallmark of MCL, the chromosomal t(11;14)(q13;q32) translocation, either by immunohistochemistry [cyclin D1 (*CCND1*) overexpression] or fluorescence *in situ* hybridisation (chromosomal translocation) is crucial to confirm the diagnosis. In rare cases that are negative for *CCND1*, *CCND2* or *CCND3* can be overexpressed.[4] Furthermore, staining for SOX11, a transcription factor specifically expressed in >90% of MCL cases, may help to establish the diagnosis.[7]

However, despite clear pathological characteristics, MCL is a heterogeneous disease with variable presentations, clinical and biological risk factors and therapy approaches. Traditionally, MCL was associated with a poor prognosis with a median overall survival (OS) of 3–5 years.[8] However, major advances in the treatment of patients with MCL have been achieved in recent years, especially with the development of induction immunochemotherapy including cytarabine and

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anti-B-lymphocyte antigen CD20 (CD20) antibodies and by introducing consolidation high-dose therapy with autologous stem cell transplantation (ASCT).[9–13] The introduction of rituximab maintenance therapy has also significantly improved survival rates after ASCT and after induction therapy in patients who are not eligible for high-dose therapy.[14,15] Yet, long-term prognosis is still limited and patients with relapsed/refractory (R/R) disease usually have a dismal outcome.[16] Therefore, improved understanding of cellular and molecular biology of MCL and the identification of relevant factors determining prognosis to optimally use risk-adapted treatment approaches will be critical to further improve outcomes in this disease.

The present review focusses on recent advances in MCL pathogenesis, molecular biology, prognostication and new therapeutic approaches.

Pathogenesis and molecular biology

The development of MCL is the result of a complex pathogenetic interplay between cellular and microenvironmental processes.[17] Genetic hallmark of MCL and considered the primary oncogenic event in the pathogenesis is the chromosomal t (11;14)(q13;q32) translocation. This translocation results in overexpression of cyclin D1 (CCND1) and dysregulation of the cell cycle at the G1–S phase transition.[18,19] *CCND1*-negative MCLs usually carry *CCND2/CCND3* rearrangements with Ig genes, including a novel IGK/L enhancer hijacking mechanism.[20] These *CCND1*-negative, *CCND2/CCND3*-positive cases are similar to *CCND1*-positive MCLs in displaying *SOX11*-positivity and have a similar genomic profile and clinical course.[20,21] A subset of $CCND1^{-}/D2^{-}/D3^{-}$ MCL with aggressive features has CCN E dysregulation.[20]

The transcription factor SOX11 is overexpressed in >90% of MCL cases, whereas a leukaemic non-nodal variant, resembling chronic lymphocytic leukaemia (CLL), lacks SOX11 expression and is associated with a more indolent course.[3] Therefore, SOX11 expression has become an important diagnostic marker to distinguish between two distinct clinicobiological subtypes of this tumour.[22] Aberrant SOX11 expression impacts MCL biology in many different ways including augmentation of B-cell receptor (BCR) signalling,[23] transcriptional regulation of B-cell lymphoma 6 (BCL6),[24] regulation of paired box 5 (PAX5) and B-lymphocyte-induced maturation protein 1 (BLIMP1) expression, promoting the shift from a mature B cell into the initial plasmacytic differentiation phenotype,[25] induction of tumour angiogenesis through transcriptional regulation of platelet-derived growth factor receptor α (PDGFA)[26] and mediating protective tumour microenvironment interactions through C-X-C motif chemokine receptor 4 (CXCR4) and focal adhesion kinase (FAK) regulation.[27] SOX11 expression was shown to be prognostically relevant in a subset of patients with leukaemic, non-nodal presentation, identifying a favourable outcome in patients with negative SOX11 with mutated *IGHV*.[22]

The constitutive activation of the BCR and its downstream signalling pathways also plays an important role in the development of the disease.[17,28,29] Activated BCR signalling induces formation of the signalosome complex that leads to the activation of key downstream effector molecules, such as Bruton tyrosine kinase (BTK), phospholipase C-γ2 (PLC-γ2), protein kinase C (PKC) and the so called 'CBM' caspase recruitment domain family member 11 (CARD11)–BCL10–mucosa-associated lymphoid tissue lymphoma translocation protein (MALT1) complex, nuclear factor kappa B (NFκB), phosphoinositide-3 kinase (PI3K), protein kinase B (AKT), mammalian target of rapamycin (mTOR), CARD11, BCL10, and MALT1, among others.[30]

Better understanding of the biological mechanisms of disease initiation and progression and the complex interplay of the components involved in BCR signalling lead to the detection of multiple molecules as potential druggable targets for MCL therapy and have already paved the way for the development and clinical introduction of targeted treatment alternatives such as temsirolimus, ibrutinib, lenalidomide and bortezomib.[29,31–33]

Furthermore, genomic profiling revealed a high number of secondary genetic alterations and recurrent mutations affecting regulation of cell cycle, DNA damage response (DDR) and apoptosis pathways that contribute to the pathogenesis and aggressiveness of MCL.[17] MCL has one of the highest levels of genomic instability among the malignant lymphoid neoplasms. These genetic abnormalities include losses of 1p22-p13, 6q, 9p21/cyclin-dependent kinase inhibitor 2A (*CDKN2A*), 9q22-q31, 11q22-q23/ATM, 13q14/retinoblastoma protein (*RB1*), 13q33-q34, 10q21.1, 15q14-q21.1 and 17p/tumour protein p53 (*TP53*) and gains of 3q25-q29 and 7p. The more aggressive behaviour of classic MCL, compared with non-nodal MCL, was shown to be associated with a higher number of driver genetic alterations, particularly copy number alterations.[34]

In recent years, next-generation sequencing approaches to unravel the genetic background of MCL has led to the identification of numerous recurrent somatic mutations[35–39] including genes involved in genotoxic stress pathways [ataxia-telangiectasia mutant (*ATM*), *TP53*, *CDKN2A*], epigenetic regulators [Wolf–Hirschhorn syndrome candidate 1 protein (*WHSC1*); histone-lysine *N*-methyltransferase 2D (*KMT2D*); myocyte enhancer factor 2B (*MEF2B*); *KMT2C*; SWItch/Sucrose Non-Fermentable (SWI/SNF)-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 4 (*SMARCA4*)] and genes regulating cell homeostasis, cell growth and cell death [*CCND1*, *TP53*, *CDKN2A*, baculoviral IAP repeat containing three (*BIRC3*), *CARD11*, tumour necrosis factor (TNF) receptor-associated factor 2 (*TRAF2*), *RB1*, protection of telomeres 1 (*POT1*), Notch receptor 1/2 (*NOTCH1/2*)]. Recently, Nadeu *et al.*[34] identified novel driver genes involved in different mechanisms relevant for MCL pathogenesis such as the cell cycle (*CDKN1B*), DNA replication and DDR [*S*-adenosylmethionine (SAM)

and HD domain containing deoxynucleoside triphosphate triphosphohydrolase 1 (*SAMHD1*)], RNA processing [heterogeneous nuclear ribonucleoprotein H1 (*HNRNPH1*)], and chromatin modification (*SMARCB1*). Among these genes, the *ATM* gene is the most frequently mutated gene in newly diagnosed MCL. In a recently published meta-analysis,[40] *ATM* (DDR) had the highest mutation rate at baseline [43·5%, 95% confidence interval (CI) 39·7–47·4%) and after relapse/progression (57·6%, 95% CI 46·6–68·1%). *ATM* aberrations facilitate genomic instability in lymphoma cells through impaired response to DNA damage. PI3K and mTOR are important downstream targets of this signalling pathway. Remarkably, mutations in this gene did not correlate with any differences in clinical outcome compared to patients with unmutated *ATM*.[39,41] Further recurrent somatic mutations with high mutation rates were detected in *TP53* (26·8%, 95% CI 24·2–29·6%), *RB1* (24·3%, 95% CI 17·6–32·1%), *CDKN2A* (23·9%, 95% CI 20·1–28·2%) and *CCND1* (20·2%, 95% CI 16·8–24·1%).[40] Yet, apart from *TP53*, the functional relevance of most mutations is currently unclear and under further investigation.

Prognostic factors

Important clinical and serological factors associated with a worse clinical outcome include older age, poor performance status, advanced stage of disease (Ann Arbor Stage III or IV), splenomegaly and anaemia, high serum levels of β_2-microglobulin and lactate dehydrogenase (LDH), blastoid cytology, extranodal presentation and constitutional symptoms. A subset of patients with a favourable outcome suitable for upfront observation (watch and wait) has recently been characterised based on asymptomatic presentation, good performance status, non-nodal disease, normal LDH and low Ki-67.[42]

A prognostic score that has been confirmed in numerous series, the Mantle cell lymphoma International Prognostic Index (MIPI), was established implementing four independent prognostic factors: age, performance status, LDH and leucocyte count.[43,44] An overwiew of current and future prognostic markers is provided in Table I.

Current evidence indicates that the most important prognostic markers independent of clinical features are the proliferation rate and p53 expression. High p53 and Ki-67 >30%, together with blastoid morphology, were recently reported to define a high-risk biology with significantly shorter failure-free survival and OS.[45] In the clinical setting, immunohistochemical determination of Ki-67 expression, a cell cycle-related protein, has been prospectively confirmed as a reliable prognostic marker and is, in combination with the MIPI (MIPI-c) a highly recommended tool to estimate individual risk profile and to identify high-risk patients (Ki-67 >30%) who may qualify for more aggressive therapeutic approaches.[6,46–48] Furthermore, a cell proliferation gene signature (MCL35) that distinguishes patient subsets differing by >5 years in median survival has been identified and validated in diagnostic material from patients treated in the prospective MCL Younger (NCT00209222) and MCL Elderly (NCT00209209) trials of the European MCL Network.[49,50] Recently, gene expression profiling in the context of the MCL-0208 clinical trial by the Fondazione Italiana Linfomi defined a six-gene signature [AKT serine/threonine kinase 3 (*AKT3*), *BCL2*, *BTK*, *CD79B*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit D (*PIK3CD*) and spleen-associated tyrosine kinase (*SYK*)] related to the BCR pathway identifying a subset of patients with MCL with shorter progression-free survival (PFS) after rituximab-cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) induction, followed by high-dose cytarabine and ASCT.[51] However, in established MCL cell lines, this signature proved to be associated with higher sensitivity to ibrutinib treatment.[52]

Some of the numerous recurrent genetic lesions observed in MCL were identified and confirmed to be associated with inferior outcomes. Deletions of 17p13 or mutations of *TP53*, as well as deletions of *CDKN2A*, were reported to be associated with worse clinical outcome in the majority of the studies published.[12,53–57] Despite optimal immunochemotherapy, high-dose cytarabine and ASCT, younger patients with MCL with deletions of *CDKN2A* (p16) and *TP53* have an unfavourable prognosis, as reported in the European MCL Younger Trial[48,55] and confirmed in the Nordic MCL2 and MCL3 trials.[57] Patients with mutations in the *NOTCH*

Table I. Prognostic markers – current and future.

In clinical routine	Potential for future use
Age	MCL35 RNA expression analysis
Performance status	SOX11 expression
Central nervous system involvement at diagnosis	*TP53* mutations/deletions by sequencing analysis or immunohistochemistry
Stage of disease (I and II vs. III and IV)	*NOTCH1* mutations
Serum level of β_2-microglobulin and LDH	*CDKN2A* mutations
Morphology (classic vs. blastoid)	*WHSC1* mutations
MIPI	*MYC* alterations
Ki-67 (<30% vs. >30%)	*CCND1* mutations
Disease pattern (nodal/non-nodal)	*BIRC3* mutations (concerning ibrutinib treatment)
	CARD11 mutations (concerning ibrutinib treatment)
	SMARCA4 mutations (concerning venetoclax treatment)
	MRD testing

MIPI, Mantle cell lymphoma International Prognostic Index.

genes[38,41] and those with *KMT2D* mutations have also been associated with an adverse prognosis.[55,56] A recent study confirmed the prognostic impact of mutations in *TP53* and *NOTCH1*, with a significantly shorter OS for patients receiving combined immunochemotherapy with R-CHOP; however, mutations in *NOTCH2* and *KMT2D* did not affect survival rates.[39] In a multivariate analysis of *CDKN2A*, *TP53* and *NOTCH1* in the MCL2 and MCL3 trials, only *TP53* mutations retained prognostic impact for OS (median, 1·8 vs. 12·7 years).[57] Furthermore, *TP53* mutations were significantly associated with high Ki-67 (>30%), blastoid morphology, MIPI high-risk score, and inferior responses to both induction and high-dose chemotherapy.

Recently, another study confirmed the prognostic impact of mutations in the *TP53* and *NOTCH1* gene with a significantly shorter OS for patients receiving combined immunochemotherapy with R-CHOP; however, mutations in *NOTCH2* and *KMT2D* did not affect survival rates.[39]

Other genetic lesions have been associated with inferior outcomes including MYC proto-oncogene (*MYC*) alterations,[58] which were recently shown to add further prognostic information to the number of copy number alterations,[34] and mutations in *WHSC1*[41] and *CCND1*.[59]

Several genetic aberrations have been linked to targeted treatment failure: mutations in the *CARD11* gene (~8% at first diagnosis), which codes for a scaffold protein that is part of the CBM complex required for BCR-induced NFκB activation in MCL cells, were reported to mediate resistance to ibrutinib and to the NFκB inhibitor lenalidomide.[35]

Deletions of 11q21-q23 in the *BIRC3* gene occur frequently in MCL with a mutation frequency of 10–15% and have been postulated to confer decreased response to ibrutinib because of failure to suppress the alternate NFκB pathway.[60] Recently, chromosome 9p21.1-p24.3 loss and/or mutations in components of the SWI-SNF chromatin-remodelling complex (including *SMARCA4* mutations) were observed in patients with primary or secondary resistance to ibrutinib plus venetoclax.[61] The authors postulated a selective advantage against ibrutinib plus venetoclax through transcriptional upregulation of BCL2L1 (Bcl-xL) due to impairment of the SWI-SNF complex.

Genome-wide microRNA (miR) microarray profiling of MCL samples from the Nordic MCL2 and MCL3 trials identified miR-18b overexpression as associated with poor prognosis and adding prognostic information to the biological MIPI.[62]

Whilst several genetic lesions have been identified as promising candidates to predict high-risk disease behaviour and inferior outcomes to available therapies, none have translated into routine clinical use. A recent study identified a strong correlation between p53 protein expression and *TP53* missense mutations, proposing immunohistochemical quantification of p53 as a valid prognostic surrogate when *TP53* sequencing is not available.[63] Nevertheless, to prospectively use biological features to individually guide MCL therapy, further biological studies investigating homogenously treated patient cohorts to validate and complement current findings are of great importance.

Concerning the prognostic impact of minimal residual disease (MRD) status, several studies have been published, providing evidence of the strong prognostic potential of MRD status predicting improved subsequent PFS for MRD-negative patients at the end of induction and before high-dose consolidation.[11,64,65] Furthermore, lack of molecular remission after the end of currently recommended standard treatment was shown to be strongly predictive for early clinical relapse within 1–2 years.[11,13,66] However, it was recently reported that MRD was no longer prognostically significant in elderly patients treated with R-CHOP-like induction and rituximab maintenance.[67] To date, MRD analysis has limited utility in routine practice. This is due in part to the technical limitations of MRD detection. Currently, real-time quantitative polymerase chain reaction (qPCR) amplification of clonal *IGH* or *BCL1/IGH* rearrangements is the 'gold standard' MRD monitoring tool in MCL.[68] Multiparameter flow cytometry (MFC) is another promising technique.[69] However, qPCR is based on relative quantification and is thus unreliable for samples with low or unknown levels of basal infiltration, as it requires a diagnostic DNA standard curve with a known level of infiltration, preferably in excess of 1–10%. MFC, although rapid and inexpensive, is not as sensitive as qPCR.[69] Droplet digital PCR (ddPCR) was recently shown to have similar sensitivity to qPCR, with many technical advantages including absolute quantification of low level positivity between 1E-5 and 1E-4.[70] The other barrier to routine adoption of MRD analysis in clinical practice is the lack of data supporting treatment adaptation based on MRD status, coupled with uncertainty about the value of MRD monitoring in the context of the targeted treatments, such as ibrutinib. Efforts to develop MRD-adapted therapy are underway alongside technical optimisation for IgH clonal detection and PCR-based quantification of t(11; 14).[71]

Treatment

The clinical course of MCL is characterised by generally high initial response rates; however, early relapses are frequent and most patients follow an aggressive clinical course. Nevertheless, 10–15% of patients present with a more indolent subtype. Most of these cases are characterised by a leukaemic, non-nodal lymphoma manifestation, a very low Ki-67 Index (<10%) or have measurable disease without markers of higher cell turnover (raised LDH and Ki-67 ≥30%).[72] In these cases, watchful waiting under close monitoring is considered an appropriate strategy,[73] with up to half of patients not requiring treatment in the first 2 years of observation according to data from the UK National Cancer Research Institute (NCRI) MCL Biobank observational study.[72] However, most newly diagnosed patients display aggressive disease features and require early initiation of therapy.

Localised stage

In the (rare) early Stages I and II with low tumour burden, long-term remissions after involved-field radiotherapy (30–36 Gy) have been reported.[74] In contrast, in a randomised trial, frequent early relapses after radiotherapy alone were observed.[75] Therefore, in these localised cases, a shortened immunochemotherapy followed by a consolidating radiotherapy is considered most appropriate.

Advanced stage

Therapy in patients aged ≤65 years. In European countries, in young and fit patients (aged ≤65 years), a dose-intensified concept containing an immunochemotherapy induction followed by a high-dose consolidation regimen and ASCT constitutes the current standard of care.[1] Fig 1 suggests a risk-adapted treatment strategy for this group of patients. In several studies, either intensified up-front therapy or the addition of high-dose consolidation followed by ASCT resulted in impressive survival rates (Table II).[11,12,15,7677]

Induction: dose-intensified, cytarabine-containing regimen—Promising results were achieved by sequential application of R-CHOP and the cytarabine-containing R-DHAP (rituximab, dexamethasone, high-dose cytarabine, cisplatine) regimen: four cycles of R-DHAP following four cycles of R-CHOP improved complete response (CR) rates from 12% to 57%.[12] In a large, randomised European trial, the administration of the R-CHOP/DHAP regimen compared to administration of R-CHOP alone prior to myeloablative consolidation with ASCT more than doubled the time to treatment failure (109 vs. 47 months).[11]

Another commonly used treatment approach, predominantly used in the USA, is the intensive immunochemotherapy regimen rituximab in combination with hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone (hyper-CVAD)/methotrexate-ara-C (R-HCVAD/methotrexate-ara-C). This regimen achieved high CR rates and long-term remissions and does not require consolidation with ASCT. In a phase II trial with 97 patients treated with R-HCVAD/methotrexate-ara-C (without consolidation autologous SCT) with a median follow up of 13·4 years, Chihara *et al.*[76] reported overall response rates (ORRs) and CR rates of 97% and 87% respectively. However, this regimen is hampered by significant therapy-associated toxicity, including secondary malignancies, and should only be considered in young, fit patients.[78,79]

Consolidation: ASCT—In several studies, the addition of high-dose consolidation followed by ASCT resulted in impressive survival rates.[11,12,15] A large randomised trial proved that consolidation by myeloablative radiochemotherapy followed by ASCT in first remission significantly prolonged PFS (3·3 vs. 1·5 years) and OS,[9,80] independently of the addition of rituximab. To define if total body irradiation (TBI) should be part of conditioning before ASCT, a retrospective comparison of different trials showed a benefit of a TBI-containing high-dose consolidation compared with the most commonly used conditioning regimen containing carmustine, etoposide, cytarabine and melphalan (BEAM) only in patients having achieved partial remission after induction, whereas the addition of conventionally dosed radioimmunotherapy did not result in this benefit.[81]

Unfortunately, even after such intensive consolidation regimens, a majority of patients relapse. '*In vivo* purging' with a

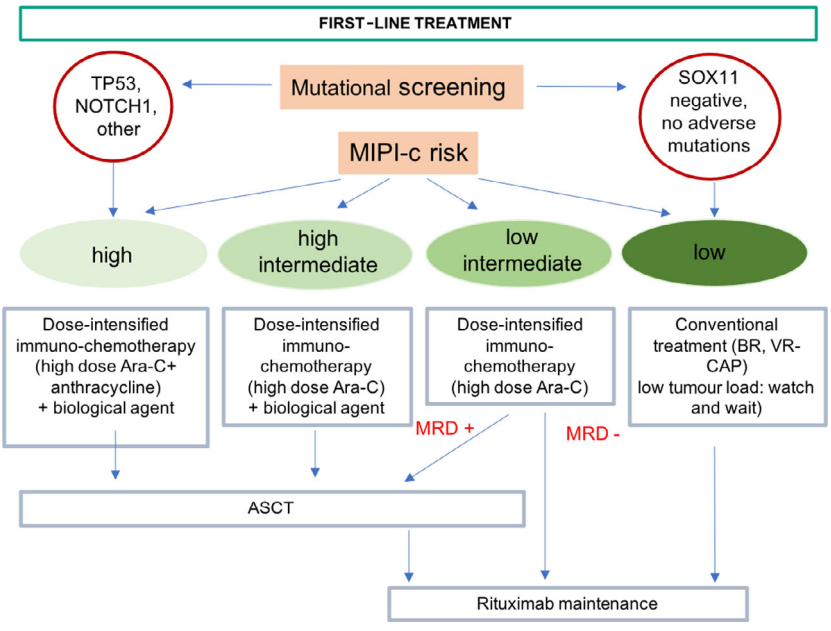

Fig 1. Suggested therapeutic algorithm for transplant-eligible patients.

Table II. Dose-intensified therapy in newly diagnosed mantle cell lymphoma (MCL).

Reference	No. of patients	Induction regimen	Consolidation regimen	ORR (CR), %	Median PFS, years (%)	Median OS, years (%)
Delarue *et al.*, 2013[12]	60	R-CHOP/R-DHAP	ASCT	93 (12) 95 (57)	6·9	5 (75)
Chihara *et al.*, 2016[76]	97	R-Hyper-CVAD/MA	–	97 (87)	4·8	7 (10)
Hermine *et al.*, 2016[11]	466	R-CHOP	ASCT	97 (61)	3·9	NR
		R-CHOP/R-DHAP	ASCT	98 (63)	9·1	9·8
Le Gouill *et al.*, 2017[15]	240	R-DHAP	ASCT + R-maintenance	89 (after induction)	4 (83)	4 (89)
		R-DHAP	ASCT + observation		4 (64)	4 (80)
Eskelund *et al.*, 2016[77]	160	R-CHOP/R-high dose-cytarabine	ASCT	96	8·5	12·7

ASCT, autologous stem cell transplantation; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; CR, complete response; DHAP, dexamethasone/high-dose cytarabine/cisplatin/dexamethasone; ORR, overall response rate; OS, overall survival; R, rituximab; PFS, progression-free survival; Hyper-CVAD, cyclophosphamide/doxorubicin/vincristine/dexamethasone; MA, high-dose methotrexate/high-dose cytarabine.

rituximab-containing induction regimen to prevent contamination of stem cell products with circulating MCL cells before apheresis has shown further improvement in long-term survival.[66] It is important to note that the relative importance of ASCT *versus* no consolidation has not been prospectively evaluated in a randomised trial evaluating modern induction therapy containing both Ara-C and rituximab. Similarly, the added value of ASCT in the era of targeted therapy remains unknown. Results of the ongoing European MCL Network Triangle trial evaluating this question in the context of ibrutinib induction and maintenance (NCT02858258) will report in 2026.

Maintenance—Rituximab maintenance after ASCT is currently considered the standard of care for younger patients with MCL based on the results of a large phase III trial showing a significant optimisation of PFS (83% vs. 64% after 4 years) and OS (89% vs. 80% after 4 years) after 3 years of rituximab maintenance compared to observation only.[15]

Recently, another phase III trial revealed a benefit from a lenalidomide maintenance after autologous transplantation with improved PFS (80% vs. 64% after 3 years) compared to observation.[82] However, due to the elevated toxicitiy profile (especially haematotoxicity), lenalidomide maintenance should be only used in patients not suitable to receive rituximab.

Therapy in patients aged >65 years. Induction—The group of patients aged >65 years ineligible for transplantation presents very heterogenously regarding age, comorbidity and performance status. A suggested therapeutic algorithm is depicted in Fig 2. Fit patients aged >65 years should receive conventional immunochemotherapy followed by rituximab maintenance.[14] A combination of bortezomib, rituximab, cyclophosphamide, doxorubicine and prednisone (VR-CAP) recently proved to be superior to R-CHOP in a large international phase III trial. In this trial, VR-CAP doubled OS after 82 months compared to R-CHOP (90·7 vs. 45·7 months). However, haematological toxicity (especially Grade >3 thrombopenia) was significantly increased in the experimental arm (57% vs. 6%).[83] Considering the clear improvement in survival rates, VR-CAP should be, in our opinion, preferably chosen for patients not eligible for high-dose therapy, especially for those with a higher risk-profile such as high Ki-67 expression or blastoid morphology. The combination of rituximab, bendamustine and cytarabine (R-BAC) offers another useful option.[84] In a multicentre phase II trial, patients received intravenously rituximab 375 mg/m^2 on day 1, bendamustine 70 mg/m^2 on days 2 and 3, and cytarabine 500 mg/m^2 on days 2–4 every 4 weeks for up to six courses. A high proportion of patients achieved a CR, with durable responses of ≥3 years for most patients. Positron emission tomography-negative CR was observed in 91%. The 2-year OS was 86% and 2-year PFS was 81%. Yet, this regimen was accompanied by severe haematotoxicities and should therefore only be administered to very fit older patients with high-risk features (e.g. blastoid variant, high LDH count).[84] Alternatively, for patients not qualifying for such intensive therapy regimens, bendamustine and rituximab (BR) offers an appropriate alternative. This combination resulted in similar response rates (93% vs. 91%) compared to R-CHOP, but superior PFS (35 vs. 21 months) and a more favourable toxicity profile.[85] In frail patients, choice of therapy should mainly be aimed at control of symptoms, with options including R-CVP and R-chlorambucil or participation in clinical trials of novel therapies with favourable safety profiles.

Taken together, VR-CAP, BR and R-CHOP represent the current standard approaches in older patients, who represent the majority of patients with MCL. Based on clinical presentation, BR or R-CHOP may be preferable especially in patients with a more indolent CLL-like presentation or in patients not qualifying for more intensive regimens, whereas VR-CAP may be appropriate in more aggressive cases. Based

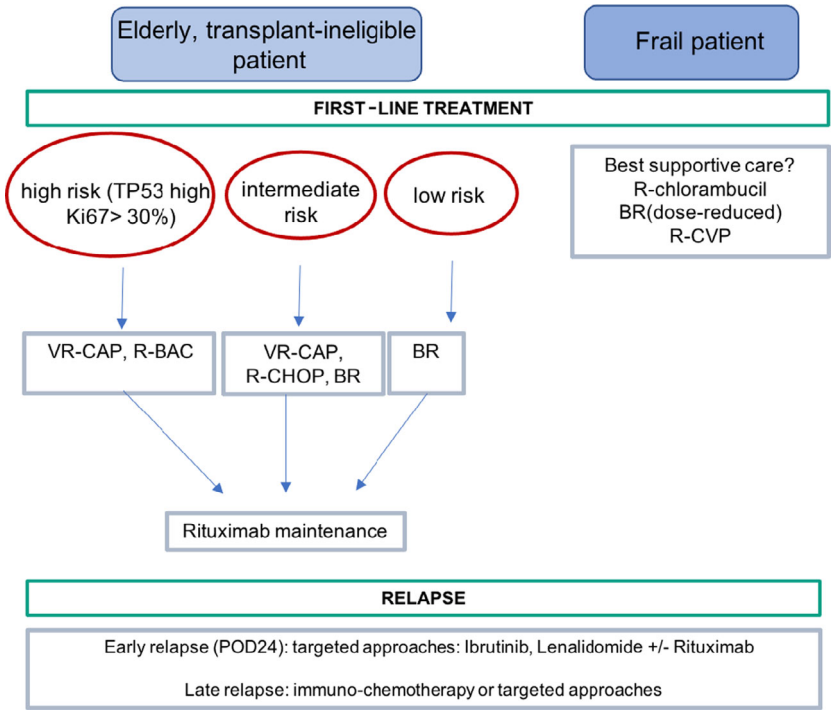

Fig 2. Suggested therapeutic algorithm for patients >65 years.

on the improved results in younger patients,[11] cytarabine-containing regimens may offer better disease control for patients with blastoid variants.

Maintenance—A large, randomised, European phase III trial compared rituximab maintenance to interferon maintenance after immunochemotherapy, and confirmed superiority of rituximab maintenance therapy. In this study, after 4 years, 58% of the patients receiving rituximab after induction therapy with R-CHOP were in remission, compared to 29% in the interferon arm ($P = 0{\cdot}01$). The PFS and OS were also significantly improved in the rituximab arm (5-year PFS rituximab vs. interferon 51% vs. 22%, 5-year-OS rituximab vs. interferon 79% vs. 59%).[53] Based on these results, rituximab maintenance is now generally recommended for patients responding to induction R-CHOP. A benefit of rituximab maintenance therapy after BR chemotherapy was not evident at interim analysis for a large randomised phase III trial, and full results are awaited.

Recurrent and refractory disease

Allogeneic transplantation. For younger high-risk patients with *TP53*-mutated and relapsed MCL, who are transplant-eligible, the option of allogeneic transplantation should be considered.[86] Reduced-intensity allogeneic stem cell transplantation (RIST) resulted in long-term disease-free survival in ~30% of the patients and may be applicable also in patients aged >60 years.[87] Transplantation-associated severe acute and delayed toxicities, including chronic graft-*versus*-host disease are common and allotransplant carries a 20–25% treatment-related mortality. Therefore, allogeneic transplantation is not recommended in the first-line setting and should be reserved for selected patients with high-risk recurrent disease, taking risks and benefits into careful consideration.[1]

Molecular targeted therapies. Several targeted therapy approaches have been investigated in different studies as single agents or in combination with immunochemotherapies or other targeted therapies (Table III).[29,31,32,88–104]

Targeting the *BCR pathway* with the BTK inhibitor ibrutinib resulted in remarkable response rates leading to its approval in relapsed MCL. In a large international phase II study, response rates of 68% were achieved with ibrutinib in patients with relapsed disease.[29] A pooled analysis of the results of three different trials testing ibrutinib as monotherapy revealed overall response rates of 66% with a median PFS and OS of 12·8 and 25 months respectively.[105] The compound is very well tolerated with only slight immunosuppression, bleeding, and atrial fibrillation being the most concerning side-effects. However, interindividual responsiveness is heterogenous and primary and secondary resistance has been reported with poor clinical outcome.[106,107] In patients with mutations in the *TP53* gene, the median PFS was shown to be significantly worse.[105] Several mechanisms of ibrutinib resistance have been described in MCL, including interactions with the tumour microenvironment.[108–110] MCL cells were shown to develop ibrutinib resistance through evolutionary processes driven by dynamic feedback between MCL cells and the tumour microenvironment, leading to kinome adaptive re-programming, bypassing the effect

Table III. Molecular targeted therapies in mantle cell lymphoma (MCL).

Regimen	Phase	No. of patients	ORR (CR), %	Median PFS, months	Reference
Bortezomib	Phase II	141	33 (8)	6·7 (TTP)	Goy *et al.*[88]
Bortezomib + R-HAD	Retrospective	8	50 (25)	5	Weigert *et al.*[89]
CHOP vs. bortezomib + CHOP	Phase II	46	48 (22)	8·1	Furtado *et al.*[90]
			83 (35)	16·5	
Temsirolimus 175/75 mg vs.	Phase III	162	22 (2)	4·8	Hess *et al.*[91]
emsirolimus 175/25 mg vs. chemotherapy			6 (0)	3·4	
			2 (2)	1·9	
Temsirolimus + BR	Phase I/II	29	89 (36)	18	Hess *et al.*[92]
R + temsirolimus	Phase II	69	59 (19)	9·7	Ansell *et al.*[31]
Lenalidomide	Phase II	134	28 (7·5)	4	Goy *et al.*[93]
Lenalidomide	Phase II	57	35 (12)	8·8	Zinzani *et al.*[94]
Lenalidomide vs. monochemotherapy	Phase II	170	46 (11)	8·7	Trneny *et al.*[95]
		84	23 (8)	5·2	
Lenalidomide + rituximab	Phase II	44	57 (36)	11·1	Wang *et al.*[32]
Lenalidomide + rituximab	Phase II	38		64% (after 5 years)	Ruan *et al.*[96]
Ibrutinib	Phase II	111	68 (21)	13·9	Wang *et al.*[29]
Ibrutinib vs. temsirolimus	Phase III	280	72 (19)	14·6	Dreyling *et al.*[97]
			40 (1)	6·2	
Ibrutinib + rituximab	Phase II	50	88 (44)		Wang *et al.*[98]
Ibrutinib + lenalidomide +rituximab	Phase II	50	76 (56)		Jerkeman *et al.*[99]
Idelalisib	Phase I	40	40 (5)	3·7	Kahl *et al.*[100]
Abt-199 (venetoclax)	Phase I	28	75 (21)	14	Davids *et al.*[101]
Abt-199 (venetoclax)+ ibrutinib	Phase II	24	71		Tam *et al.*[102]
Acalabrutinib	Phase II	124	81 (40)		Wang *et al.*[103]
Zanubrutinib	Phase II	86	84 (68·6)	22·1	Song *et al.*[104]

CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; CR, complete response; HAD, high-dose cytarabine/dexamethasone; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R, rituximab; TTP, time to progression.

of ibrutinib and reciprocal activation of PI3K-AKT-mTOR and integrin-β1 signalling.[110]

The combination of ibrutinib with rituximab was reported to be effective in relapsed disease with low Ki-67 expression; however, only half of the patients with highly proliferating disease responded to this approach.[98] Up-front evaluation of this combination compared to immunochemotherapy is under investigation in patients aged >60 years in the NCRI ENRICH clinical trial [European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) number 2015-000832-13]. Ibrutinib given in combination with BR in patients aged ≥65 years with newly diagnosed MCL is currently being evaluated in the phase III SHINE trial (NCT01776840).

The second-generation BTK inhibitor acalabrutinib was approved in October 2017 by the United States Food and Drug Administration (FDA) for patients with R/R MCL who had received at least one prior therapy as promising results, especially regarding tolerability, were observed in an open-label phase II study.[103] Acalabrutinib in combination with BR compared to BR alone in previously untreated patients with MCL aged >65 years is currently being evaluated in an ongoing phase III study (NCT02972840).

The next-generation BTK inhibitor zanubrutinib is a highly potent, selective, bioavailable, and irreversible BTK inhibitor with maximised BTK occupancy, which was approved in 2019 in the USA and China for the treatment of patients with R/R MCL. This approval was based on results from a phase II study in Chinese patients with R/R MCL reporting high ORRs with durable CRs and improved safety and tolerability over existing treatments.[104] The potential for use of zanubrutinib in the first-line setting is currently under evaluation in the randomised phase III MANGROVE study (NCT04002297) in which patients with treatment-naive MCL are randomised between zanubrutinib + rituximab or BR.

Patients with early disease relapse after ibrutinib therapy were shown to have a poor response to salvage therapy with ORRs and CR rates of 32% and 19% respectively, and a median OS of just 8·4 months at median (range) follow-up of 10·7 (2·4–38·9) months.[107] For this high-risk group of patients, a monotherapy with the BCL2-inhibitor Abt-199 (venetoclax) might be a promising alternative, as a phase I trial showed response rates of 75% in patients with relapsed MCL[101] and 60% in patients after failure of prior ibrutinib therapy.[111] Recently, the combination of ibrutinib and venetoclax proved to be highly effective in a small study cohort.[102] The potential advantage of ibrutinib combined with venetoclax over ibrutinib alone is currently being examined in an ongoing phase III study SYMPATICO (NCT03112174).

Bortezomib, a first-generation proteasome inhibitor, has shown response rates of 30–40% in relapsed disease, with a median PFS of ~6 months, leading to the first FDA approval of a targeted drug in relapsed MCL.[88] Bortezomib in combination with rituximab, cyclophosphamide, doxorubicine and prednisone (VR-CAP) is currently the only approved front-line therapy containing a biological agent in MCL.[83]

The mTOR inhibitor temsirolimus has been approved for relapsed disease based on the results of a large randomised trial proving it to be superior compared to monotherapy in a highly refractory patient population (response rate, 22% vs. 2%).[91] Convincing response rates have also been observed in combination with BR.[92]

Immunotherapies. Immunotherapy approaches have already been integrated in treatment algorithms of MCL. Various studies confirmed a benefit for the orally available immunomodulatory drug lenalidomide in relapsed MCL, with response rates of 35–50%.[32,93–95] In a randomised phase II trial, this approach was superior to monochemotherapy (response rate 46% vs. 23%).[95] Based on an *in vitro* synergism, lenalidomide in combination with rituximab resulted in durable remissions in first-line therapy, albeit most of the treated patients had low-risk disease.[96]

The role of T-cell-based immunotherapy approaches, such as immune checkpoint inhibitors and bispecific T-cell engagers, seems to be limited in MCL, as MCL cells only marginally express programmed cell death (PD) ligands (PDL1, PDL2), and almost no PD-1^{+} cells were detected in MCL biopsies.[112]

Very promising results leading to FDA approval were recently reported for the autologous CD19 chimeric antigen receptor (CAR) T-cell construct brexucabtagene autoleucel (formerly KTE-X19; tecartus) based on results of the ZUMA-2 trial (NCT02601313). Treatment with brexucabtagene autoleucel was associated with durable overall responses in 92% of patients with R/R MCL (67% CR rate). Serious but manageable toxicities were reported, consistent with the expected toxicity profile for this agent, and this will necessitate careful selection of appropriate candidates for this.[113] A second CD19-directed CAR T-cell product (lisocabtagene maraleucel) for R/R MCL is currently being evaluated in the ongoing phase I study TRANSCEND non-Hodgkin lymphoma (NHL) 001 (NCT02631044). Results to date are promising and may even be curative in some patients with MCL, but more mature follow-up is needed to confirm this. Moreover, to better understand which patients are more likely to respond to CAR T-cell therapy *versus* other agents, such as combinations of targeted drugs, further research is warranted.

Outlook

The prospects of patients have significantly improved over recent decades due to the optimisation of chemotherapy regimens, notably the addition of rituximab and cytarabine to induction regimens. These stepwise improvements were soon followed by clinical development of ibrutinib, leading to the first breakthrough treatment for R/R disease.

Combined targeted therapy and immunochemotherapy approaches are currently under evaluation in the first-line setting to evaluate their potential to deliver durable remissions and challenge the role of ASCT in younger patients. Novel BCL-2 inhibitors and CAR-T strategies in clinical development have the potential to continue this improving trajectory, but it is premature at this time to forecast a cure in this challenging disease.

Improved clinical (MIPI), immunohistochemical (Ki-67, SOX11) and molecular genetic (*TP53*) diagnostic tools are also paving the way for individual risk assessment and adapted therapy approaches, with the potential for even greater strides as researchers slowly unravel the prognostic and functional relevance of a host of recurrently mutated genes in MCL.

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